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Investigation of response of patients with non-small cell lung cancer to docetaxel (plus ramucirumab) therapy in second-line treatment

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Abstract

Background: Several options for second-line therapy are available for patients with advanced non-small cell lung cancer (NSCLC); however, the optimal therapy remains unclear. Docetaxel (DTX) monotherapy and DTX plus ramucirumab (RAM) are the recommended second-line treatment options. However, the efficacy of these treatments remains unsatisfactory. The aim of this study was to identify the clinical characteristics of patients with NSCLC who respond to DTX or DTX + RAM and factors that predict response.

Methods: Patients with NSCLC treated with DTX or DTX + RAM after second-line therapy were retrospectively analyzed. Patients were compared with those who responded or did not respond to the post-treatment efficacy assessment.

Results: Of 53 patients, 12 (22.6%) had lung cancer that responded to DTX or DTX + RAM therapy (response group). Multivariate analysis identified the absence of immune checkpoint inhibitors (ICIs) in the immediate prior therapy and a reduced dose of DTX after the second cycle as significant independent risk factors predicting nonresponse to DTX and DTX + RAM therapy in patients with NSCLC. The overall survival was significantly longer in the response group compared to the nonresponse group ($p = 0.016$).

Conclusions: Our results suggest that DTX and DTX + RAM therapies immediately after treatment with ICI-containing regimens as well as continuation of DTX without dose reduction after the second cycle may increase the response rate and prolong survival in patients with NSCLC.

KEYWORDS
docetaxel, immune checkpoint inhibitor, NSCLC, ramucirumab, second-line therapy

INTRODUCTION

Although the combination of chemotherapy and immune checkpoint inhibitors (ICIs) is becoming the standard regimen for first-line treatment of advanced non-small cell lung cancer (NSCLC), most patients progress sooner or later and require second-line therapy.

Docetaxel (DTX) monotherapy and DTX plus ramucirumab (RAM) are the standard treatment regimens for advanced NSCLC after second-line therapy.[1–3]

However, the response rate to DTX monotherapy is <20%, and a favorable response is difficult to determine.[4,5]

The addition of RAM to DTX has been shown to improve response rates compared with DTX monotherapy. However, the response rate remains low (<30%). Furthermore, DTX + RAM is associated with increased toxicity, including neutropenia, and its indications are limited to patients with a good performance status (PS).[3,6]

In addition, the incidence of febrile neutropenia (FN) with DTX + RAM has been reported to be >30% in a study

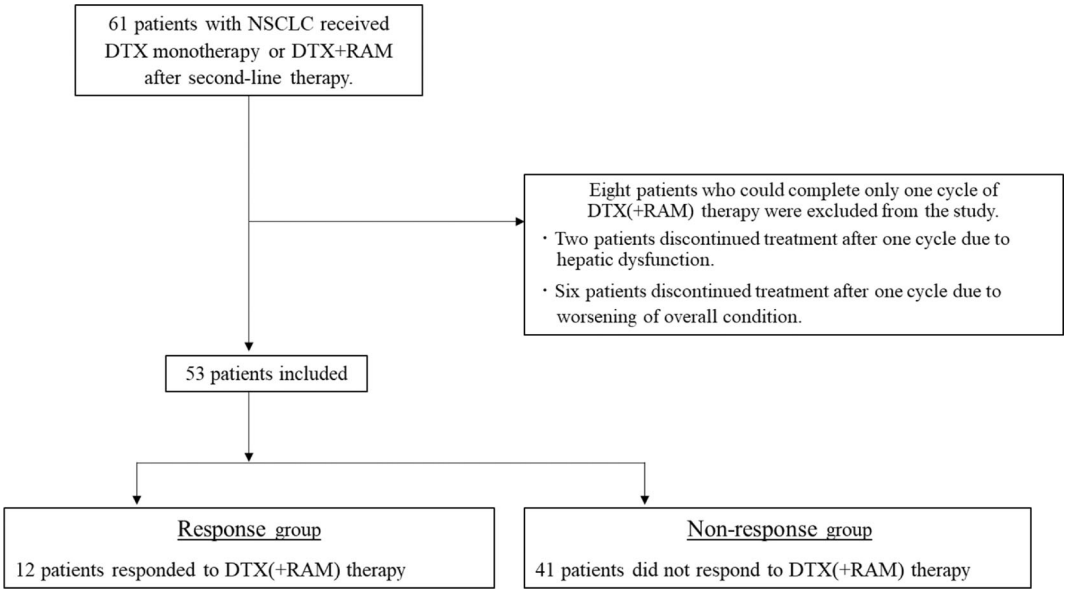

FIGURE 1 Study flow chart. In this study, 61 patients with non-small cell lung cancer (NSCLC) were initially included. Of these, two patients who discontinued DTX (+RAM) therapy after one cycle due to the development of liver dysfunction and six patients who discontinued DTX (+RAM) therapy after one cycle due to deterioration of their general condition were excluded. Finally, 53 patients were included in the study.

on Japanese patients,[7] and the risk of FN is clearly higher with DTX + RAM than with DTX monotherapy, which is a problem in clinical practice.

Furthermore, promising clinical biomarkers for predicting the therapeutic efficacy of DTX and DTX + RAM are still unknown.[8]

Amongst the patients with NSCLC, identification of a group of patients who are expected to respond to DTX (+RAM) therapy after second-line therapy may help in the selection of a treatment plan and contribute to an improved prognosis.

Hence, the primary endpoint of this study was to identify factors that may predict the response to DTX(+RAM) therapy.

Therefore, the purpose of this study was to identify the clinical characteristics of patients with NSCLC who are expected to respond to DTX (+RAM) therapies and to identify factors that could predict response.

This study compared groups of patients with NSCLC who received DTX or DTX + RAM after second-line therapy and achieved a response to those who did not.

METHODS

Between August 2016 and December 2022, patients with advanced-stage (stages IIIB and IV, postoperative recurrence) NSCLC who were newly introduced to DTX monotherapy or DTX + RAM therapy after second-line treatment were retrospectively identified.

At the time of DTX (+RAM) therapy, data on age, sex, smoking history, PS, histological type of lung cancer, tumor proportion score (TPS), *EGFR* mutation, and stage were collected.

Responses were evaluated based on the response evaluation criteria in solid tumors (RECIST; version 1.1). Patients with complete (CR) and partial (PR) response were classified into the response group ($n = 12$), and those with stable (SD) or progressive (PD) disease were classified into the nonresponse group ($n = 41$); the clinical information of the two groups was compared.

Patients who could receive only one cycle of DTX (+RAM) therapy due to deterioration of their general condition or development of liver dysfunction after starting DTX (+RAM) therapy were excluded from the study because of the difficulty in assessing the response rate.

Of the 61 cases initially considered for enrollment, only 53 were included in the final analysis after applying the aforementioned exclusion criteria (Figure 1).

Statistical analysis

All analyses were performed using the statistical software SPSS 26.0 (SPSS Inc.). Two-sided p-values of <0.05 were considered statistically significant. All categorical variables were analyzed using the chi-square test, except for those with a predicted frequency of <5, which were analyzed using Fisher's exact probability test. t-tests without correspondence were used for mean comparisons of continuous variables between the two groups. Multivariate analysis was performed using logistic regression.

Survival curves were generated using the Kaplan–Meier method and the analysis was performed from the start of lung cancer treatment to death or treatment termination. Survival analysis was conducted in mid-July 2023.

TABLE 1 Comparison of patient characteristics between response and nonresponse groups.

Characteristics	PR group	Non-PR group	*p*-value
n (%)	12 (22.6%)	41 (77.4%)	
Age (years), mean (range)	68.6 (59–79)	66.3 (29–77)	0.333
Sex (male/female)	8/4	29/12	1.000
Smoking history (never/prior, current)	7/5	33/8	0.140
ECOG PS (0–1/2–4)	11/1	38/3	1.000
Tumor type (adenocarcinoma/nonadenocarcinoma)	9/3	28/13	0.476
EGFR mutation (yes/no)	3/9	7/34	0.677
PDL1 expression (22C3) (%), (0–49/50–100/untested)	2/8/2	10/26/5	0.819
Clinical stages (IV, postoperative recurrence/III)	10/2	38/3	0.315
Distant metastasis (yes/no)			
Brain metastasis	3/9	11/30	1.000
Liver metastasis	1/11	2/39	0.545
Number of cycles of DTX (+RAM) therapy, mean (range)[a]	8.17 (4–14)	4.34 (2–13)	0.001
Treatment setting for DTX (+RAM) (second-/third-line or later)	9/3	16/25	0.079
ICIs in the immediate prior regimen (yes/no)	9/3	16/25	0.079
History of ICI administration (yes/no)[b]	10/2	24/17	0.174
Duration from ICI administration (month)[c]	4.56 (0.5–25.2)	7.24 (0.8–22.4)	0.352
Full dose (yes/no)	8/4	21/20	0.512
Dose reduction (yes/no)[d]	6/6	22/19	0.213
RAM (yes/no)	5/7	21/20	0.560
PEG-G-CSF (yes/no)	8/4	20/21	0.337
G4 neutropenia/FN (yes/no)	6/6	19/22	0.823

Abbreviations: DTX, docetaxel; ECOG PS, Eastern Cooperative Oncology Group performance status; FN, febrile neutropenia; G4, grade 4; ICI, immune checkpoint inhibitor; PEG-G-CSF, primary prophylactic pegylated-granulocyte-colony stimulating factor; PR, partial response; RAM, ramucirumab.

[a]Based on unpaired *t*-test.

[b]History of ICI administration, history of ICIs administered, not limited to the immediately prior regimen.

[c]Duration from ICI administration, time from last ICI administration to start of DTX (+RAM) therapy.

[d]Dose reduction, dose reduction after the second cycle of DTX therapy.

The log-rank test was used to determine whether there was a difference in survival owing to the differences in the response rate to DTX (+RAM) therapy. Differences were considered statistically significant if the risk rate was <5%. This study was approved by the review board of the Kanazawa Medical School Hospital (approval no.: C013).

RESULTS

Patient background

In this study, 53 cases of NSCLC were identified. DTX monotherapy was administered to 26 patients: six PR (23.1%), five SD (19.2%), and 15 PD (65.2%) patients. The response and disease control rates were 23.1% and 47.8%, respectively.

A total of 27 patients received DTX + RAM therapy: six PR (22.2%), nine SD (33.3%), and 12 PD (44.4%) patients. The response and disease control rates were 22.2% and 55.6%, respectively.

A total of 12 patients (22.6%) achieved a response to the DTX (+RAM) therapy (response group). Forty-one patients (77.4%) were included in the nonresponse group. The patient characteristics have been compared in Table 1.

DTX (+RAM) therapy treatment duration was significantly longer for the response group (8.17 vs. 4.34 cycles; $p = 0.001$). No significant differences were noted between the two groups in cases of concomitant RAM.

Overall, 64.2% (34/53) of the patients received ICIs before (not necessarily immediately before) DTX (+RAM) therapy. A total of 47.2% (25/53) of patients were treated with ICI-containing regimens immediately prior to DTX (+RAM) administration.

The ICIs administered were anti-PD-1/L1 antibodies, such as nivolumab, pembrolizumab, atezolizumab, and durvalumab, and none of the patients received cytotoxic T lymphocyte antigen 4 inhibitors.

The number of patients whose regimens included ICIs before the introduction of DTX (+RAM) therapy did not differ significantly between the two groups.

The mean time between ICI administration in the previous regimen and DTX(+RAM) therapy was 4.56 and 7.24 months in the response and nonresponse groups, respectively, but no significant differences were observed between the two groups.

The incidences of grade 4 neutropenia/FN were 50.0% (6/6) and 46.3% (19/41) in the response and nonresponse groups, respectively. No significant differences were noted in the incidence of grade 4 neutropenia/FN between the two groups. No other significant differences were found in age, sex, smoking history, PS, tumor histology, *EGFR* mutation, stage, or timing of treatment between the two groups.

Univariate and multivariate analyses were performed to identify the risk factors for nonresponse to DTX(+RAM) therapy (Table 2).

The presence or absence of a response was the dependent variable in regression analysis, and the independent variables were presence of RAM administration, ICIs in the immediate prior regimen, and DTX dose reduction after the second cycle.[9]

In the univariate model, the only statistically significant risk factor predicting nonresponse was no administration of ICIs in the immediate prior regimen ($p = 0.047$; odds ratio [OR], 0.225; and 95% confidence interval [CI], 0.052–0982).

TABLE 2 Univariate and multivariate analyses of risk factors for nonresponse in NSCLC patients treated with DTX (+RAM) therapy.

	Univariable analysis		Multivariable analysis	
Characteristics	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Age (≥75 vs. <75 years)	0.694 (0.117–4.131)	0.689		
Sex (female vs. male)	0.828 (0.209–3.276)	0.787		
Smoking history (never/prior vs. current)	2.946 (0.739–11.751)	0.126		
ECOG PS (0–1 vs. 2–3)	1.152 (0.109–12.203)	0.907		
EGFR mutation (yes/no)	0.618 (0.133–2.879)	0.540		
TPS (<1% vs. 1–49%)	0.778 (0.124–4.754)	0.763		
Clinical stages (IV, postoperative recurrence vs. III)	0.618 (0.371–17.280)	0.343		
Brain metastasis (yes or no)	1.100 (0.251–4.823)	0.899		
Liver metastasis (yes or no)	0.564 (0.047–6.817)	0.652		
RAM (yes or no)	1.470 (0.400–5.398)	0.562	1.887 (0.423–9.574)	0.423
Full dose (yes or no)	0.525 (0.136–2.020)	0.343		
Dose reduction (yes or no)[a]	5.333 (0.707–40.216)	0.104	12.330 (1.015–149.749)	0.049
ICIs in the immediate prior regimen (yes or no)	0.225 (0.052–0.982)	0.047	0.149 (0.027–0.824)	0.029
History of ICI administration (yes or no)[b]	0.282 (0.055–1.456)	0.131		
Tumor type (adenocarcinoma/nonadenocarcinoma)	0.718 (0.166–3.100)	0.657		
PEG-G-CSF (yes or no)	0.476 (0.124–1.832)	0.280		
G4 neutropenia/FN (yes or no)	0.864 (0.238–3.129)	0.828		

Abbreviations: CI, confidence interval; DTX, docetaxel; ECOG PS, Eastern Cooperative Oncology Group performance status; FN, febrile neutropenia; G4, grade 4 neutropenia; ICIs, immune checkpoint inhibitors; NSCLC, non-small cell lung cancer; OR, odds ratio; PEG-G-CSF, primary prophylactic pegylated-granulocyte-colony stimulating factor; RAM, ramucirumab; TPS, tumor proportion score.

[a]Dose reduction, dose reduction after the second cycle of DTX therapy.

[b]History of ICI administration, history of ICIs administered, not limited to the immediately prior regimen.

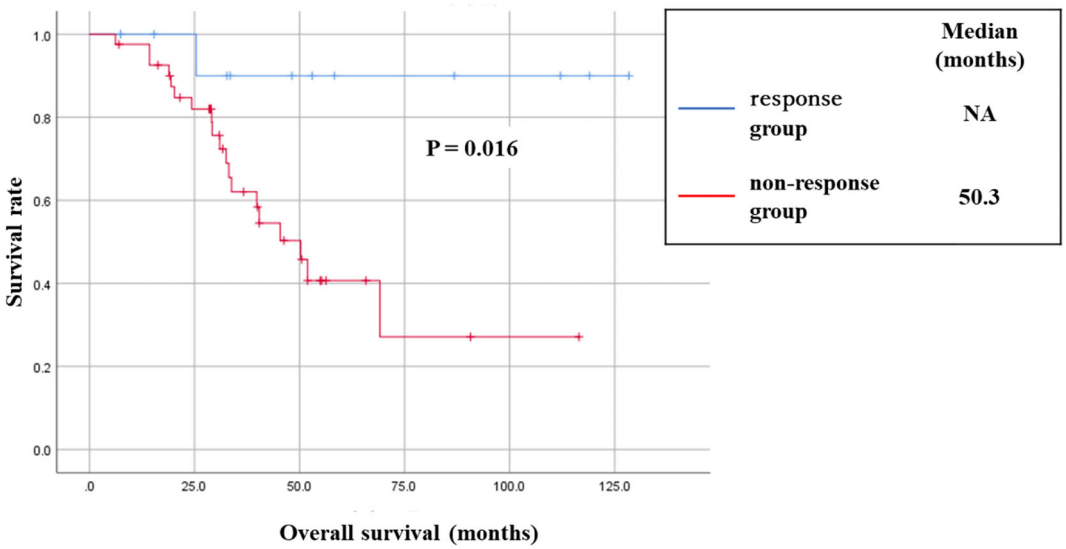

FIGURE 2 Overall survival for patients in the response and nonresponse groups. The median survival in the response group was NA, whereas it was 50.3 months in the nonresponse group, with a significant difference ($p = 0.016$, log-rank). NA, not applicable.

In the multivariate analysis, no ICIs in the immediate prior regimen ($p = 0.029$; OR, 0.149; and 95% CI, 0.027–0.824) and DTX dose reduction[9] after the second cycle ($p = 0.049$; OR, 12.330; and 95% CI: 1.015–149.749) were statistically significant risk factors for nonresponse (Table 2).

The survival curves for the response and nonresponse groups are shown in Figure 2. A statistically significant survival benefit was observed in the response group ($p = 0.016$, log-rank test).

For the results of the subgroup analysis by treatment method, the survival curves for the immediate previous ICI group and the nonimmediate previous ICI group are shown in Figure S1. No significant differences were observed between the two groups ($p = 0.341$, log-rank test).

In addition, the survival curves for the DTX dose-reduction and dose-maintenance groups are shown in Figure S2. No significant differences were noted between the two groups ($p = 0.0592$, log-rank test).

DISCUSSION

Recent studies have shown that the efficacy of DTX[10–14] and DTX + RAM[8,13–21] therapies may be enhanced in patients who were previously treated with ICIs.

Although the detailed mechanism is yet to be elucidated, it has been suggested that immunotherapy may have a tumor synergistic effect on the subsequent cytotoxic therapy.[11,22,23]

In this study, "no prior treatment with ICIs" was not identified as a risk factor for a nonresponse in the univariate analysis. However, the absence of ICIs in the "immediate prior" regimen was identified as an independent risk factor for the nonresponse of patients with NSCLC to DTX (+RAM) therapies. The study findings suggest that sequential DTX (+RAM) therapy after pretreatment with ICIs is effective in improving response rates. The treatment, including the immediately preceding ICIs, may be a factor related to the response to DTX (+RAM) therapy because the therapeutic effect of ICIs lasts for several months[24–26]; however, the extent to which they last is currently unknown.

In this study, the mean time from the last ICI administration to the initiation of DTX (+RAM) therapy was shorter in the response group than in the nonresponse group; however, no significant differences were noted between the two groups. Therefore, in clinical practice, DTX (+RAM) therapy should be administered as a sequential therapy as early as possible after the ICI treatment.

The addition of RAM to DTX has been shown to improve response rates as compared with DTX monotherapy.[3] However, no significant differences were found in the number of patients receiving RAM between the two groups in this study, and multivariate analysis showed that RAM was not a predictor of an increased response rate. Therefore, the question of whether DTX monotherapy or DTX + RAM should be chosen after the ICI treatment could not be clarified in this study.

However, compared with the DTX monotherapy, DTX + RAM has shown to prolong the overall survival of patients with NSCLC.[3]

Furthermore, some reports suggest that after anti-PD-1/PD-L1 antibody administration, DTX monotherapy does not exhibit enhanced efficacy, and only DTX + RAM therapy may increase efficacy.[14]

Moreover, basic research has shown that concurrent administration of ICIs and anti-VEGFR2 antibody synergistically inhibits tumor growth in vivo.[27]

Therefore, selecting DTX + RAM therapy in eligible cases seems critical.

The results of this study confirm that DTX dose reduction after the second cycle is an independent risk factor for the nonresponse of patients with NSCLC to DTX (+RAM) therapy (Table 2).

In clinical practice, DTX dose reductions are performed after the second cycle based on the physician's experience to reduce hematological toxicity.[28] In this study, 50.0% (6/12) of the response group and 58.5% (22/41) of the nonresponse group received a DTX dose reduction after the second cycle.

As per the study findings, administering patients with NSCLC with reduced DTX doses after the second cycle of DTX (+RAM) therapy may increase the risk of disease progression, resulting in a decreased survival rate. Therefore, a treatment strategy of continuing DTX without dose reduction after the second cycle may contribute to improved survival.

However, in this study, the incidence of grade 4 neutropenia/FN was 50.0% (6/12) and 45.2% (19/41) in the response and nonresponse groups, respectively, with higher rates in both groups.

An increased risk of death has been observed in cancer patients who develop FN.[29]

Although no significant differences were noted in the incidence of grade 4 neutropenia/FN in each group, measures against neutropenia should be taken when DTX (+RAM) therapy is administered, because the development of FN may deteriorate the general condition of the patient, making it impossible to continue chemotherapy.

In DTX + RAM therapy, the efficacy of primary prophylactic pegylated (PEG)-granulocyte-colony stimulating factor (G-CSF) administration has been reported to suppress the onset of FN.[28,30,31] In addition, the use of PEG-G-CSF in combination with DTX(+RAM) therapy is preferable to DTX dose reduction to prevent FN onset in the next cycle after its onset of FN.[26] Based on the high incidence of FN with DTX(+RAM) therapy and the consistently reported reduction in the risk of developing FN with PEG-G-CSF, incorporating prophylactic administration of PEG-G-CSF into the treatment regimen is considered a reasonable measure for DTX(+RAM) therapy. Large prospective multicenter studies are required to determine whether the prevention of FN and neutropenia by PEG-G-CSF induction and the consequent maintenance of therapeutic intensity achieved by avoiding DTX dose reduction contribute to improved response rates and prolonged survival.

Notably, this study had a few limitations. First, it was a retrospective, single-center study with a small sample size. Therefore, further studies with larger sample size are required to determine whether the results of this study can be generalized.

However, our findings in practice may help identify the optimal patient population with NSCLC to benefit from DTX (+RAM) therapy, and thus, improve the prognosis of patients with NSCLC.

Second, treatment protocols (e.g., with or without DTX dose reduction after the second cycle, or when to start DTX (+RAM) therapy after ICIs) in some studies were not clearly defined and were at the discretion of the attending physician, which may bias the groups.

In this study, the duration of treatment with DTX (+RAM) therapy was significantly longer in the response group. We cannot completely dismiss the possibility that a substantial number of patients in the response group were able to continue the DTX (+RAM) treatment for a longer period because of their good general condition.

Future large prospective multicenter studies are required to eliminate confounding factors and to determine whether DTX (+RAM) therapy, introduced as sequential therapy after ICI treatment and continued after the second cycle without dose reduction, is effective for response.

Third, this study did not examine the efficacy of chemotherapies other than DTX (+RAM) therapy. The efficacy of anticancer agents other than DTX also increases after administration of ICIs.[11,13,32]

Therefore, it remains unclear whether DTX (+RAM) is the best sequential therapy post ICI administration. Therefore, further studies evaluating anticancer therapies other than DTX (+RAM) are required to address this issue.

In future, we plan to examine patients treated with chemotherapies other than DTX (+RAM) as second-line chemotherapy (e.g., pemetrexed and nab-paclitaxel monotherapies).

In conclusion, our study findings suggest that DTX and DTX + RAM may improve response rates and prolong survival in patients with NSCLC when introduced as sequential therapy after treatment with ICIs, and when continued after the second cycle without DTX dose reduction.

AUTHOR CONTRIBUTIONS

All authors had full access to the study data and take responsibility for the integrity of the data and accuracy of the data analysis. All the authors have read and approved the submission of the manuscript. *Conceptualization*: Yutaka Takahara. *Resources*: Yutaka Takahara, Ryudai Abe, Sumito Nagae, Takuya Tanaka, Yoko Ishige, Ikuyo Shionoya, Kouichi Yamamura, Kazuaki Nishiki, Masafumi Nojiri, Ryo Kato, Shohei Shinomiya, and Taku Oikawa. *Investigation*: Ryudai Abe, Sumito Nagae, Takuya Tanaka, Yoko Ishige, Ikuyo Shionoya, Kouichi Yamamura, Kazuaki Nishiki, Masafumi Nojiri, Ryo Kato, and Taku Oikawa. *Methodology*: Yutaka Takahara and Taku Oikawa. Writing–original draft preparation, Yutaka Takahara, with support from Shohei Shinomiya and Taku Oikawa.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets used in this study are available from the corresponding author upon request.

CONSENT TO PARTICIPATE

The need for informed consent was waived due to the retrospective nature of this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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