Original Article

Efficacy and safety analysis of a docetaxel-plus-trastuzumab regimen in patients with early-stage HER2-positive breast cancer: a retrospective single-arm study

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Background: A regimen of weekly paclitaxel and trastuzumab (WPH) is the standard treatment for patients with early-stage human epidermal growth factor receptor 2 (HER2)-positive breast cancer but has certain limitations. Weekly hospital visits are burdensome for patients and increase healthcare resource use. Docetaxel is currently used in several chemotherapy regimens for HER2-positive breast cancer, such as four cycles of docetaxel and cyclophosphamide plus trastuzumab (TC4H) or THP (paclitaxel, trastuzumab plus pertuzumab), and its safety and efficacy have been well established. Therefore, for patients who cannot visit the hospital for treatment every week, we have implemented a 3-week docetaxel regimen to replace the weekly paclitaxel schedule for these early-stage HER2-positive breast cancer patients. Our retrospective analysis conducted from 2014 to 2019 assessed the efficacy and safety of a docetaxel-and-trastuzumab (TH) regimen in patients with early-stage HER2-positive breast cancer, with the aim of establishing a more accessible and efficient treatment approach.

Methods: This is a single-arm retrospective study analysis of TH therapy for early-stage HER2-positive breast cancer conducted in The First Affiliated Hospital, School of Medicine, Zhejiang University between January 2015 and December 2019. Patients included were lymph node-negative, aged 50 years or older, and had received TH regimen after surgery, with comprehensive follow-up data available. Patients received six cycles of docetaxel (100 mg/m^2) every 3 weeks and trastuzumab (8 mg/kg in cycle 1, followed by 6 mg/kg) every 3 weeks for 1 year. Disease-free survival (DFS), overall survival (OS), and adverse events were evaluated as prognosis outcomes of the TH regimen.

Results: A total of 144 breast cancer patients were enrolled. The median age of the patients was 61.5 years and 80 patients (55.6%) had hormone receptor-positive disease. In the entire study population, 34.7% of

patients had tumors 1 cm or smaller. The median follow-up time of the included patients was 7.1 years, the 5-year DFS rate was 96.5%, and the OS rate was 98.6%. Among the five patients who experienced invasive disease events or death, three had local or regional recurrences. Three patients (2.1%) experienced at least one episode of grade 3 neuropathy, and five patients had a significant decrease in ejection fraction, leading to a 3.5% interruption of trastuzumab treatment. None of the patients experienced grade 3 or 4 hypersensitivity reactions to the study treatment

Conclusions: The TH regimen demonstrated promise as a novel treatment alternative for patients with early-stage HER2-positive breast cancer. It offers a similar degree of efficacy and safety to those of the conventional WPH regimen while requiring fewer hospital visits, which could result in reduced healthcare costs and enhanced patient convenience.

Keywords: Human epidermal growth factor receptor 2-positive breast cancer (HER2-positive breast cancer); docetaxel-and-trastuzumab regimen (TH regimen); disease-free survival (DFS)

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Introduction

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer, marked by an overexpression of HER2, accounts for approximately 15–20% of all breast cancer cases (1,2). This type of cancer is linked to more aggressive clinical behavior and poorer prognosis (3). Pivotal clinical trials have established two standard treatment regimens for HER2-positive breast cancer: the AC-TH (doxorubicin and cyclophosphamide follow paclitaxel and trastuzumab) regimen, which includes doxorubicin, cyclophosphamide, paclitaxel, and trastuzumab, and the non-anthracycline-based TCH (paclitaxel, carboplatin plus trastuzumab) regimen, which consists of docetaxel, carboplatin, and trastuzumab (4-6). However, these trials focused largely on patients with stage II or stage III HER2-positive breast cancers. A study has also explored the efficacy and safety of neoadjuvant pertuzumab plus trastuzumab in combination with chemotherapy regimens in Chinese patients with HER2-positive early breast cancer (7). Additionally, the impact of different chemotherapy backbones, such as those containing anthracyclines versus those that are anthracycline-free, on the efficacy and cardiotoxicity of dual HER2 blockade has been investigated (8). These findings provide valuable insights into the treatment strategies for HER2-positive breast cancer across various stages.

The weekly paclitaxel and trastuzumab (WPH) regimen has emerged as a standard treatment modality for early-stage HER2-positive breast cancer, being particularly effective in low-risk patients with tumors smaller than 2 cm in size and negative lymph node status (9). This regimen can offer favorable outcomes by maximizing treatment efficacy while reducing the toxic effects commonly associated with anthracyclines. However, the requirement for weekly hospital visits presents challenges, placing a significant burden on patients and resulting in higher healthcare resource utilization. Therefore, while WPH has proven beneficial, the treatment landscape calls for alternative regimens that offer similar efficacy with reduced logistical

Highlight box

Key findings

- A docetaxel-and-trastuzumab (TH) regimen in patients with early-stage human epidermal growth factor receptor 2 (HER2)-positive breast cancer yielded a 5-year disease-free survival rate of 96.5% and an overall survival rate of 98.6%, showing similar efficacy to the standard regimen of weekly paclitaxel and trastuzumab (WPH).

What is known and what is new?

- The WPH regimen is a standard treatment for early-stage HER2-positive breast cancer but requires frequent hospital visits, incurring logistical and economic difficulties.
- The TH regimen offers a promising alternative with fewer hospital visits, potentially reducing healthcare costs and improving patient convenience without compromising efficacy.

What is the implication, and what should change now?

- The TH regimen's cardiac safety and reduced logistical burden may offer a shift toward more patient-centric treatment. Future randomized controlled trials conducted across multiple centers are needed to validate these findings and guide clinical practice.

and economic challenges for patients.

Within the therapeutic landscape for early-stage HER2-positive breast cancer, the US Oncology single-arm trial is noteworthy for its investigation of a combination therapy consisting of four cycles of docetaxel and cyclophosphamide plus trastuzumab (TC4H) (10). This trial has contributed valuable insights into the potential benefits of incorporating docetaxel into treatment regimens for this patient population. Furthermore, the Neosphere trial in the neoadjuvant setting and the CLEOPATRA study in the metastatic setting both employed treatment regimens that combined docetaxel with either single or dual targeted therapies (11,12). These studies have robustly demonstrated the safety and efficacy of docetaxel in various treatment contexts for HER2-positive breast cancer, reinforcing its role as a key component in both early and advanced stages of the disease.

In light of these concerns, our retrospective analysis was conducted to evaluate the prognosis and safety of a regimen combining docetaxel-and-trastuzumab (TH) for patients with early-stage HER2-positive breast cancer treated at the Department of Breast Surgery, The First Affiliated Hospital, School of Medicine, Zhejiang University (Hangzhou, China) from 2014 to 2019. This investigation aimed to identify a more convenient, cost-effective, and efficient treatment strategy for managing HER2-positive early breast cancer, with the goal of enhancing patient care and optimizing resource use. We present this article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-2024-549/rc).

Methods

Study population

Between January 2015 and December 2019, we selected all patients who received the TH regimen after surgery with comprehensive follow-up records at our center. After applying the inclusion and exclusion criteria, we ultimately enrolled 144 women aged 50 years or older with node-negative, HER2-positive breast cancer. These patients received a regimen of docetaxel (100 mg/m^2) every 3 weeks for 6 cycles and trastuzumab (8 mg/kg in cycle 1, followed by 6 mg/kg) every 3 weeks for 1 year at the Department of Breast Surgery, The First Affiliated Hospital, School of Medicine, Zhejiang University (Hangzhou, China) (13). We retrospectively gathered patient demographic information and clinical data from follow-up records and a prospectively maintained electronic database. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Clinical Research Ethics Committee of The First Affiliated Hospital of Zhejiang University (No. IIT20240090B-R1). As this study did not involve patient intervention, the ethics committee waived the requirement for informed consent. All patient data were kept confidential.

Eligibility criteria

The study inclusion criteria consisted of (I) a pathological diagnosis of breast adenocarcinoma, characterized by a HER2 protein expression of 3+ on immunohistochemical staining or *HER2* gene amplification verified via fluorescence in situ hybridization (ratio of HER2 to chromosome 17 centromere of ≥2.0); (II) invasive tumors measuring no more than 3 cm in the greatest dimension with no minimum size limit; (III) histologically confirmed node-negative status; (IV) age ≥50 years old; (V) adequate renal, liver, and bone marrow function; (VI) an Eastern Cooperative Oncology Group (ECOG) performance status <2; and (VI) a left ventricular ejection fraction (LVEF) of 55% or higher along and no impairment in ventricular movement.

Meanwhile, the exclusion criteria were as follows: (I) any previous malignancy aside from nonmelanoma skin cancer or curatively treated carcinoma *in situ* of the cervix; (II) significant psychiatric disorders; and (III) trastuzumab treatment administered for less than 1 year.

Treatments

During the treatment period, patients received weekly evaluations of blood counts and chemistry profiles, with additional evaluations being administered as needed. Cardiac ultrasounds were performed prior to the first chemotherapy cycle and subsequently checked each cycle or when patients exhibited heart-related symptoms, continuing every 3 months for at least 1 year after trastuzumab treatment. For patients with hormone receptor positivity, standard endocrine therapy was administered. Adverse events were documented both at baseline and after each chemotherapy cycle. Toxicity was graded according to the standards set by the World Health Organization and the American Society of Clinical Oncology. Patients were followed up at 3-month intervals for up to 5 years after

Table 1 Baseline characteristics of the patients

Characteristic	Patients (N=144), n (%)
Age group, years	
50–59	57 (39.6)
60–69	63 (43.8)
≥70	24 (16.7)
Primary tumor size	
T1a: >0.1 to ≤0.5 cm	22 (15.3)
T1b: >0.5 to ≤1.0 cm	28 (19.4)
T1c: >1.0 to ≤2.0 cm	54 (37.5)
T2: >2.0 to ≤3.0 cm	40 (27.8)
Histologic grade	
I: well-differentiated	12 (8.3)
II: moderately differentiated	61 (42.4)
III: poorly differentiated	71 (49.3)
Estrogen-receptor status	
Positive	80 (55.6)
Negative	64 (44.4)
Progesterone-receptor status	
Positive	43 (29.9)
Negative	101 (70.1)
Hormone-receptor status	
Positive	80 (55.6)
Negative	64 (44.4)
Surgical approach	
Conservative surgery	30 (20.8)
Mastectomy	114 (79.2)

surgery. At each follow-up visit, examinations, laboratory tests, and ultrasounds (breast, abdominal, and gynecological) were conducted alongside assessments of health status. Pulmonary computed tomography, bone scans, and head magnetic resonance imaging were performed annually or as clinically indicated.

Disease-free survival (DFS) was defined as the interval between the date of surgical operation and the date when disease progression or death occurred (14). Patients who remained alive without any disease progression at the study's conclusion were censored based on their final follow-up date. All patients underwent evaluation of histological type, tumor grade, and the status of estrogen receptor (ER), progesterone receptor (PR), HER2, and KI-67 using immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH). ER or PR positivity was considered present if more than 1% of cancer cells exhibited positive staining via IHC.

Statistical analysis

Data are presented as counts (n) and percentages (%). We used the Kaplan-Meier method for survival analysis. Statistical analyses were completed with SPSS 23 (IBM Corp., Armonk, NY, USA). Kaplan-Meier survival curves were generated and analyzed via GraphPad Prism version 8.0 (GraphPad Software Inc., La Jolla, CA, USA).

Results

Patient demographics

Between January 2015 and December 2019, 144 patients were enrolled in the study. All patients were evaluated for toxicity. Patient and baseline tumor characteristics are shown in *Table 1*. The median age of the patients was 61.5 years (range, 50–73 years), and 80 patients (55.6%) had hormone receptor-positive disease. In the entire study population, 34.7% of patients had tumors 1 cm or smaller, including T1mic (≤0.1 cm), T1a (>0.1 to ≤0.5 cm), and T1b (>0.5 to ≤1.0 cm). An additional 37.5% had T1c tumors (>1.0 to ≤2.0 cm), and 27.8% had tumors between 2–3 cm in size, classified as T2 stage. Moreover, 30 (20.8%) patients underwent breast-conserving surgery. The median follow-up time was 7.1 years, and the maximum follow-up period was 9.7 years.

Efficacy

Five patients experienced invasive disease events or death (*Table 2*). This included three patients with local or regional recurrence and two patients who died from unrelated causes. One patient was diagnosed with contralateral ductal carcinoma *in situ* (not classified as an event of invasive disease recurrence) and was continued on follow-up for invasive disease recurrence. The 5-year DFS and overall survival (OS) rates were 96.5% and 98.6%, respectively, as shown in *Figure 1A,1B*. The survival curves were stratified by tumor size (≤1 *vs.* >1 cm) and hormone receptor status (positive *vs.* negative). These findings are presented in *Figure 1C,1D*, respectively.

Table 2 Events observed for the primary endpoint of disease-free survival

Event	Patients (N=144), n (%)	Time to event, months
Any recurrence or death	5 (3.5)	–
Local or regional recurrence	3 (2.1)	21, 47, 50
New contralateral primary breast cancer	1 (0.7)	24
Ductal carcinoma *in situ*	1 (0.7)	24
Distant recurrence	0	
Death		
Breast-cancer-related	0	
Not breast-cancer-related	2 (1.4)	22, 66

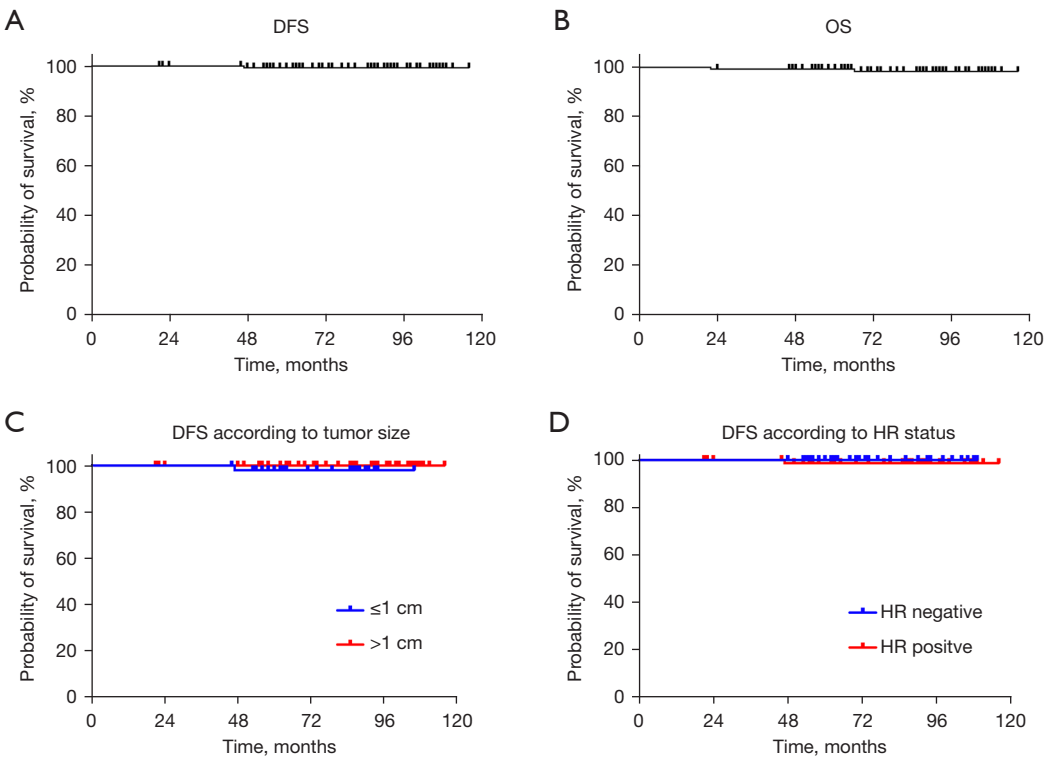

Figure 1 Probabilities of DFS and OS. (A) The probability of DFS in the population; (B) the probability of OS in the population; (C) the probability of DFS according to tumor size; (D) the probability of DFS according to hormone receptor (estrogen receptor or progesterone receptor) status. The tick marks represent the time of censoring for patients who were recurrence free. DFS, disease-free survival; OS, overall survival; HR, hormone receptor.

Adverse events

During the combination therapy, three patients (2.1%) experienced at least one episode of grade 3 neuropathy, but no grade 4 neurotoxicity was reported. In addition, one patient (0.7%) developed grade 3 edema, which was managed with diuretic treatment and did not result in chemotherapy discontinuation. Five patients experienced a significant decrease in ejection fraction, leading to a 3.5% interruption of trastuzumab treatment. All patients enrolled in this study completed 1 year of trastuzumab therapy,

Table 3 Most common adverse events occurring during protocol therapy

Event	Maximum grade, n (%)			Total, n (%)
	Grade 2	Grade 3	Grade 4	
Neuropathy	10 (6.9)	3 (2.1)	0	13 (9.0)
Neutropenia	11 (7.6)	2 (1.4)	0	13 (9.0)
Leukopenia	8 (5.6)	1 (0.7)	0	9 (6.3)
Allergic reaction	3 (2.1)	0	0	3 (2.1)
Anemia	5 (3.5)	0	0	5 (3.5)
Edema	5 (3.5)	1 (0.7)	0	6 (4.2)

therefore; there was insufficient assessment of severe cardiac events that could lead to treatment cessation. No patients experienced grade 3 or 4 hypersensitivity reactions to the study treatment, and alopecia occurred in the majority of patients, but the data regarding its incidence were not collected.

According to the National Comprehensive Cancer Network (NCCN) guidelines (15), treatments that include docetaxel are associated with a high risk of febrile neutropenia (FN), with rates over 20%. Consequently, primary prophylaxis with long-acting granulocyte colony-stimulating factors (G-CSFs) was administered during chemotherapy to prevent severe FN. This preventive strategy was effective, as there were no instances of severe FN observed during the chemotherapy period. The incidence of grade 3 neutropenia was observed in approximately 1.4% of patients, typically within 10 days of chemotherapy. The majority of these patients recovered to have normal neutrophil counts without the need for additional short-acting G-CSFs. There were no occurrences of grade 4 neutropenia or neutropenic fever. *Table 3* summarizes the other specific toxicities reported during the treatment period.

Discussion

In the management of early-stage HER2-positive breast cancer, the WPH regimen, which includes weekly paclitaxel and trastuzumab, has emerged as a preferred treatment choice, particularly for patients with small, node-negative tumors (9). The regimen's efficacy is supported by high DFS rates, as evidenced by the pivotal trial by Tolaney *et al.*, which reported a 3-year invasive DFS rate of 98.7%. The WPH regimen's lower toxicity profile compared to traditional adjuvant therapies that incorporate anthracycline chemotherapy drugs offers a significant advantage, particularly for patients with pre-existing cardiac conditions or those at an elevated risk of cardiac toxicity. Consequently, the WPH regimen is often recommended for patients with tumors ≤3 cm in diameter and without lymph node involvement.

Within the spectrum of therapeutic options for early-stage HER2-positive breast cancer, the US Oncology single-arm trial deserves attention for its exploration of a TC4H (10). With a 2-year invasive DFS rate of 97.8% and a 2-year OS rate of 99.2%, it exhibits comparable outcomes to our TH regimen, despite variations in dosing and treatment duration. Furthermore, it is noteworthy that in the US Oncology trial, patients with tumors larger than 2 cm constituted a significant portion, accounting for 32.9% of the study population. Also, in patients with TOP2A amplification may derive significant therapeutic benefits from treatment regimens that exclude anthracyclines and incorporate anti-HER2 therapy.

In the context of treatment regimen applicability, it is important to note that in the WPH regimen, only 8.9% of patients had tumors with a diameter of 2–3 cm, suggesting that WPH is primarily utilized for stage 1 HER2-positive patients in the U.S. Notably, despite 27.8% of patients in our trial having tumors larger than 2 cm, the low recurrence rate observed is comparable to that of the WPH regimen, which is a promising finding. Consequently, both nationally and internationally guidelines have designated anti-HER2 targeted therapy combined with anthracycline-free chemotherapy as the first-line adjuvant treatment for HER2-positive early-stage breast cancer. The efficacy of anthracycline-based drugs in the treatment of early-stage HER2-positive breast cancer seems to be becoming increasingly limited.

Furthermore, the CompassHER2 study aims to optimize subsequent adjuvant treatment plans based on the efficacy of neoadjuvant therapy, enabling the identification of patients who may avoid chemotherapy (16). The trial also compares the efficacy of adjuvant trastuzumab emtansine (T-DM1) combined with tucatinib versus T-DM1 and placebo in high-risk HER2-positive residual disease patients following a predefined course of neoadjuvant chemotherapy. The outcomes of this trial are anticipated to provide further guidance on treatment strategies for HER2-positive breast cancer.

Addressing the challenges posed by the current healthcare environment, characterized by a scarcity of

hospital beds and constrained medical resources, our center initiated the TH regimen for patients with early-stage HER2-positive breast cancer in 2014. Our retrospective analysis of 144 patients treated with the TH regimen revealed a 5-year DFS rate of 96.5% and an OS rate of 98.6%. These outcomes are comparable to those reported for the WPH regimen and TC4H regimen, suggesting that the TH regimen's efficacy and safety profile are not significantly different. Notably, no patients in our study experienced grade 3 or higher cardiac dysfunction, further supporting the cardiac safety of the TH regimen.

The TH regimen's economic benefits are substantial, as it minimizes the need for frequent hospital visits, thereby reducing healthcare costs and promoting more efficient resource utilization. This is especially pertinent in regions with limited medical facilities. Moreover, by reducing the emotional burden associated with regular hospital visits, the TH regimen enhances patient satisfaction and treatment adherence, which is crucial for treatment efficacy (17). The regimen also alleviates logistical concerns surrounding therapy, potentially improving patients' mental health.

In the domain of premedication, the TH regimen's reduced dependence on dexamethasone is a notable advantage. Dexamethasone is commonly used to prevent allergic reactions related to paclitaxel administration (18-20). However, it is not without its drawbacks, as it has been linked to a spectrum of adverse effects, including insomnia, weight gain, and immunosuppression (21). Moreover, emerging evidence suggests at a potential correlation between dexamethasone use and an elevated risk of breast cancer recurrence, necessitating further exploration (22). Many studies have focused on improving dexamethasone use in chemotherapy protocols that include paclitaxel, but the results have not met expectations (23,24). Recent research has revealed the effect of dexamethasone on the spread of breast cancer and has demonstrated that high doses of dexamethasone affect the tumor microenvironment and cellular metabolic pathways, suggesting its possible impact on oncological treatment (25). Furthermore, a study has implicated dexamethasone in the facilitation of pulmonary metastasis in breast cancer through the PI3K-SGK1-CTGF signaling axis, highlighting its role in tumor propagation (26). Adjusting the frequency and dosage of dexamethasone in the TH regimen is likely to lead to better long-term health outcomes. This strategy is especially advantageous for patient cohorts with pre-existing conditions such as diabetes, as it attenuates the risk of corticosteroid-induced complications.

Despite the promising results of this study, several limitations must be acknowledged. The small sample size and single-center retrospective design may limit the generalizability of our findings, with the potential selection bias impacting outcomes. Future research should prioritize multicenter trials to include a larger and more diverse patient population. Additionally, conducting prospective randomized controlled trials (RCTs) will be essential to validating the efficacy and safety of the TH regimen in comparison to standard treatments such as WPH. Such efforts will contribute to a more robust evidence base, guiding clinical practice in the management of early-stage HER2-positive breast cancer.

Conclusions

The TH regimen is a feasible alternative to the WPH regimen for early-stage HER2-positive breast cancer, providing similar efficacy and safety, reducing hospital visits, lowering healthcare costs, and enhancing patient convenience. Our study's 5-year DFS rate of 96.5% and OS rate of 98.6% are comparable to those of the WPH regimen, demonstrating similar effectiveness. The lack of grade 3 or higher cardiac dysfunction in our patients supports the cardiac safety of the TH regimen. However, the study's limitations, including its small sample size and single-center design, indicate the need for larger, multicenter trials and RCTs to confirm the results and better guide clinical practice.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-2024-549/rc

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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 Clinical Research Ethics Committee of The First Affiliated Hospital of Zhejiang University (No. IIT20240090B-R1). As this study did not involve patient intervention, the ethics committee waived the requirement for informed consent. All patient data were kept confidential.

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