Effect of Adjuvant Paclitaxel and Carboplatin on Survival in Women With Triple-Negative Breast Cancer
A Phase 3 Randomized Clinical Trial

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IMPORTANCE The value of platinum-based adjuvant chemotherapy in patients with triple-negative breast cancer (TNBC) remains controversial, as does whether BRCA1 and BRCA2 (BRCA1/2) germline variants are associated with platinum treatment sensitivity.

OBJECTIVE To compare 6 cycles of paclitaxel plus carboplatin (PCb) with a standard-dose regimen of 3 cycles of cyclophosphamide, epirubicin, and fluorouracil followed by 3 cycles of docetaxel (CEF-T).

DESIGN, SETTING, AND PARTICIPANTS This phase 3 randomized clinical trial was conducted at 9 cancer centers and hospitals in China. Between July 1, 2011, and April 30, 2016, women aged 18 to 70 years with operable TNBC after definitive surgery (having pathologically confirmed regional node-positive disease or node-negative disease with tumor diameter >10 mm) were screened and enrolled. Exclusion criteria included having metastatic or locally advanced disease, having non-TNBC, or receiving preoperative anticancer therapy. Data were analyzed from December 1, 2019, to January 31, 2020, from the intent-to-treat population as prespecified in the protocol.

INTERVENTIONS Participants were randomized to receive PCb (paclitaxel 80 mg/m² and carboplatin [area under the curve = 2] on days 1, 8, and 15 every 28 days for 6 cycles) or CEF-T (cyclophosphamide 500 mg/m², epirubicin 100 mg/m², and fluorouracil 500 mg/m² every 3 weeks for 3 cycles followed by docetaxel 100 mg/m² every 3 weeks for 3 cycles).

MAIN OUTCOMES AND MEASURES The primary end point was disease-free survival (DFS). Secondary end points included overall survival, distant DFS, relapse-free survival, DFS in patients with germline variants in BRCA1/2 or homologous recombination repair (HRR)–related genes, and toxicity.

RESULTS A total of 647 patients (mean [SD] age, 51 [44-57] years) with operable TNBC were randomized to receive CEF-T (n = 322) or PCb (n = 325). At a median follow-up of 62 months, DFS time was longer in those assigned to PCb compared with CEF-T (5-year DFS, 86.5% vs 80.3%; hazard ratio [HR] = 0.65; 95% CI, 0.44-0.96; P = .03). Similar outcomes were observed for distant DFS and relapse-free survival. There was no statistically significant difference in overall survival between the groups (HR = 0.71; 95% CI, 0.42-1.22; P = .22). In the exploratory and hypothesis-generating subgroup analyses of PCb vs CEF-T, the HR for DFS was 0.44 (95% CI, 0.15-0.99; P = .04) and 0.39 (95% CI, 0.15-0.99; P = .04) in those with the HRR variant. Safety data were consistent with the known safety profiles of relevant drugs.

CONCLUSIONS AND RELEVANCE These findings suggest that a paclitaxel-plus-carboplatin regimen is an effective alternative adjuvant chemotherapy choice for patients with operable TNBC. In the era of molecular classification, subsets of TNBC sensitive to PCb should be further investigated.

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Approximately 15% to 20% of breast cancers are classified as triple-negative breast cancer (TNBC), which is characterized by a lack of estrogen receptor and progesterone receptor expression and no ERBB2 gene amplification.\(^1\) Compared with other subtypes, TNBC tends to have a higher histologic grade, increased aggressiveness, and more risk of local recurrence and visceral metastasis.\(^2\) The reported prevalence of BRCA1 and BRCA2 (BRCA1/2) variants in unselected patients with TNBC is 11.2%.\(^3\) Both BRCA-associated breast cancer and sporadic TNBC exhibit characteristics consistent with abnormal DNA repair and genomewide instability, which supports the use of DNA-damaging compounds, such as platinum derivatives.\(^2\)

Platinum agents are cytotoxic DNA-damaging compounds that cause DNA strand breaks and consequently lead to apoptosis; this unique mechanism of action renders these drugs particularly active in cancer cells with DNA repair deficiency, such as those harboring deleterious variants in BRCA genes.\(^4\) On the basis of this biologic rationale, several studies have investigated the possible role of platinum agents in the treatment of patients with TNBC in both metastatic and neoadjuvant settings. For example, the results from the Triple Negative Trial\(^5\) suggested that carboplatin performed similarly to docetaxel as first-line therapy in patients with unselected metastatic TNBC but that the former was more effective in patients carrying BRCA variants. The CBCSG006 trial\(^6\) reported superior efficacy for the cisplatin-plus-gemcitabine regimen vs the paclitaxel-plus-gemcitabine regimen as first-line chemotherapy for patients with metastatic TNBC. In the neoadjuvant setting, several randomized controlled trials have found that the addition of carboplatin on the backbone of a taxane with or without an anthracycline increased the proportion of pathological complete response.\(^7,8\)

The value of platinum-based chemotherapy in the adjuvant setting in TNBC patients remains controversial. We initiated the present PATTERN (adjuvant Platinum and Taxane in Triple-Negative Breast Cancer) trial to investigate whether a paclitaxel-plus-carboplatin regimen as adjuvant treatment in TNBC patients would offer superior benefit compared with a standard regimen of anthracycline and docetaxel.

### Methods

#### Study Design and Participants

The PATTERN trial is a randomized, open-label, multicenter, phase 3 clinical trial performed in 9 cancer centers and hospitals in China (eTable 1 in Supplement 2) designed on the premise of demonstrating the effects of a carboplatin-containing regimen. The independent institutional review boards of the participating centers approved the study protocol (Supplement 1). This trial followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. We performed the study according to the International Conference on Harmonisation Good Clinical Practice guidelines and ethical principles of the Declaration of Helsinki.\(^9\) All patients provided written informed consent.

Patients were screened between July 1, 2011, and April 30, 2016. Women aged 18 to 70 years with operable, primary invasive TNBC were eligible for enrollment following definitive surgery. Patients were eligible if they had pathologically confirmed regional node-positive disease or node-negative disease with primary tumor diameter >10 mm. Estrogen receptor, progesterone receptor, and ERBB2 statuses were identified locally at each participating center based on immunohistochemical analysis of tumor sections. The immunohistochemical cutoff for estrogen receptor/progesterone receptor-negative status was less than 1% staining in nuclei according to the American Society of Clinical Oncology/College Of American Pathologists test guideline.\(^10\) ERBB2-negative status was a score of 0 or 1 by immunohistochemical analysis or the absence of ERBB2 amplification by fluorescence in situ hybridization with an immunohistochemistry score of 2 according to the American Society of Clinical Oncology/College Of American Pathologists guideline.\(^11\) Eastern Cooperative Oncology Group performance status was required to be less than 2, and the following criteria for adequate organ function needed to be met: adequate hematologic function and hepatic and renal function and normal cardiac function.

Patients were ineligible if they had metastatic or locally advanced disease, had non-TNBC, or received preoperative anticancer therapy (including chemotherapy and radiotherapy). Full inclusion and exclusion criteria can be found in the study protocol (Supplement 1).

We hypothesized that carriers with deleterious gBRCA1/2 variants might obtain more survival benefits from carboplatin-containing chemotherapy than with the traditional regimen.\(^12\) For all participants, a germline variant test of BRCA1/2 was recommended but not mandatory; variant status was determined using blood samples obtained before chemotherapy. As the BRCA1/2 test requires time and we could not obtain variant information before chemotherapy was initiated, randomization could not be stratified according to gBRCA1/2 status. All coding regions and exon-intron boundaries of the BRCA1/2 genes were screened. Genetic testing was conducted in the central laboratory of Fudan University Shanghai Cancer Center (FUSCC).\(^13\) The detailed sequencing procedure and interpretation of the variants are described in the eMethods in Supplement 2. All variants considered pathogenic or likely pathogenic were validated via Sanger sequencing.

### Key Points

#### Question

Does a paclitaxel-plus-carboplatin (PCb) as adjuvant treatment in women with operable triple-negative breast cancer offer superior benefit compared with a standard-dose CEF-T regimen (cyclophosphamide, epirubicin, and fluorouracil followed by docetaxel)?

#### Findings

In this randomized phase 3 clinical trial conducted at 9 cancer centers and hospitals in China and including 647 patients, after a median follow-up of 62 months, 5-year disease-free survival rate was statistically significantly higher in the PCb group compared with the CEF-T group.

#### Meaning

Results of this study suggest that a paclitaxel-plus-carboplatin regimen may be an alternative adjuvant chemotherapy choice for patients with operable triple-negative breast cancer.
With the development of this trial, several novel reports have shown that BRCA1/2 variant is not the only surrogate of homologous recombination deficiency (HRD), which is probably an indicator of platinum salt sensitivity, and a few assays for HRD status have been reported. Thus, we examined a set of genes involved in homologous recombination repair (HRR) using DNA samples from peripheral blood in a 2-step process. First, we identified candidate HRR genes with germline variants in the Chinese population. By testing 405 patients with TNBC (samples obtained between 2005 and 2010 in FUSCC) using whole exome sequencing, as described elsewhere, we found germline variants in 12 HRR-related genes: ATM, ATR, BARD1, BRCA1, BRCA2, BRIPI, CHEK2, FANCN, PALB2, RAD51C, RAD51D, and RECQL. Second, we assessed germline variants in these 12 HRR-related genes in the trial population. The details of the methodology are provided in the eMethods in Supplement 2.

Randomization and Masking
We randomly assigned eligible patients (1:1) to receive either paclitaxel and carboplatin (PCb) or cyclophosphamide, epirubicin, and fluorouracil followed by docetaxel (CEF-T). Randomization was performed via an interactive web-response system. Investigators sent the random assignment forms by fax to the research coordination office in FUSCC. The study coordinator sent the allocated treatment group to the investigator by fax after checking the inclusion and exclusion criteria. Randomization was stratified according to pathological node status (negative vs positive), age (younger than 50 years vs 50 years and older), and pathological tumor size (pT1 vs pT2-3). Because this was an open-label study, the patients, investigators, and study team were not masked to the treatment group.

Procedures
The participants’ baseline characteristics were recorded at randomization. Patients were randomly assigned to receive PCb, ie, paclitaxel 80 mg/m² and carboplatin (area under the curve = 2) on days 1, 8, and 15 every 28 days for 6 cycles; or CEF-T, ie, fluorouracil 500 mg/m², epirubicin 100 mg/m², and cyclophosphamide 500 mg/m² intravenously on day 1 every 3 weeks for 3 cycles followed by docetaxel 100 mg/m² intravenously on day 1 every 3 weeks for 3 cycles. Chemotherapy should be initially administered within 8 weeks after initial breast cancer surgery. Concurrent or extended treatments of adjuvant capecitabine as well as other chemotherapeutic regimens were forbidden. Timing of adjuvant radiotherapy and the follow-up schedule are described in the eMethods in Supplement 2.

Outcomes
The primary endpoint was disease-free survival (DFS). The DFS events included noninvasive and invasive breast cancer recurrences (local, regional, or distant), second primary noninvasive and invasive breast and cancers other than basal/squamous-cell carcinoma of the skin and carcinoma in situ of the cervix, and death from any cause. Secondary end points included the following: distant disease-free survival (DDFS), relapse-free survival (RFS), overall survival (OS), and toxicity. Detailed definitions of survival outcomes are provided in the eMethods in Supplement 2. Another prespecified secondary end point was DFS in gBRCA1 variant carriers. An exploratory analysis of the interaction between carboplatin-containing chemotherapy and HRR-related gene variant was amended in 2017. Toxicity was graded according to National Cancer Institute Common Toxicity Criteria version 4.0 and was assessed in patients who received at least 1 cycle of chemotherapy.

Statistical Analysis
Data were analyzed from December 1, 2019, to January 31, 2020. The study was designed to detect an absolute 7% improvement in the 5-year DFS rate for the PCb group (assumed 89%) compared with the CEF-T group (assumed 82%), with a corresponding hazard ratio (HR) of 0.60. Under these assumptions, a 2-sided log-rank test with 80% power required 614 patients (307 in the CEF-T group and 307 in the PCb group) to show a 5% level of significance, with 112 DFS events expected after a minimum 5-year follow-up time. Considering 5% loss to follow-up, 645 randomized patients were required. No interim analysis was planned for DFS. In a superiority trial, a 1-sided P value (at a significance level of .025) should be used for decision-making in analyses. A 1-sided P value at a significance level of .025 corresponded to a 2-sided P value at a significance level of .05. We determined 2-sided P values at a significance level of .05 according to usual practice.

The intention-to-treat principle was used for the primary analysis, which was performed on all randomly assigned patients with follow-up. For continuous and categorical factors, the Wilcoxon rank-sum test and the χ² test (or Fisher exact test when necessary) were used to evaluate differences between the 2 groups. The Kaplan-Meier method was used to estimate the distributions of survival outcomes. Comparisons in survival rates between the treatment groups were assessed by the stratified log-rank test. Hazard ratios and 95% CIs were obtained using the stratified Cox proportional hazards model. The Cox model was also used to control intergroup confounding prognostic variables. In addition, we performed a test for the interaction between treatment and clinicopathological factors. The stratification factors at randomization were used in stratified analyses unless otherwise stated. All analyses were conducted using the R programming language and environment, version 3.5.0 (R Project for Statistical Computing) and STATA statistical software, version 16.0 (StataCorp LLC).

Results
Between July 1, 2011, and April 30, 2016, 672 women with TNBC were screened at 9 cancer centers and hospitals in China, and 647 patients were enrolled and randomly assigned to 2 treatment groups: 322 in the CEF-T group and 325 in the PCb group (Figure 1). Baseline characteristics were well balanced between the groups (Table 1). The median age was 51 years (interquartile range, 44-57 years) at the time of study entry. Most enrolled patients had early-stage TNBC (74% were node-negative; median number of positive nodes, 2 [interquartile range, 1-4]). Chemotherapy was completed by 305 patients (94.7%) in the CEF-T group and by 302 patients (92.9%) in the
PCb group. Dose reductions were needed for 30 patients (9.3%) in the CEF-T group and 28 patients (8.6%) in the PCb group.

At a median follow-up of 62 months, 104 of 647 randomized patients (16.1%) experienced DFS events, as summarized in Table 2. The Kaplan-Meier curves for DFS are depicted in Figure 2A. The absolute benefit of the 5-year DFS rate was 6.4% for the PCb group, which was greater than that of the CEF-T group (86.5% vs 80.3%), with a statistically significant difference (42 events among 325 patients in the PCb group vs 62 events among 322 patients in the CEF-T group; HR, 0.65; 95% CI, 0.44-0.96; stratified log-rank test P = .03).

The Kaplan-Meier curve for OS is shown in Figure 2B, and the Kaplan-Meier curves for RFS and DDFT are in eFigure 1 in Supplement 2. Although there was no significant difference in 5-year OS between the 2 treatment groups (23 events among 325 patients in the PCb group vs 31 events among 322 patients in the CEF-T group; OS, 93.4% vs 89.8%; HR, 0.71; 95% CI, 0.42-1.22; P = .22), adequate efficacy assessment of PCb on OS will require long-term follow-up and more events. RFS at 5 years was higher in the PCb group than in the CEF-T group (26 events among 325 patients vs 46 events among 322 patients; RFS, 91.2% vs 84.4%; HR, 0.54; 95% CI, 0.34-0.88; P = .01), and similar results were observed for DDFT (22 events among 325 patients vs 36 events among 322 patients; DDFT, 92.6% vs 87.9%; HR, 0.59; 95% CI, 0.35-0.999; P = .05).

According to the exploratory subgroup analyses of DFS, patients with younger age or high-grade tumor appeared to have benefited more from PCb (Figure 3). We focused particularly on the subgroup analysis of 538 patients with known gBRCA1/2 status. The HR for the effect of PCb vs CEF-T on DFS according to gBRCA1/2 status was 0.44 (95% CI, 0.15-0.81; P = .14) for patients with this variant and 0.68 (95% CI, 0.43-1.08; P = .10) for those without this variant, with an interaction P value of 0.37, indicating that this difference could be attributed to chance given the small number of participants with BRCA1/2 variants (n = 66). The effects of the interaction of BRCA1/2 status and chemotherapy regimens on DFS are illustrated in eFigure 2A in Supplement 2.

We further assessed HRD status by testing germline variants in HRR-related genes. First, we analyzed the spectrum of germline variants in the Chinese TNBC population and found 22 genes with germline variants. Among them, 12 genes are related to HRD; the variant rate was 20.2% in TNBC cases (eTable 2 in Supplement 2). Next, we assessed the variants of 12 HRD genes in 472 non-BRCA1/2 carriers of the trial population. Among them, 17 patients were not tested because of the unavailability of DNA samples, and 54 showed deleterious variants in HRR genes. Overall, there were 120 carriers of deleterious HRR variants (66 with BRCA1/2 variants and 54 with non-BRCA1/2 variants) and 401
Table 2. First Disease-Free Survival Event by Treatment

<table>
<thead>
<tr>
<th>Disease-free survival event</th>
<th>CEF-T (n = 322)</th>
<th>PCb (n = 325)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local and regional recurrence</td>
<td>10 (3.1)</td>
<td>4 (1.2)</td>
</tr>
<tr>
<td>Contralateral breast tumor</td>
<td>8 (2.5)</td>
<td>9 (2.8)</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>33 (10.2)</td>
<td>20 (6.2)</td>
</tr>
<tr>
<td>Second primary malignancy</td>
<td>8 (2.5)</td>
<td>7 (2.2)</td>
</tr>
<tr>
<td>Death</td>
<td>3 (0.9)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Total</td>
<td>62 (19.3)</td>
<td>42 (12.9)</td>
</tr>
</tbody>
</table>

Abbreviations: CEF-T, fluorouracil, epirubicin, and cyclophosphamide followed by docetaxel; PCb, paclitaxel and carboplatin.

noncarriers. For the 54 carriers with HRR other than a BRCA1/2 variant, the DFS HR for PCb vs CEF-T was 0.12 (95% CI, 0.02-1.28; \( P = .08 \)) owing to a small sample size and rare events. In the combination analysis, HRR variant carriers displayed a significantly better DFS with the PCb regimen compared with the CEF-T regimen (88.4% vs 76.3%; HR, 0.39; 95% CI, 0.15-0.99; \( P = .04 \)). In contrast, the DFS difference between PCb and CEF-T was insignificant among noncarriers (85.9% vs 81.2%; HR, 0.70; 95% CI, 0.42-1.14; \( P = .15 \)), with a borderline \( P \) value of 0.08 for interaction. The Kaplan-Meier plots of interactions between HRR status and chemotherapy regimens on DFS are shown in eFigure 2B in Supplement 2.

Treatment-related grades 3 to 4 adverse events are listed in eTable 3 in Supplement 2. Both treatments were generally well tolerated, and treatment-related deaths or life-threatening events were not observed. As expected, hematologic toxicity was predominant with both regimens. Grade 3 or 4 febrile neutropenia occurred more often in patients allocated to the PCb group, whereas peripheral neuropathy, anemia, and thrombocytopenia were more common in the PCb group.

Discussion

The PATTERN trial was designed to determine whether PCb is superior to CEF-T in the adjuvant settings of TNBC, and the results indicated the greater benefit of the platinum-based regimen compared with the standard anthracycline/taxane regimen. To our knowledge, this is the first randomized trial comparing adjuvant PCb with CEF-T in patients with TNBC.

Triple-negative breast cancer is often associated with a dysfunctional BRCA pathway with deficient mismatch repair and genomic instability; correspondingly, platinum-containing regimens have been proven to be effective in gBRCA1/2 variant carriers. A meta-analysis that included the pivotal trials GeparSixto and CALGB 40603 confirmed the activity of adding platinum for treatment of patients with the gBRCA variant compared with non-BRCA1/2 carriers in the neoadjuvant setting. Moreover, in the neoadjuvant GeparSixto study, adding carboplatin resulted in significantly better DFS in patients with TNBC. In the adjuvant setting, however, such evidence is lacking. We demonstrated for the first time to our knowledge that the carboplatin-containing regimen is superior to the anthracycline/taxane regimen for early-stage TNBC.

The survival results from GeparSixto are consistent with our findings. It is worth noting that the absolute DFS benefit in GeparSixto of 10% was higher than that in our study (6.2%). The reason might be that our participants had a lower tumor burden, namely, 54% were pT1 tumors and 74% were node-negative tumors, and correspondingly the degree of benefit was relatively small. The strength of our study is that DFS was designed as the primary end point, with sufficient sample size and adequate statistical power.

Although the observed differences in DFS were significant in the entire population with unselected TNBC, a clinical profile of patients sensitive to the PCb regimen might show similar characteristics, such as younger age and higher tumor grade, according to the exploratory subgroup analyses. The exploratory analysis also indicated a strong association with treatment benefit from a carboplatin-containing regimen in patients with TNBC with defects in homologous recombination. Initially, we hypothesized that the BRCA1/2 variant is an indicator for carboplatin treatment, as BRCA1/2 is a clinically validated biomarker that is associated with a greater response in patients treated with carboplatin than in those treated with
other therapeutic drugs, but we failed to prove this hypothesis in our study. Potential explanations are as follows. First, the sample size of BRCA1/2 variant carriers was small, and the statistics for difference comparison were underpowered. Second, even among gBRCA1/2-negative patients, some might be sensitive to carboplatin because of HRD due to HRR variation rather than to BRCA1/2 variants, and thus non-BRCA1/2 HRR variant carriers would dilute and affect the results. Therefore, we further stratified patients according to HRR variant and demonstrated that patients carrying HRR variants might benefit more from PCb than from CEF-T. However, our findings from exploratory subgroup analysis are hypothesis-generating, and further prospective randomized trials are required to confirm our results.

Limitations
There are some limitations in our study. First, CEF-T, a preferred regimen when the trial was first designed, is no longer a primary recommendation in the National Comprehensive Cancer Network guidelines. According to updated data from ECOG 1199,21 epirubicin and cyclophosphamide followed by weekly paclitaxel (EC-wP) might be the optimal choice for TNBC. However, we lack a head-to-head comparison between CEF-T and EC-wP, and we must point out that our trial predominantly enrolled patients with early-stage TNBC (74% were node-negative, and the median number of positive nodes was 2 [interquartile range, 1-4]). In such patients with a lower tumor burden, whether an EC-wP regimen is the optimal choice remains inconclusive. Second, the current study was limited to Chinese patients, and validation trials for ethnic extrapolation are warranted. Third, the current analysis regarding HRR variation or BRCA1/2 subgroups was underpowered because of the relatively small sample size, and some germline variants might not have been included in the set of 12 HRR-related genes. Our findings suggest that deleterious variants in BRCA1/2 occur in 12% of TNBC cases and that variants in other non-BRCA1/2 genes occur in approximately 8% to 10% of cases. A standard approach for genetic testing in TNBC is needed for risk assessment as well as treatment guidance in the era of precision medicine. Finally, genetic and epigenetic inactivation of homologous recombination might also lead to HRD, and the development of different surrogates of HRD will be key to expanding the therapeutic utility of HRD-targeting agents across a broad spectrum of tumor types.

Conclusions
In conclusion, this randomized clinical trial found that compared with the conventional anthracycline and docetaxel regimen, the paclitaxel-plus-carboplatin regimen may be an alternative adjuvant chemotherapy strategy for patients with operable TNBC. However, the results should be considered with caution, as high-level evidence is still lacking to make platinum-based chemotherapy the new standard of care. Moreover, identifying predictive biomarkers is imperative for the selection of appropriate patients for platinum-based regimens in the adjuvant setting.
Effect of Adjuvant Paclitaxel and Carboplatin on Survival in Women With TNBC


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Author Contributions: Drs Yu and Shao had full access to all of the data in the study and take full responsibility for the accuracy of the data and the accuracy of the data analysis. Drs Yu, Ye, M. He, and Fan contributed equally to this work. Concept and design: Yu, Li, Di, Zeng, P.-Q. He, K.-J. Wu, Hou, C. Wang, Zhejiang, Shao. Acquisition, analysis, or interpretation of data: Yu, M. He, Fan, Ma, Mo, J. Wu, J. Wang, Song, Lin, Toss, Ricci, Shen. Drafting of the manuscript: Yu, M. He, Fan, C. Wang, Zhejiang, Zhejiang. Critical revision of the manuscript for important intellectual content: Yu, Ma, Mo, J. Wu, Di, Zeng, P.-Q. He, K.-J. Wu, Hou, J. Wang, Lin, Toss, Ricci, Shao. Statistical analysis: Yu, M. He, Fan, Ma, Mo, C. Wang, Zhejiang. Obtained funding: Yu, Zhejiang. Administrative, technical, or material support: Yu, Fan, J. Wu, Liu, Di, Zeng, P.-Q. He, K.-J. Wu, Hou, J. Wang, Zhejiang, Song. Supervision: Yu, Fan, J. Wu, Di, J. Wang, Toss, Ricci, Shao.

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