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Combination of interventional oncology local therapies and immunotherapy for the treatment of hepatocellular carcinoma

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Interventional oncology (IO) local therapies of hepatocellular carcinoma (HCC) can activate anti-cancer immunity and it is potentially leading to an anti-cancer immunity throughout the body. For the development of an effective HCC treatment regime, great emphasis has been dedicated to different IO local therapy mediated immune modulation and possible combinations with immune checkpoint inhibitor immunotherapy. In this review paper, we summarize the status of combination of IO local therapy and immunotherapy, as well as the prospective role of therapeutic carriers and locally administered immunotherapy in advanced HCC. **(J Liver Cancer 2022;22:93-102)**

Keywords: Hepatocellular carcinoma; Interventional radiology; Immunotherapy; Nanomedicine

INTRODUCTION

Most systemic and regional therapies for hepatocellular carcinoma (HCC) offer palliation rather than cure. Systemic chemotherapy offers limited survival benefit.[1,2] The first line systemic sorafenib therapy has shown less than 1 year median survival time and the tumor response rate of less than 5%. Local ablation therapies, including thermal and chemical ablation, have limited efficacy with significant recurrence.[3,4] Representatively, the 5-year overall survival (OS) of radiofrequency ablation (RFA) has been reported as 40.1-86.0%,[5,6] but recurrence after ablation of early-stage HCC occurs in up to 60-85% of patients by 5 years.[7] Other treatment options include catheter-directed therapies, such as transcatheter arterial embolization, transarterial chemoembolization (TACE), and ^{90}Y (yttrium)-radioembolization (^{90}Y-RE).[8] Catheter directed therapies improve liver cancer patient survival but the overall prognosis of these patients remains poor with potential metastasis.[9,10] The overall median survival of the catheter directed therapies is about 8.0-30.0 months.[11] As demonstrated promising immuno-therapeutic outcomes in various types of tumors such as melanoma, lung cancer and renal cell carcinoma and so on,[12] immune checkpoint inhibitors (ICIs) immunotherapy have emerged as an effective and promising treatment for HCC.[13,14] Currently, the US Food and Drug Administration (FDA) approved ICIs have been being evaluated for the treatment of HCC in clinical trials (Table 1). Nivolumab (programmed cell death protein-1, PD-1) ICI was approved for the treatment of advanced HCC patients after sorafenib treatment by FDA with an accelerated process. FDA also granted the use of pembrolizumab for the

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HCC with a clinical result of 20% objective tumor remission rate and prolonged survival. However, following this FDA approvals, phase III studies of single-agent nivolumab (CheckMate 459) and pembrolizumab (KEYNOTE-240) in the first line and second-line settings, respectively, did not meet their primary overall survival end points.[14,15] Nivolumab monotherapy was voluntarily withdrawn from the US market. Unique immune suppressive tumor microenvironment (TME) of HCC might be a significant challenge to achieve satisfactory therapeutic efficacy level of ICI monotherapies. Indeed, TME of HCC is dominated by various immunosuppressive cells including macrophages (Kupffer cells), monocyte-derived macrophages, regulatory T (Treg) cells and myeloid-derived suppressor cells (MDSCs) and signals that foster immunosuppressive roles implicated in HCC immune evasion.[16]

Additional therapeutics which can convert immune suppressive TME in HCC are required. Recent studies revealed that the response to PD-1/programmed cell death ligand-1 (PD-L1) ICI immunotherapy significantly relies on a pre-existing immune status. Various immunogenic interventional oncology (IO) local therapies such as RFA, cryoablation, percutaneous ethanol ablation, irreversible electroporation, TACE, ^{90}Y-RE and so on that can overturn the immune suppressive TME of HCC have been actively investigated in clinical trials. However, finding optimal synergistic combination and managing the treatment-related adverse effects (TRAEs) or immune-related adverse effects (irAEs) are the main challenges. More understanding on immune response of IO local therapies and subsequent evaluation for the synergistic combination with ICI immunotherapies are required. Development of new therapeutic regimens with advanced image guide technique and therapeutic delivery technologies will be imperative tasks for advancing immunotherapy for the treatment of HCC. Recent development of various multifunctional carriers and locally administered immunotherapy will allow enhanced immunotherapy of HCC. Here we are summarizing recent progress of combination of IO local therapies and ICI immunotherapy. Future direction and potential role of therapeutic carriers and local combination immunotherapy for an advanced immuno-therapeutic of HCC will be discussed.

COMBINATION OF IMMUNOGENIC IO LOCAL THERAPY AND SYSTEMIC ICI IMMUNOTHERAPY

IO local therapies treating the primary tumor induces the

Table 1. Food and Drug Administration approved immune checkpoint inhibitors and clinical trials on HCC

HCC stage	Immune checkpoint inhibitor drugs	Target	Phase	Clinical trial ID
Advanced HCC	Nivolumab	PD-1	I/II	NCT01658878
Advanced HCC	Nivolumab (+sorafenib)	PD-1	III	NCT02576509
Advanced HCC	Pembrolizumab	PD-1	III	NCT02702401
Advanced HCC	Pembrolizumab (vs. sorafenib)	PD-1	II	NCT02702414
Advanced HCC	Durvalumab+tremelimumab vs. sorafenib	PD-L1 + CTLA-4	III	NCT03298451 (HIMALAYA)
Advanced HCC	Atezolizumab+cabozantinib vs. sorafenib	PD-L1	III	NCT03755791 (COSMIC-312)
Unresectable HCC	Pembrolizumab (+lenvatinib)	PD-1	Ib	NCT03006926 (KEYNOTE-524)
Unresectable HCC	Atezolizumab (+bevacizumab)	PD-L1	Ib	NCT02715531
Unresectable HCC	Atezolizumab (+bevacizumab+sorafenib)	PD-L1	III	NCT03434379 (IMbrave150)
Unresectable HCC	Durvalumab+tremelimumab	PD-L1 + CTLA-4	I/II	NCT02519348

HCC, hepatocellular carcinoma; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; CTLA-4, cytotoxic T lymphocyte-associated antigen-4.

shrinkage of untreated distant tumors as known as abscopal effect. The immunogenicity of IO local therapies can activate antigen presenting cells (APCs) being recognized by the dendritic cells and it is potentially activating an anti-cancer immunity throughout the body. Indeed, the investigation of various IO local therapy mediated immune modulation and anti-cancer immunity are now in great interest for the potential combination with ICI immunotherapy. Such local tumoral accessibility of clinical IO therapies makes HCC ideal for the local interventions that can cause immunogenic cell death (ICD) or local immune conversion in immune suppressive TME of HCC.

ICD induced by IO local therapies commonly can convert the immune suppressive TME in HCC. ICD releases the tumor-associated antigens, high mobility group box 1, and adenosine triphosphate to recruit the various immune cells to TME and expresses the surface calreticulin as a "eat-me" signal. Circulating phagocytic APCs accumulate to immunogenic TME by ICD and subsequently synergize with ICI cancer immunotherapy (Fig. 1).[17] Therefore, various kinds of clinical trials in a different combinations of immunogenic IO local therapy and ICI immunotherapy are on-going to improve the overall therapeutic outcomes and survival benefit versus monotherapy.[18-20] Recently, Duffy et al. showed enhanced cytotoxic lymphocytes (CTLs) accumulation in the tumor after a synergistic combination of anti-cytotoxic T lymphocyte-associated antigen-4 (aCTLA-4) immunotherapy and various ablation techniques such as TACE, RFA, and cryoablation.[21,22] Partial tumor ablation with RFA or TACE in advanced HCC patients receiving systemic tremelimumab resulted

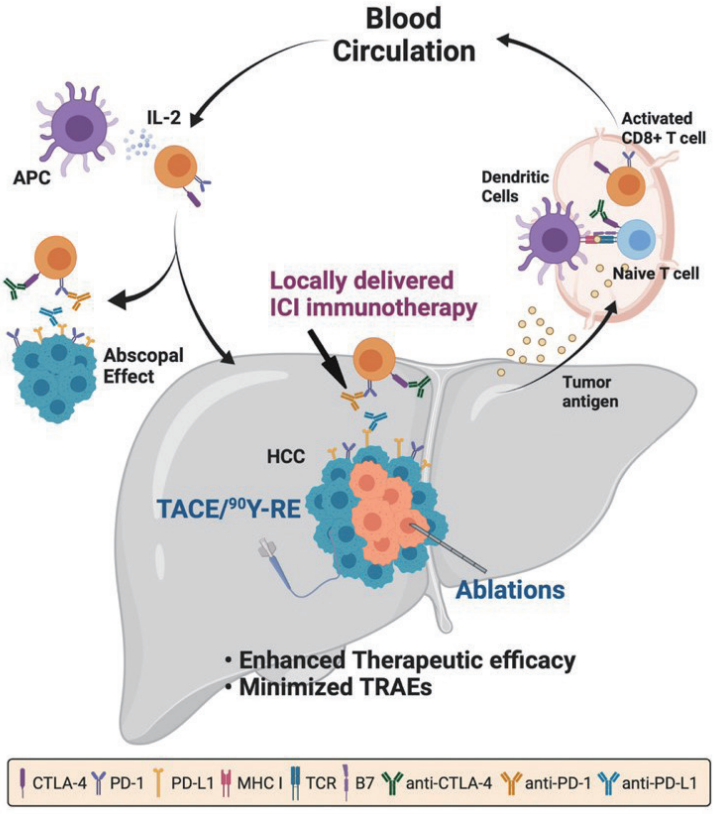

Figure 1. Combination of IO local therapy and ICI immunotherapy of HCC. Combination of IO local therapies and locally delivered ICI immunotherapy enhances local immunogenicity, releasing tumor antigen and inducing immunogenic cell death. Modulated immunity in HCC effectively unleash the suppressed anti-cancer immune responses with circulating educated CTLs. IO, interventional oncology; ICI, immune checkpoint inhibitor; HCC, hepatocellular carcinoma; CTL, cytotoxic lymphocyte; APC, antigen presenting cell; IL-2, interleukin-2; TRAE, treatment related-adverse effect.

in a response rate of 26% and a disease control rate of 89%, with 45% of the stabilizations lasting longer than 6 months, and an overall survival of 12.3 months.[23] These encouraging data have triggered many different combinational clinical trials in which systemically administered ICIs are given in combination with IO local therapies of ablations, TACE or TARE. Percutaneous ablation (KEYNOTE-937 [NCT03867084], EMRALD-2 [NCT03847428], CHECKMATE-9DX [NCT03383458], IMBRAVE-050 [NCT04102098], and so on), TACE (EMRALD-1 [NCT03778957], CHECKMATE-74W [NCT04340193], TACE-3 [NCT04268888], and so on), and ROWAN [NCT05063565], and so on) are primarily ongoing to evaluate the various forms of combination IO local therapies and ICI immunotherapy. Additional information is added in Table 2 and more details can be found in other review papers.[11,24,25] Indeed, combination of IO local therapy and ICI immunotherapy is an emerging strategy to overcome current challenges of both IO local therapies and immunotherapies. More effort to develop the image guided combination IO local therapy and ICI immunotherapy are urgently required to establish optimal benefit of combination IO local therapy and immunotherapy in overall therapeutic outcomes and safety.

CURRENT CHALLENGES ON COMBINATION IO LOCAL THERAPY AND ICI IMMUNOTHERAPY

Combination of IO local therapy and ICI immunotherapy is promising for enhancing the therapeutic efficacy. However, current standard approaches to combine IO local thera-

Table 2. Clinical trials of combination interventional oncology local therapy and immune checkpoint inhibitor immunotherapy

Interventional oncology local therapy	Immune checkpoint inhibitor drugs	Target	Phase	Clinical trial ID
Radiofrequency ablation	Toriplimab	PD-1	I/II	NCT03864211
	Carrizumab	PD-1	II	NCT04150744
	Pembrolizumab	PD-1	II	NCT03753659
	Pembrolizumab	PD-1	III	NCT03867084 (KEYNOTE-937)
	Nivolumab	PD-1	II	NCT03383458 (CHECKMATE-9DX)
	Atezolizumab (+bevacizumab)	PD-L1	III	NCT04102098 (IMBRAVE-050)
Transarterial chemoembolization	Nivolumab	PD-1	II	NCT03572582 (IMMUTACE)
	Durvalumab+tremelimumab	PD-L1 + CTLA-4	II	NCT02821754
	Camrelizumab	PD-1	II	NCT04191889 (TRIPLET)
	Pembrolizumab (+lenvatinib)	PD-1	II	NCT04246177 (LEAP-012)
	Sintilimab	PD-1	II	NCT04297280
	Nivolumab	PD-1	I	NCT03143270
	(durvalumab+bevacizumab)	PD-L1	III	NCT03778957 (EMRALD-1)
	Nivolumab+ipilimumab	PD-1 + CTLA-4	III	NCT04340193 (CHECKMATE-74W)
	Nivolumab	PD-1	II	NCT04268888 (TACE-3)
^{90}Y-radioembolization	Nivolumab	PD-1	II	NCT03033446
	Nivolumab	PD-1	I	NCT02837029
	Pembrolizumab	PD-1	I	NCT03099564
	Durvalumab+tremelimumab	PD-L1 + CTLA-4	II	NCT05063565 (ROWAN)
Local radiation	Sintilimab	PD-1	II/III	NCT04167293 (ISBRT01)
	Nivolumab	PD-1	II	NCT03380130 (NASIR-HCC)
	Pembrolizumab	PD-1	II	NCT03316872

PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; CTLA-4, cytotoxic T lymphocyte-associated antigen-4.

pies with systemically administered ICI immunotherapy are initiated based on minimum data with a shortage of clinical information. Most recent data showed that systemically administered ICI immunotherapy can induce therapeutic resistance/ignorance and severe side effects involved with autoimmunity. When it combined with IO local therapies, additional TRAEs can be occurred and ended up being moderate therapeutic outcomes. Severe side effect (Grade 3 or 4) incidence has been reported as high as 90% in the combination of systemic ICIs immunotherapies following an IO local therapy.[26]

1. Pharmacokinetics of ICIs

Current ICI immunotherapies are performed with systemic administration of anti-CTLA4, anti-PD-1 (aPD-1) or anti-PD-L1 (aPD-L1) immunoglobulin G (IgG) based monoclonal antibodies (mAbs). Those ICI mAbs may not be effective to achieve an anti-cancer immune response with IO local therapies in immune-suppressive HCC.[27-29] Upon systemic administration of mAb, non-specific binding and short circulation time of ICI mAbs can affect the therapeutic efficacy.[30] Current ICI mAbs are mostly humanized or human IgG antibodies. The pharmacokinetics of ICI mAbs are similar with other therapeutic mAbs in the systemic administration. Systemically administrated ICI mAbs circulate in the central vasculature and are distributed to peripheral tissues and tumors. During the circulation, off-target binding with IC molecules of normal tissues and proteolytic clearance limits the tumor specific ICI mAb dose.[30-32]

2. TRAEs

The limited pharmacokinetics of ICI mAbs can induce an excessive immune response after combination of ICI immunotherapy and IO local therapy.[33] These symptoms are mostly accompanied with the pneumonitis, colitis, hepatitis, myocarditis, as a category of irAEs.[34] Steroid-based treatments are commonly given to suppress the immune responses. Those irAEs and concurrent immunosuppressive treatment subsequently reduces the efficacy of immunotherapy by increasing incident rate and mortality.[35] In the clinical data, 85% patients treated with ipilimumab (aCTLA-4) ICI immunotherapy in monotherapy experienced irAEs.[36] 26% patient treated with PD-1 ICIs (nivolumab, pembrolizumab, and cemiplimab), and 14% patient treated with PD-L1 ICIs (atezolizumab, avelumab, and durvalumab) showed irAEs.[37] The combination of ICIs with IO local therapy for better therapeutic response led to more severe incidence of irAEs (93%).[38-41] The combination ICI immunotherapies and IO local therapy might need additional consideration of additive side effect of IO local therapies. Unfortunately, once irAEs is occurred with autoimmunity, discontinued ICI immunotherapies might not be resumed with immunological memory effect.[42] Intensive investigation of minimizing TRAEs including irAEs is required to find the synergistic combination of IO local therapy and ICI immunotherapy.

LOCAL TUMOR TARGETED COMBINATION IO LOCAL THERAPY AND ICI IMMUNOTHERAPY

Development of new strategy to enhance targeting and controlled release of ICI molecules at desired immune activation sites is the key to increase the response rates and control the TRAEs of combination IO local therapy and ICI immunotherapy. Multifunctional carriers including injectable therapeutic carriers, nanocarriers, and local administration routes may overcome physical TME barriers and enhance the controlled immune modulation for the treatment of HCC.

1. ICI delivery carriers

Drug delivery carriers have shown excellence in improving the pharmacokinetics of anti-cancer agents. Currently, 45 different nano-drug carrier-formulations have been approved for the clinical uses by the FDA, and over 80 clinical trials are on-going to evaluate the potential clinical translation of nanocarriers.[43] Nanocarriers basically provides high surface area where can load various therapeutic molecules and the size scale is compatible with cellular component allowing easy penetration. An enhanced permeability and retention (EPR) effect using the characteristic high permeability of tumor vessels and the retention effect in tumors by poor lymphatic clearance demonstrated the potential of nanocar-

riers for delivering ICI mAbs.[44] Active targeting utilizing tumor specific molecules can further increase targeting efficiency of nanocarriers. In preclinical studies, nanocarriers have been suggested for the delivery of various immunotherapies, as a form of nano-immunotherapy. For ICI cancer immunotherapy, nanocarriers incorporating ICI molecules have suggested to improve the therapeutic efficacy of ICI immunotherapy. Many preclinical studies have demonstrated the enhanced targeted delivery of ICI and sustained ICI release of ICI loaded nanocarriers.[45-48] Various ICI mAb conjugated nanocarriers have shown enormous potential to improve the efficacy of ICI immunotherapy and combinational ICI immunotherapy.[49-51] However, ICI mAb-nanocarriers often lose the available Fab which can bind with immune checkpoints and at the same time, Fc γ R of ICI mAb are exposed outside that causes rapid clearance with the Fc γ R mediated endocytosis.[52-55] More efforts to improve the ICI mAbs loading protocol is necessary for the high affinity and specificity of ICI mAb-nanocarrier.[56] Beyond the nanocarriers, injectable carriers are a promising approach to deliver and release ICI locally and combine additional IO local therapy together. Lipiodol, iodinated ethyl esters of fatty acids from poppy seed oil, exhibits transient and plastic embolic effects and facilitates localized delivery of doxorubicin to HCC during cTACE of HCC.[57,58] The development of lipiodol-based formulations or various injectable gels that can enhance targeted ICI delivery may allow an opportunity for safe incorporation of potent ICI immunomodulatory agents with IO local therapies.

2. Hepatic intra-arterial delivery of ICIs

Current limitations relying on systemic administration of ICI immunotherapy and ICI loaded carriers might be overcome with image guided local ICI administration route.[59] Image guided local delivery including intra-tumoral injection and tumor associated vascular injection may result in high doses of ICI combination therapy in local tumor and TME without systemic exposure of toxic therapeutics. HCC receives most of their blood supply from hepatic arteries unlike the normal liver. Even hepatic metastases >3 mm derive 80-100% of their blood supply from the hepatic arterial rather than the portal venous circulation.[60] Moreover, the density of arterial vessels around a metastatic lesion is estimated to be 3 times more than in normal liver tissue.[61] Thus, if ICI molecules or ICI loaded carriers are infused into the hepatic artery, the infused dose preferentially reaches the tumor as opposed to the normal liver. Currently, ICI agents, lipiodol, gel-form, microspheres, nanocarriers and so on have been tested for the hepatic intra-arterial infusion for high local delivery of therapeutics in HCC.[46,62-68] During the IA infusion, MRI, CT and X-ray angiography are used to practice tumor specific hepatic arterial infusion, monitor the procedure, and confirm the distribution of infused therapeutics. A phase III clinical trial (NCT03949231) is ongoing to compare the effects of IA infusion and IV administration of PD-1/PD-L1 ICIs on the survival benefit of patients with advanced liver cancer, including ORR, DCR, median survival time, and safety. Clinical trials (NCT04945720 and NCT04191889) also are testing IA infused chemotherapy and aPD-1/aPD-L1 (durvaluamab or camrelizumab) mixture for the efficacy and safety in advanced HCC. A clinical trial (NCT02850536) also testing hepatic arterials infusion of CAR-T for CEA-Expressing Liver Metastases. Another clinical trial (NCT04823403) is investigating the optimized dosage of hepatic IA administration of Ipilimumab in combination with IV administered nivolumab for advanced HCC (HIPANIV).

3. Percutaneous intra-tumoral delivery of ICIs

Percutaneous intra-tumoral therapeutic delivery also plays a key role in the management of HCC. Percutaneous intratumoral ethanol injection is a well-established technique for the treatment of HCC.[69] Ultrasound real-time guidance of intratumoral ethanol injection allows faster procedure, precise centering of the needle in the tumor target, and continuous monitoring of the injection. This local injection is conveniently performed under local anesthesia on an out-patient basis and the treatment sessions and schedule can be flexible according to the distribution of the injected ethanol within the tumor and the prognosis. Several clinical trials of local intratumoral administration of immunotherapy are on-going. Intratumorally injected aPD-1 and aCTLA-4 ICIs (NCT03058289) are being tested in HCC. A phase 1 clinical

trials are testing tumor targeted injected TLR9 agonist CpG oligonucleotides and OX40 agonist (NCT03831295). Phase I-II study (NCT03792724) evaluates the safety and activity of intratumoral urelumab combined with systemic nivolumab in patients with advanced solid tumors. Additionally, intracavitary infusions[70,71] and the direct lymph node infusion could be available for the local delivery of toxic immune adjuvants.

PERSPECTIVES

Various clinical trials evaluating the combination of IO local therapies and ICI immunotherapy has been tested and promising interim data has been released.[11] When the IO local therapies are combined with ICI immunotherapy, the median survival, ORR, PFS are surpassing those indications of IO local therapy alone. It is implicating the rationale for the combination of IO local therapy and ICI immunotherapy can be synergistic (Fig. 1). Although additional robust clinical evidence is further required, the development of various synergistic combination strategies should be investigated in a consideration of TRAEs. Since each IO local therapy and ICI monotherapy itself showed high percentage of complications, new approaches that can minimize side effect of the combination IO local therapy and ICI immunotherapy are urgently required. Specially, those side effect can easily impair liver functions during the HCC treatment, lowered side effect during the combination will be an important consideration. Developed multifunctional therapeutic carriers and effective local delivery routes can critically contribute to the safe and effective combination of IO local therapy and ICI immunotherapy. Carriers mediated ICI delivery, controlled ICI release, and immune modulation have demonstrated the effectiveness to overcome the ICI therapeutic tumor resistance, ignorance, and off-target side effect (irAEs). Additionally, the multifunctionality of carriers in imaging and therapeutic delivery have shown excellent potential for improving the interventional procedures. Development of delivery route for ICI immunotherapy or ICI loaded carriers is another essential component to further enhance the therapeutic efficacy of combination IO local therapy and ICI immunotherapy. Most of ICI immunotherapy has been tested with systemic administration. The efficacy evaluation of local administration of ICI immunotherapy comparing to systemic administration of ICI has been initiated recently. Established hepatic artery local administration and percutaneous intra-tumoral administration routes in HCC will allow rapid development and optimization of local ICI immunotherapy and the combination of IO local therapy and ICI immunotherapy. During the process, current ICI dosage regime should be revised for each administration routes and in-depth biodistribution studies are further needed. Additionally, ICI residence time and following time-dependent immunity changes after the locally administered combination immunotherapy should be investigated and compared with systemic administration of ICI immunotherapy. Optimal sequencing and interval of IO local therapies and ICI immunotherapy in the combination also need to be investigated. Lastly, it is critical to develop key biomarkers that can identify immune response and therapeutic response to the combination of IO local therapy and ICI immunotherapy. Considering the complexity of the immune suppressive TME and anti-cancer immunity in HCC, substantial effort is required to integrate multifunctional carriers and image guided local delivery technique into the novel combination of IO local therapy and ICI immunotherapy strategies for treating various stages of HCC safely and effectively.

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Conflicts of Interest

D.H.K, a contributing editor of the Journal of Liver Cancer, was not involved in the editorial evaluation or decision to publish this article.

Ethics Statement

This review was exempted from the IACUC or IRB.

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Data Availability

Data sharing not applicable to this article as no datasets were generated or analyzed during this study.

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Author Contribution

Conceptualization, Funding acquisition, Investigation, Project administration, Writing-original draft, Writing-review & editing, Approval of final manuscript: DHK.

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