Percutaneous microwave ablation for HCV-related hepatocellular carcinoma: Efficacy, safety, and survival

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ABSTRACT

Background/Aims: Hepatocellular carcinoma (HCC) has a poor prognosis if managed late. Percutaneous microwave ablation (MWA) emerged as one of the top therapeutic decisions for non-surgical patients. The aim of the present study aim was to evaluate the efficacy, side effects, and survival after MWA of hepatitis C virus (HCV)-related HCC tumors with spectrum sizes up to 5 cm.

Materials and Methods: Fifty-nine patients with early HCC were treated in the Hepatology Department using percutaneous MWA. Patients were assessed for side effects and efficacy that includes the rate of complete ablation, primary or de novo recurrence, and survival.

Results: Complete ablation was achieved in 57 (96.6%) patients treated by MWA, with a minor complication rate of 3.3% (n=2) including liver abscess formation and abdominal skin burn. The ablation rates in lesions <3 versus 3-5 cm were not different. Of the patients, 3 (5%) had primary recurrence in the treated HCC tumors, de novo lesions (secondary recurrence) developed in 8 (13.5%), 5 of them >3 cm, and 2 (3.3%) had malignant portal vein thrombosis. The survival rates were 95.4% and 69% at 1 and 2 years, respectively.

Conclusion: Percutaneous MWA had achieved a safe and effective treatment with good overall survival in patients with HCV-related HCC.

Keywords: Hepatocellular carcinoma, microwave ablation, safety, efficacy, survival

INTRODUCTION

The recent advances in the different therapeutic approaches of hepatocellular carcinoma (HCC), including percutaneous radiofrequency ablation (RFA) and microwave ablation (MWA), had led to a real change in its unpromising picture (1-3). MWA was demonstrated in different reports to have equivalent efficacy, safety, and survival rates with shorter procedure time than RFA for HCC management, especially lesions that are nearby vessels (4,5). Dong et al. (6) studied 234 patients with MWA and demonstrated satisfactory survival without noticeable complications. Shibata et al. (7) prospectively compared MWA and RFA in HCC ablation, and the rates of residual or partially ablated tumors showed no significant difference. Lu et al. (5) retrospectively found no significant difference in survival or complications between 102 patients divided into two groups (underwent either MWA or RFA).

Moreover, recent studies with modern MW systems have clearly confirmed the effectiveness of MWA in HCC tumors. Qian et al. (8) prospectively compared MW and RFA in treating small (<2 cm) HCC and found that MWA produces complete ablation rates with significantly larger zones better than RFA, but the local tumor progression (LTP) rates were similar in both techniques. By using multiple antennas, MWA is effective in ablating bigger lesions (>3 cm) (9,10), which have usually been problematic for RFA (11), and the obtained larger ablation volumes make these tumors more efficiently treatable.

In addition, intraoperative MWA was compared with hepatic resection by Takami et al. (12) and found that in patients with <3 lesions, all <3 cm, no difference is found in overall survival, disease-free survival, or local recurrence.

Regarding all the preceding clinical trials, we aimed to prospectively determine the outcome (efficacy and safety) and survival after MWA of hepatitis C virus (HCV)-related HCC lesions reaching 5 cm. The primary end point was complete ablation of HCC lesion to determine MW efficacy, and the secondary end points were procedure-related side effects in addition to mortality during the follow-up period.

MATERIALS AND METHODS

Patients’ characteristics

This prospective study was performed on 59 patients with HCV-related HCC presenting to the Hepato-Gas-
tiroenterology and Endemic Medicine Department between 2013 and 2015. All HCC lesions were diagnosed by a typical enhancement in triphasic computerized tomography (CT) (homogeneous tumor enhancement in the arterial phase with washout in the portal and delayed phases) or percutaneous biopsy from atypical lesions by triphasic CT. All patients were subjected to MWA for their HCC lesions and were diagnosed and managed according to the Barcelona Clinic Liver Cancer practice guidelines for the management of HCC (12).

Patients with (1) early stage and acceptable liver profile (Child-Pugh A and B), (2) a Model for End-Stage Liver Disease score <14 with ≤3 lesions (the largest ≤5 cm), (3) performance status 0, (4) proper coagulation profile (international normalized ratio (INR) ≤1.4 and platelet count >50.000/mm$^3$), and (5) not feasible or eligible for resection or liver transplantation (financial issues or unavailability of donors) were included in the study.

Patients with (1) Child-Pugh C, (2) PV thrombosis, (3) metastases outside the liver, (4) bleeding diathesis, (5) tumors >5 cm or >3, (6) uncooperative, (7) technically difficult or not feasible lesions (near the PV, gallbladder, or inferior vena cava (IVC)), and (8) cardiac diseases, uncontrolled diabetes mellitus, or renal diseases were excluded from the study.

In the general classification of HCC lesions according to size, lesions are divided into small (<3 cm), medium (3-5 cm), and large (>5 cm). We included lesions with a maximum 5 cm diameter to be able to compare the MW technique with the RFA technique, which usually fails in lesions >5 cm.

The Hepato-Gastroenterology and Endemic Medicine Department committee (institution review board) and the institution ethics committee approved the study. The study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was obtained from the participants after explanation of the procedures.

Prior to the procedure, all patients were subjected to the following investigations: liver profile (bilirubin, aspartate transaminase, alanine transaminase, alkaline phosphatase, albumin, and INR), complete blood count, alpha-fetoprotein (AFP), conventional abdominal ultrasound (US), and triphasic CT of the abdomen. US-guided tru-cut biopsy from lesions was performed if the results of triphasic CT and AFP were inconclusive.

**Technique of MWA**

Microwave ablation was performed on outpatient bases with the patient under conscious sedation (intravenous (IV) diazepam 10–20 mg or propofol). Skin anesthesia was achieved (after cleansing with Betadine and alcohol) by using 5 ml of 2% lidocaine (Xylocaine, Astra) to anesthetize the skin and subcutaneous tissue, muscles, and diaphragm along the assumed track of entry. A small opening was applied to the skin using a scalpel.

Microwave ablation was performed using an AMICA-GEM machine (HS AMICA MW machine; HS Hospital Service S.p.A., Roma, Italy). With a frequency of 2.450 MHz, the generator is capable of producing up to 100 W of power with 150 mm and 200 mm cooled 14.5-gage shift electrodes called AMICA probes inserted inside lesions. The procedure was US-guided by a Hitachi US machine with a 3.5–5 MHz probe using the free-hand technique. All our MW ablation sessions were performed in our department where the US machine is available, leading to easier performance, less radiation, and shorter sessions than MW-guided CT.

Each session lasted for 5–20 min according to the tumor size and the use of the pull-back technique. As MW energy was applied to the probe, a hyperechoic focus was observed to develop around the uninsulated portion of the electrode. This was attributed to microbubble formation and tissue vaporization. The area of hyperechogenicity increased progressively in size over the course of ablation and generally enveloped the entire tumor with variable extension into the surrounding liver by the end of the treatment.

**The pull-back technique:** In lesions >4 cm, repositioning of the electrode (for the second cycle) would be difficult due to the MW-generated hyperechogenicity obscuring the tumor deeper portions. Therefore, deeper portions were ablated first (2–3 min first cycle); then, the electrode was pulled up for 1 cm (pull-back), and MW was reapplied for another cycle.

Unlike RFA machine and because of the inherent characters of the electromagnetic wave, the MW device does not need grounding, thus alleviating the problem of burns caused by grounding pads. Intratumoral temperatures can be measured with a separately placed thermocouple.

Following MWA therapy, patients were placed under observation for 6 h, vitals were checked every 30 min, and then they were discharged after obtaining the next appointment.
**Post-MWA procedure assessment**

All the laboratory tests that were done before MWA were repeated. AFP and triphasic CT were performed 1 week and 1 month after the procedure, respectively.

The response to MWA was considered complete when triphasic CT showed no intralesional enhancement in the arterial phase. The response was considered partial when triphasic CT showed intralesional areas of enhancement in the arterial phase, or the pathology showed viable cells. Biopsy was performed if the triphasic CT result was not conclusive after MWA (lesion not visible or enhancement not typical).

Therapeutic efficacy and safety were assessed for all patients. Patients were followed up for approximately 2-3 years with special emphasis on the primary (in the same lesion) or de novo recurrence. MW procedure-related minor complications were noted, such as abdominal pain, skin burn, fever, increased jaundice, increased transaminases or INR, or serious complications, including the development of liver decompensation, abscess formation or hemoperitoneum, pleural effusion in the right lobe lesions, and hematemesis or death.

Patients with ablated lesions were followed up by AFP and US every 3 months and triphasic CT every 6 months.

**Definitions of treatment response**

Microwave ablation response definitions were based on the Society of Interventional Radiology (SIR) Standardization of Terminology and Reporting (13). Technical success addresses whether the tumor was treated according to the protocol and covered completely by the ablation zone assessed either during or immediately following the procedure with contrast-enhanced CT. Technique efficacy refers to complete ablation at the prospectively defined time point (i.e., 1 week or 1 month after treatment) as evidenced by imaging. LTP describes the appearance of tumor foci at the edge of the ablation zone, after at least one contrast-enhanced follow-up. Primary or local tumor recurrence implies the appearance of new tumor foci at the ablative margin after ablation of all tumor cells.

Treatment course was defined as all MW sessions performed per lesion based on the first imaging up to 3 months. Primary technique efficacy means no evidence of residual enhancement in the ablated lesion by the last available imaging within 3 months, after which any imaging enhancement was considered LTP. LTP could have MWA retreatment for continued local control, and patients are considered locally disease-free. Secondary or overall technique efficacy means successful retreatment of index tumor after LTP.

We have adopted new terms to describe more events occurring during the follow-up period, such as secondary or de novo recurrence, which is a malignant recurrence elsewhere in the liver, and cancer-free success, which is the absence of primary or secondary malignant recurrence throughout the follow-up period but not excluding the development of other nonmalignant complications.

Complications were stratified according to the SIR standard classification (14). Major complication is an event that leads to substantial morbidity and disability that increases the level of care, leads to a longer stay, or results in hospital admission. This includes any case in which a blood transfusion or interventional drainage procedure is required. All other complications are considered minor. Differentiation among immediate complications (up to 6-24 h following the procedure), periprocedural complications (within 30 days), and delayed complications (>30 days after ablation) is adopted.

Side effects are expected, undesired consequences of the procedure that although occurring commonly, rarely, if ever, result in substantial morbidity. These include pain, post-ablation syndrome, asymptomatic pleural effusions, and minimal asymptomatic perihepatic (or renal) fluid collections.

**Statistical analysis**

Data were coded and entered using the Statistical Package for Social Sciences (SPSS) version 22 statistical package (IBM Corp.; Armonk, NY, USA). Quantitative variables were presented as mean±SD, median, and minimum and maximum values. Qualitative data were presented as frequency and percentage (%).

The Student’s t-test and chi-square test are used when appropriate. A p value <0.05 was considered statistically significant. Survival analysis (Kaplan-Meier method) was performed from the date of tumor diagnosis to the date of death or last follow-up.

**RESULTS**

Table 1 shows the basic clinical features of our patients, Child-Pugh classification, performance status, and AFP levels. Radiological features of the HCC lesions showed that 53 (89.8%) had a single lesion, 5 (8.5%) had two le-
sions, and 1 (1.7%) had three lesions. Fifty-four (91.5%) lesions were in the right lobe, 44 (74.5%) were <3 cm, and 15 (25.5%) had a size of 3-5 cm.

The comparison of patients with single versus multiple lesions was not statistically feasible and reliable as the multiple lesions group will be very small (six patients). In addition, in patients with multiple lesions, one lesion was treated by MWA and included in the study; the other lesions were treated with percutaneous ethanol in multiple sessions until ablation (only MWA and percutaneous ethanol injection ablation techniques were used); therefore, it could be assumed that the patient had one lesion in regard to technical success.

All the patients had triphasic CT before the procedure, but 2 (2/59) had inconclusive enhancement findings. These two patients were diagnosed by US-guided tru-cut biopsy from the lesion. All the lesions had their ablation in one session that lasted for 5–10 min depending on lesion size.

The two patients diagnosed by biopsy before MW were also assessed by biopsy after the procedure. Biopsy was performed after approximately 2 weeks from MW ablation; thus, the possible “mummification” of tumor cells caused by MW would decrease and do not affect the pathologist’s judgment.

One minute of MW energy produces larger ablation volume than 1 min of RFA. Therefore, lesions near large vessels, such PV and IVC, were considered technically difficult as the ablation volume produced by MW is unpredictable; thus, with >1-2 min, the large vessel could be injured leading to marked bleeding.

### Success rate of MWA

By studying the success rates of MWA, complete ablation (technique efficacy) was attained in 57 (96.6%) patients as evidenced by triphasic CT (+biopsy) (Figure 1) after 2–3 weeks; in addition, power Doppler showed absent intraleosomal signals (Figure 2). Power Doppler, which is used to detect intraleosomal signals, was performed after 1 week in the follow-up visit. In addition, the complete ablation rates were statistically non-significant when we subdivided lesions to <3 and 3-5 cm (Table 2). The two patients with failed MWA were treated with percutaneous ethanol in multiple sessions until ablation but not with MWA; thus, secondary effectiveness could not be attained.

### Safety and long-term effect of MWA in HCC

The reported MWA-related side effects and complications showed that abdominal pain during the procedure was reported in 40 (67.7%) patients, and fever (24 h after MWA session) occurred in 4 (6.7%) patients. The abdominal pain was transient during the session, and for approximately 2 to 3 h later, it was moderate in most of the cases and was treated with IV analgesics. The fever was low grade in all the patients, lasting for 1 day and was treated by oral antipyretics. While the procedure-related noteworthy major and minor com-

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**Table 1. Basic characteristics of the studied patients**

<table>
<thead>
<tr>
<th>Item</th>
<th>Microwave ablation (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.2±6</td>
</tr>
<tr>
<td>Male</td>
<td>44 (74.5%)</td>
</tr>
<tr>
<td>Female</td>
<td>15 (25.5%)</td>
</tr>
<tr>
<td>Child-Pugh classification</td>
<td></td>
</tr>
<tr>
<td>Child A</td>
<td>22 (37.2%)</td>
</tr>
<tr>
<td>Child B</td>
<td>37 (62.8%)</td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>24 (40.6%)</td>
</tr>
<tr>
<td>1</td>
<td>32 (54.3)</td>
</tr>
<tr>
<td>2</td>
<td>3 (5.1%)</td>
</tr>
<tr>
<td>Alpha-fetoprotein (ng/ml)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>23</td>
</tr>
<tr>
<td>Range</td>
<td>6–3900</td>
</tr>
</tbody>
</table>

**Table 2. Success rate of MWA technique and according to size**

<table>
<thead>
<tr>
<th>Item</th>
<th>Microwave ablation (n=59)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete ablation</td>
<td>57/59 (96.6%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Partial ablation</td>
<td>2/59 (3.4%)</td>
<td></td>
</tr>
<tr>
<td>Tumors &lt;3 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete ablation</td>
<td>43/44 (97.7%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Partial ablation</td>
<td>1/44 (2.3%)</td>
<td></td>
</tr>
<tr>
<td>Tumors 3–5 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete ablation</td>
<td>14/15 (93.3%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Partial ablation</td>
<td>1 (6.7%)</td>
<td></td>
</tr>
</tbody>
</table>
Applications were reported in 3.3% (Table 3) and included abscess formation in 1 (1.7%) (Figure 3) and abdominal wall skin burn in 1 (1.7%).

Follow-up of the 57 successful patients showed that primary technique efficacy in the first 3 months was 100%. Subsequently, 3 (5%) patients had local tumor recurrence (all of them >3 cm) (Figure 4), 8 (13.5%) developed de novo lesions (secondary recurrence, 5 of them had lesions >3 cm), and 2 (3.3%) developed PV thrombosis (Table 3). The local recurrence and de novo lesions were treated on a case-by-case basis; patients suitable for MWA or percutaneous ethanol were treated with the suitable modality, and some were beyond the local ablation criteria. Therefore, secondary effectiveness could not be attained.

Ascites developed in 2 (3.3%) patients mostly after 1 year, so it is not related to the MW procedure. None of the patients had an increase in jaundice, encephalopathy, or bleeding varices. The median event-free time for MWA-treated patients was 14 months, and the MWA cancer-free success was 77.9%.

**Survival after MWA**

After the follow-up period, the overall survival rates at 1 and 2 years were 95.4% and 69%, respectively, for the studied patients. When subdivided by size, patients with medium HCC had worse prognosis; the overall survival rates for patients with small (≤3 cm) and medium (3-5 cm) HCC were 100%, 95.4%, 89%, and 49% at 1 and 2 years, respectively. The overall median survival rate was 31 months from the date of the MWA procedure (Figure 5).
The patients’ follow-up mean duration was 34±1 months. At the end of follow-up, most mortalities were due to liver-related events (liver failure, encephalopathy, gastrointestinal bleeding, recurrent multiple HCC, sepsis, and renal failure), whereas two patients had non-hepatic events, and three patients dropped out of the study.

**DISCUSSION**

Microwave ablation in HCC offers many of the benefits of RFA and has several other advantages that increase its efficacy. The benefits of the MW technology include consistently higher intratumoral temperatures, larger ablation volumes, faster ablation times (<10 min), ability to use multiple applicators working simultaneously, better convection profile, optimal heating of cystic masses, avoidance of thigh skin burn, and less procedural pain (15).

Microwave technology has continued to progress. MW early models had fairly large non-cooled applicators. Owing to emitted power and needle shaft heating, low-power short ablation phases had to be used to avoid dermal burns. Subsequently, low-power water-cooled machines were invented, followed by higher power water-cooled machines. Recently, machines with cooled smaller needle active size with a phased pattern had finally started to use the benefits of the MW technology in HCC ablation (16).

Microwave ablation incurs the use of electromagnetic methods with marked heating, leading to coagulation, cellular death, and tumor destruction (17). In our experience, we achieved good primary technique effectiveness (96.6%) with MWA. In addition, we highlight a lower incidence of HCC recurrence in MW-treated patients during the follow-up period (approximately 18%) when compared with RFA in other studies. This is probably because MWs appear to be more able to overcome perfusion and large heat sinks than other heat-based ablation modalities, such as RFA, leading to larger ablation volumes and better tumor destruction with a safety margin.

Our result was slightly higher than Ziemlewicz et al. (18) who treated 107 HCCs in 75 patients with MWA (n=85) or MWA+TACE (n=22). In their study, the overall primary technique effectiveness was 91.6%; it was 93.7% (89/95) for ≤4 cm and 75.0% (9/12) for >4 cm and 91.8% (78/85) for MWA alone and 90.9% (20/22) for combination therapy. All treatments were technically successful in a single session. However, they reported no major complications or procedure-related mortality.

Our results were similar to Thamtorawat et al. (19) who retrospectively studied 173 MWA-treated HCCs up to 5 cm in 129 patients. Technical success, primary efficacy, and secondary efficacy were 96.5%, 99.4%, and 94.2%, respectively, at a mean follow-up of 11.8±9.8 months.
The 1- and 2-year secondary treatment efficacy rates were 91.2% and 82.1% for ≤3 cm and 92.3% and 83.9% for 3.1-5 cm, respectively. Unfortunately, we had not attained secondary efficacy rates as recurrent cases, in our study, were treated by another modality.

Most of the clinical studies on HCV-related HCC showed either an equivalent role for both techniques (MW or RF) (5,20,21) or even an upper hand for MW (8,22). However, some studies showed superiority in the success rate for RF (23). The equivalent or higher success rates for RFA were mostly related to the older MW devices, but with modern devices, MWA achieved better results than RFA, especially in larger lesions.

Microwaves appear to be more able to overcome perfusion and large heat sinks than other heat-based ablation modalities (12). MW can ablate areas around big hepatic vessels (approximately 10 mm) and even in high perfusion tissues; it creates large ablation areas (24,25).

Moreover, one of the independent predictors of incomplete HCC destruction is high perfusion rates in vessels >3 mm, thus limiting the effectiveness of RFA (26). Fan et al. (27) compared paired MW and RF probes and indicated that the short- and long-axis diameters of created lesions in in vivo porcine liver for all MW power sets are bigger than RFA with significantly faster rates of heat increase to 60°C for MW.

Multiple MW antennas can be powered continuously and simultaneously, unlike RF, to take advantage of thermal synergy when placed in close proximity or widely spaced to ablate several tumors simultaneously (12,13,28,29). MWA also has a unique feature as multiple needles can be positioned and phased to achieve electromagnetic field overlap (12,13,28,29), leading to better ablation even in larger lesions.

This was confirmed in our study as 3-5 cm lesions were similar to smaller ones (<3 cm) in having complete ablation rates. In addition, Lu et al. (5) reported similar results when they studied MWA for lesions <3 cm and >3 cm. Moreover, Yin et al. (30) treated lesions between 3 and 7 cm, and large lesions had a satisfactory tumor ablation and long-term outcome.

Owing to the drawbacks of RFA, several researchers have successfully proven the effectiveness and great safety of MWA in HCC treatment. In our study, we recorded a small rate of minor complications (3.3% only), and significant complications or death did not occur.

Similarly, a multicenter Italian study by Livragi et al. (31) that performed MWA for 736 patients with 1037 HCC lesions presenting in 14 centers proved MWA high safety with a small major complication rate. In addition, a systematic review of both ablative techniques (MWA and RFA) stated the same safety of MWA with low tolerable complications (4.6% for MWA) (20).

Thamtorawat et al. (19) reported more complications than in our study with 173 MWA-treated HCCs. They had 3 (2.2%) major complications, with one hemoperitoneum requiring transfusion and two severe transaminitsis requiring prolonged hospitalization. They also had 5 (3.7%) minor complications, with two insignificant intrahepatic biliary strictures, one small biloma resolved spontaneously, and two vascular thrombosis (branch of the right PV and left main PV), both did not require treatment.

Follow-up of our patients showed events similar to other studies, for example, a study by Lubner et al. (16) with MW-treated 96 hepatic lesions (62 HCCs and 34 metastases) in 58 patients. At a median of 6-month follow-up (62 HCCs in 44 patients, average diameter 2.3 cm), 4 (6.5%) had LTP. In the 34 metastases (average diameter 2.5 cm) at a median of 5-month follow-up, none of the patients had LTP.

Survival of patients with HCC without treatment is poor (32). The survival rates, after the follow-up period for our patients, were satisfactory and comparable to other studies (5,30) and are corresponding to the survival rates from surgical liver resections.

Moreover, Ziemlewicz et al. (18), with MW-treated 107 HCCs, had lower survival rates than our study in the shorter follow-up period. In their study, the overall survival rate was 76.0% at a median of 14-month follow-up, with most deaths related to end-stage liver disease (n=11) or multifocal HCC (n=5).

In addition, the follow-up period was retrospectively compared between MW (136 tumors) and RFA (69 tumors) in the study by Potretzke et al. (33). RF and MW devices included straight 17-gage applicators (larger than our machine). RF and MW cohorts were similar in tumor size (mean 2.4 cm and 2.2 cm, respectively). The median follow-up was 31 months for RF and 24 months for MW. The LTP rates were 17.7% for RF and 8.8% for MW. There was improved survival for MW-treated patients, although this was not statistically significant. There were few major complications (two for RF and one for MW).
In conclusion, our clinical work illustrates the efficacy and safety of MWA in the treatment of HCC reaching up to 5 cm. The physical properties of the MW technology make it an ideally suited energy source for ablation. This technology is very promising, and clinical implementation will help improve the care of patients with HCC whether they are fit for surgical intervention or not. Studies on lesions >5 cm are needed in clinical practice to achieve optimum results in this difficult cohort.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Ethics Committee of Cairo University, Kasr AlAini School of Medicine.

**Informed Consent:** Informed consent was obtained from the patients who participated in this study.

**Peer-review:** Externally peer-reviewed.


**Conflict of Interest:** The authors have no conflicts of interest to declare.

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**REFERENCES**


