CAR-T cells and other cellular therapies for solid tumors: Current challenges and emerging solutions

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ABSTRACT

Recent advances in cancer immunotherapy have transformed adoptive cellular therapy, yielding remarkable clinical outcomes in hematological malignancies, whereas its efficacy in solid tumors remains severely limited by the immunosuppressive tumor microenvironment, antigen heterogeneity, and on-target/off-tumor toxicities. To address these challenges, this article reviewed the principal biological and translational barriers hindering solid tumor treatment, examining advanced modalities such as tumor-infiltrating lymphocytes, engineered T-cell receptors, and novel CAR-expressing immune cells based on a comprehensive literature search across PubMed and Scopus.

Keywords: Immunotherapy, Adoptive. Neoplasms. Tumor Microenvironment. Lymphocytes, Tumor-Infiltrating. Receptors, Chimeric Antigen.

INTRODUCTION

Over the past few decades, cell-based therapies have emerged as a central pillar of modern immuno-oncology, representing one of the most promising strategies for improving cancer treatment. Unlike conventional therapeutic modalities, such as chemotherapy and radiotherapy, adoptive cellular therapy (ACT) leverages the patient's own immune system to recognize and eliminate malignant cells. This personalized therapeutic concept involves isolating autologous immune cells, genetically engineering or expanding them *ex vivo*, and subsequently reinfusing them into the patient. Among available ACT platforms, tumor-infiltrating lymphocytes (TILs), engineered T-cell receptors (TCRs), and chimeric antigen receptor (CAR) T cells represent the most clinically advanced modalities.

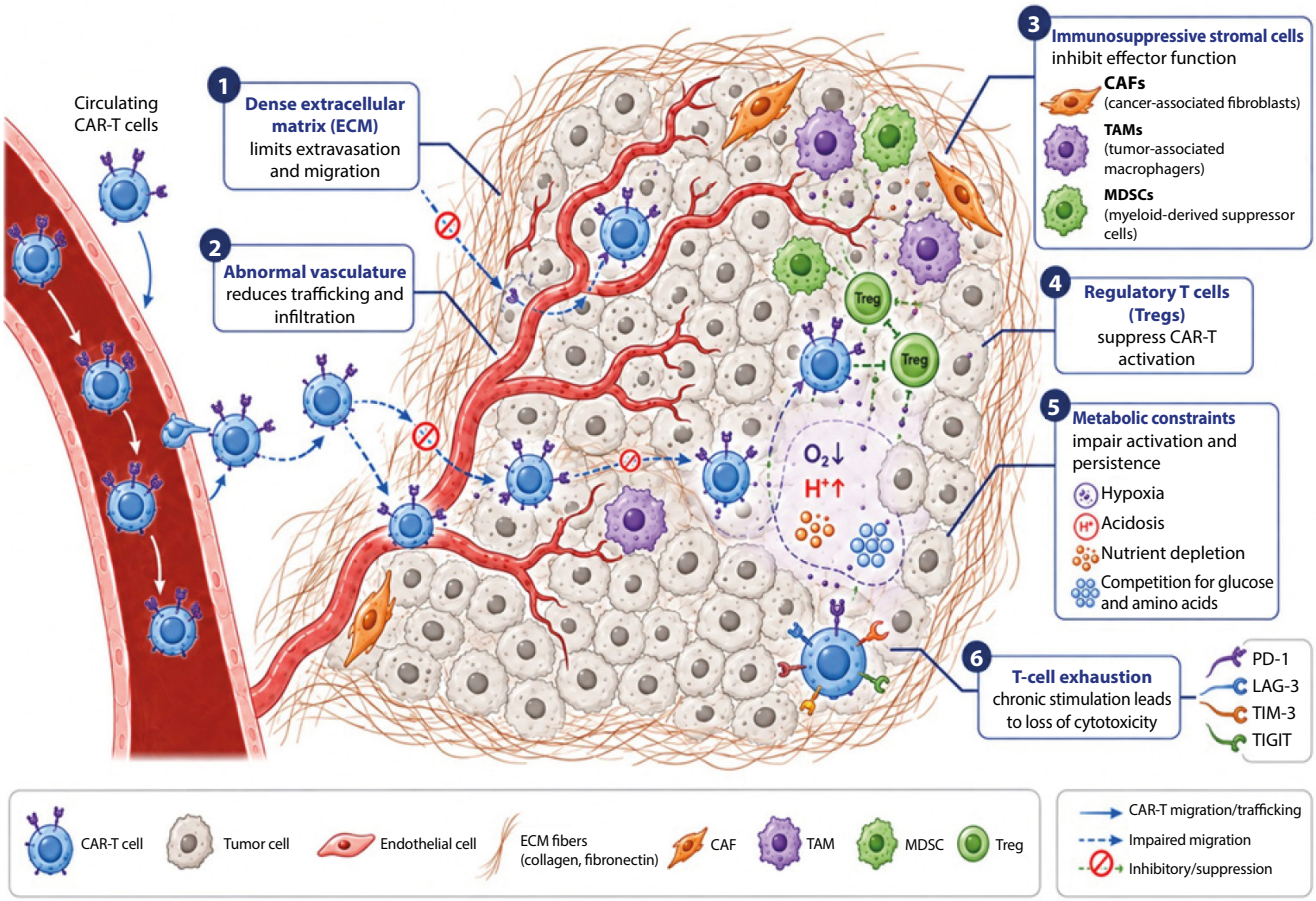
ACT has produced transformative outcomes in hematological malignancies, particularly with CD19- and BCMA-targeting CAR-T cell products, which have achieved unprecedented complete response rates in otherwise refractory disease. In contrast, the clinical experience derived from ACT in solid tumors remains modest. Most engineered T-cell approaches for solid cancer are still being evaluated in early-phase clinical trials (phase I/II), with limited objective responses. This disparity stems largely from the highly heterogeneous, antigen-diverse, and profoundly immunosuppressive tumor microenvironment (TME) characteristic of solid tumors. These factors restrict T-cell trafficking, survival, and effector function, while also complicating the identification of suitably tumor-restricted targets. Additionally, treatment-related toxicities resulting from on-target/off-tumor (OTOT) reactivity remain a significant concern.

This short review synthesizes the major biological and translational barriers to successful ACT for solid tumors and outlines the leading cellular immunotherapy modalities currently under investigation, including TILs, engineered TCRs, and CAR-expressing lymphoid and myeloid cells. For that purpose, public biomedical

databases, such as PubMed and Scopus, were used to find original research articles and reviews, searching for those articles that contained the term "solid tumor" in combination with one of the following words: "CAR-T cells," "CAR-M," "CAR-DC," "CAR-NK," "TCR-T cells," "tumor-infiltrating lymphocyte," "immune checkpoint," "radiotherapy," and "oncolytic virus."

LIMITATIONS OF CELL-BASED THERAPIES TARGETING SOLID TUMORS

The success of CAR-T cells in hematologic malignancies is attributed to the accessibility of malignant cells in circulation or bone marrow, as well as the existence of well-defined antigens such as CD19. Solid tumors present a markedly different therapeutic landscape, as summarized in Fig. 1.



Source: Elaborated by the authors using AI.

Figure 1. Major limitations imposed by tumor microenvironment of solid tumors for T cell therapies The main factors that impair solid tumor elimination by T cells (here represented by CAR-T cells) are: (i) a dense extracellular matrix, which limits infiltration and extravasation; (ii) impaired trafficking to tumor sites due to abnormal vasculature; (iii) the presence of immunosuppressive stromal cells, such as MDSCs, TAMs, and CAFs, which impair T-cell activity by secreting immunosuppressive cytokines, expressing inhibitory ligands, or secreting molecules that contribute to immune evasion and angiogenesis; (iv) regulatory T cells that drive direct immunosuppression, mainly through IL-2 competition and the release of inhibitory cytokines; (v) metabolic stressors arising from a hypoxic and acidic TME, low nutrient availability caused by abnormal vasculature, and competition for glucose and amino acids consumed at elevated rates by tumor cells; and (vi) chronic antigen stimulation, which, alongside immunosuppressive mechanisms and metabolic stress, contributes to functional exhaustion, characterized by the inability of T cells to effectively cells.

Tumor antigen heterogeneity and target selection challenges

One of the most significant limitations is the intrinsic antigenic heterogeneity of solid malignancies. Unlike hematologic tumors, which frequently express lineage-restricted antigens, many solid tumor-associated antigens are heterogeneously expressed within the same tumor mass and are often shared with healthy tissues. This complicates the identification of truly tumor-specific targets suitable for ACT. When target antigens are expressed in normal tissues, even at low levels, engineered T cells may attack those tissues, resulting in potentially severe OTOT toxicity[1].

A well-documented example of antigen escape was observed in a clinical trial evaluating EGFRvIII-targeted CAR-T cells in recurrent glioblastoma. Post-treatment analyses revealed significant downregulation of EGFRvIII in five of seven treated patients, accompanied by increased expression of immunosuppressive molecules associated with T-cell dysfunction[2]. These findings illustrate two major issues: antigen heterogeneity directly contributes to immune evasion and treatment resistance, and selective pressure exerted by targeted therapies can further modulate tumor antigen expression.

Barriers imposed by the tumor microenvironment

Even when a suitable target is identified, CAR-T cells must still access and persist within the tumor. The solid TME presents a combination of physical, metabolic, and immunological obstacles that collectively impair ACT efficacy. Key barriers include:

- Dense extracellular matrix: limits extravasation and migration of effector cells;
- Abnormal vasculature: disrupts directed trafficking and reduces immune cell infiltration;
- Immunosuppressive stromal cells: tumor-associated macrophages, fibroblasts, and myeloid-derived suppressor cells inhibit effector functions;
- Metabolic constraints: hypoxia, acidosis, nutrient depletion, and competition for glucose and amino acids undermine T-cell activation and persistence;
- Immunoregulatory cells: Tregs play a central role in suppressing CAR-T activation through cytokine consumption, checkpoint ligand expression, and contact-dependent inhibition.

T-cell differentiation and exhaustion

The therapeutic performance of engineered T cells is directly influenced by their differentiation state. Less differentiated subsets, such as stem cell memory (T_{SCM}) or central memory (T_{CM}) T cells, correlate with superior engraftment, expansion, and persistence following infusion. However, solid tumors often induce chronic antigen stimulation, accelerating T-cell exhaustion through pathways involving PD-1, LAG-3, TIM-3, and transcriptional regulators such as TOX. Exhausted T cells lose proliferative capacity and cytotoxic potential, limiting the durability of antitumor responses.

Toxicities

Cell-based therapies can induce immune hyperactivation, mainly cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Most common symptoms in CRS are fever, hypotension, hypoxia, and organ dysfunction, managed with supportive care, tocilizumab, and corticosteroids, according to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading for toxicities associated with immune effector cell therapies. ICANS manifests as encephalopathy, seizures, or cerebral edema and is treated mainly with corticosteroids and neurological monitoring[3]. More specifically related to solid tumors treatment, a critical risk is OTOT toxicity, as recognition of the target antigen on healthy tissues can cause potentially life-threatening organ damage. The prediction remains difficult since toxicity depends on the anatomical distribution, density and expression level of antigen in normal tissues, as well the

affinity and activation threshold of the construct. Therefore, preclinical validation of CAR activation across relevant antigen densities, combined with post-infusion control mechanisms and locoregional delivery to limit systemic exposure, is essential to mitigate OTOT[1].

Collectively, these constraints underscore the need for novel engineering solutions and combinatorial approaches to achieve clinically meaningful outcomes in solid tumors.

CELLULAR THERAPY APPROACHES FOR SOLID TUMORS

Much progress has been made in the field of adoptive cell transfer over the last decades. In this section, some of the cellular types studied for solid tumor treatment are highlighted, and their mechanism and state-of-the-art usage are summarized in Table 1.

Table 1. Principal cellular therapies for treating solid tumors, their mechanism, advantages, and disadvantages.

Cell therapy	Mechanism	Advantages	Limitations	Regulatory status	Representative clinical trials
TILs	Expansion of tumor-reactive T cells with native, MHC-restricted TCRs	Broad antigen recognition; naturally tumor-specific; clinical validation	Limited TIL recovery; labor-intensive, patient-specific manufacturing; variable TIL quality; HLA restriction	Clinical approval for melanoma	Lifileucel (C-144-01): melanoma
Engineered TCRs	T cells genetically engineered to express a tumor-specific, high-affinity TCR	Intracellular antigens recognition via MHC; high specificity	HLA restriction; antigen escape through MHC-I downregulation; and TME-mediated suppression of TCR signaling	Clinical approval for synovial sarcoma	Afami-cel (SPEARHEAD-1): synovial sarcoma
CAR-T	T cells engineered with CARs for MHC-independent recognition of surface antigens	High specificity; potent cytotoxicity; rapid activation; established platform	Autologous therapy; limited target availability; poor trafficking/persistence; T-cell exhaustion; on-target/off-tumor toxicity	Clinical approval for hematological malignancies and investigational for solid tumors	NCT03373097: GD2-CART01, neuroblastoma
CAR-NK	CAR-mediated recognition by NK cells, combined with innate cytotoxicity	Allogeneic/off-the-shelf potential; lower GvHD risk; innate cytotoxicity	Low genetic engineering efficiency; limited persistence/ expansion; poor trafficking; manufacturing challenges	Clinical development	NCT05213195: NKG2D CAR-NK, colorectal cancer
CAR-M	CAR-mediated tumor recognition, phagocytosis and immunomodulation	Strong tumor infiltration; TME remodeling; phagocytic activity	Early-stage; limited persistence; manufacturing complexity; safety concerns	Early clinical development	NCT04660929: HER2 CAR-M, solid tumors HER+
CAR-DC	CAR-mediated tumor targeting combined with antigen presentation	Tumor targeting; endogenous immune activation; antigen presentation	Limited clinical evidence; complex manufacturing; uncertain persistence	Early clinical development	NCT05631899 and NCT05631886: EphA2 CAR-M for solid tumors

CAR: chimeric antigen receptor; TIL: tumor-infiltrating lymphocyte; MHC: major histocompatibility complex; TCR: engineered T-cell receptors; HLA: human leukocyte antigen; TME: tumor microenvironment; NK: natural killer; GvHD: graft-*versus*-host disease; CAR-M: CAR-macrophages; DC: dendritic cell. Source: Elaborated by the authors.

Tumor-infiltrating lymphocytes

TIL therapy represents one of the earliest forms of ACT and leverages the natural presence of tumor-reactive T cells within the tumor mass. These cells recognize tumor antigens through their native TCRs in a major histocompatibility complex (MHC)-restricted manner. The workflow involves surgical tumor resection, isolation of TIL populations, rapid *ex-vivo* expansion with high-dose interleukin (IL)-2, and reinfusion following lymphodepleting chemotherapy, which facilitates engraftment and enhances *in-vivo* expansion.

TIL therapy has achieved particularly notable success in metastatic melanoma. Early work in 1988 reported an objective response rate of 55%[4], establishing TILs as a viable treatment modality. Subsequent studies

demonstrated durable responses and the capacity of TILs to reshape the TME, including in tumors refractory to immune checkpoint blockade. These promising results culminated in the U.S. Food and Drug Administration (FDA) approval of lifileucel (AMTAGVI), the first commercially available TIL product, for anti-PD-1–refractory melanoma.

Nevertheless, limitations persist. TIL therapy depends on sufficient TIL recovery from resected tumors, which is often unfeasible for tumors with low lymphocyte infiltration or anatomically inaccessible locations. Manufacturing is labor-intensive, patient-specific, and influenced by TIL quality, which varies markedly across individuals. Importantly, the approach remains constrained by human leukocyte antigen (HLA) restriction and tumor-driven immunosuppression.

For these reasons, genetically engineered T cells, with enhanced specificity and resistance to immunosuppression, have emerged as a complementary strategy.

Engineered T-cell receptors

Genetically engineered TCR therapy aims to enhance natural TCR-mediated tumor recognition by introducing high-affinity, tumor-specific receptors into patient T cells. In the late 1990s, National Institutes of Health (NIH) researchers pioneered retroviral transduction of human lymphocytes with a TCR specific for the melanoma antigen MART-1[5]. Clinical trials demonstrated that TCR-redirected cells could mediate tumor regression, validating the therapeutic concept[6].

Since then, several TCR-based therapies have advanced into clinical testing. TCRs targeting NY-ESO-1, MAGE-A4, and other cancer-testis antigens have shown promising activity across melanoma, sarcoma, and non-small cell lung cancer. In 2024, the FDA approved afamitresgene autoleucel (TECELRA), a TCR-engineered product targeting MAGE-A4 in metastatic synovial sarcoma, achieving a 43% objective response rate with a median response duration of six months[7].

Despite these successes, TCR-based ACT remains subject to important constraints, such as:

- HLA restriction, as patients must express specific HLA alleles compatible with the engineered TCR;
- Antigen escape, due to the downregulation of MHC class I expression by tumor cells to evade TCR recognition;
- TME suppression, especially by immune checkpoint ligands engagement with inhibitory receptors in T cells and the presence of suppressive cytokines, which reduce TCR signaling intensity.

Overcoming these limitations has motivated the development of synthetic, MHC-independent antigen-recognition platforms such as CARs.

CAR-T cells

CAR-T cells represent a major technological leap in ACT due to their ability to recognize antigens regardless of MHC. A CAR is composed of an extracellular antigen-binding domain, usually a single-chain variable fragment (scFv), linked to intracellular signaling motifs derived from CD3ζ and costimulatory molecules such as CD28 or 4-1BB. Upon binding its target antigen, the CAR transduces both activation and costimulatory signals, enabling robust T-cell activation.

Seven CAR-T products are currently approved by major regulatory agencies worldwide, such as FDA, European medicines agency, Health Canada, and Chinese National Medical Products Administration. Among approved products, satricabtagene autoleucel (Satri-cel) is the only CAR-T product for solid tumor treatment targeting Claudin18.2, for patients with Claudin18.2-positive, HER2-negative advanced gastric/gastroesophageal junction adenocarcinoma (G/GEJA), who have failed at least two prior lines of therapy. This cellular product was approved in June 2026 by the Chinese regulatory agency.

The latest updated data from meta-analyses regarding CAR-T cell efficacy against solid tumors are from 2019. Hou et al.[8] examined 22 clinical trials of CAR-T therapy for solid tumors (> 200 patients) and reported that fewer than 10% of patients achieved partial responses, with only 2.3% achieving complete responses. Additionally, Grigor et al.[9] evaluated 18 solid tumor CAR-T studies, finding a 4.1% complete response prevalence across eight studies (86 patients) and a 10% overall response rate across 10 studies (112 patients). These data contrast sharply with the high remission rates observed in leukemia and lymphoma and highlight the unique challenges posed by solid tumors.

However, recent data show encouraging progress for CAR-T cells against solid tumors. Notably, the phase II satri-cel trial[10] reported a 26% objective response rate (mITT, independent review) compared to physician's choice, illustrating important advancements in treating solid tumors.

Engineering solutions under investigation

Several next-generation CAR designs and manufacturing strategies have been developed to enhance efficacy in solid tumors:

- Metabolic and epigenetic reprogramming strategies, such as optimizing culture conditions to enrich for memory-like CAR-T subsets, improve expansion, persistence, and antitumor potency;
- Cytokine- and chemokine-enhanced CAR-T cells, given that CAR-T cells have been engineered to express or secrete cytokines and chemokines, as well as chemokine receptors, have demonstrated improved trafficking and enhanced TME infiltration;
- Multispecific CAR designs, like dual-target or tandem CAR constructs, may mitigate antigen escape issue by simultaneously recognizing two tumor antigens;
- Checkpoint-resistant CAR-T cells, by the knockout/knockdown of inhibitory receptors (*e.g.*, PD-1, LAG-3, and TIM-3) using CRISPR/Cas9 or other gene-editing tools has been shown to reduce exhaustion and augment antitumor activity;
- Local CAR-T delivery, as intratumoral or intracavitary administration improves local concentration of effector cells while reducing systemic toxicity.

While these innovations show potential, CAR-T therapy for solid tumors remains an evolving field, and many strategies are still in early clinical development[11].

CAR-engineered alternative immune cell types

Given the challenges of autologous CAR-T manufacturing and the limited infiltration of T cells into solid tumors, alternative immune cell platforms have gained substantial attention.

CAR-NK cells

Natural killer (NK) cells offer several advantages, such as MHC-independent tumor recognition, rapid innate cytotoxicity, low risk of graft-*versus*-host disease (GvHD), and potential for allogeneic, off-the-shelf production. Although viral transduction of NK cells can be inefficient, innovative gene-delivery strategies, such as transposon-based vectors, and coexpression of IL-15 within CAR constructs have significantly improved NK persistence, and this research field has made significant progress. A clinical trial evaluating anti-NKG2D CAR-NK cells for advanced colorectal cancer reported that two patients treated in combination with anti-PD-1 therapy survived beyond two years, suggesting that CAR-NK platforms may be particularly valuable in combination regimens (ClinicalTrials.gov ID: NCT05213195).

CAR-macrophages

Macrophages naturally infiltrate the TME and can remodel the extracellular matrix, making them attractive for solid tumor targeting. When polarized to an M1-like phenotype, macrophages support antitumor immunity

through phagocytosis, proinflammatory cytokine release, and antigen presentation. First-in-human study using HER2-targeted CAR-macrophages (CAR-M) showed that nearly half of enrolled patients achieved stable disease at eight weeks (ClinicalTrials.gov ID: NCT04660929). Additionally, CAR-M cells can recruit endogenous immune responses and convert immunologically "cold" tumors into "hot" ones.

CAR-dendritic cells

Dendritic cells (DCs) are powerful antigen-presenting cells capable of initiating both CD8+ and CD4+ T-cell responses. CAR-engineered DCs can combine tumor recognition with enhanced antigen uptake and cross-presentation. Their ability to prime endogenous T-cell responses positions them as potential amplifiers of CAR-mediated immunity. Two ongoing clinical trials (NCT05631899 and NCT05631886) have been evaluating CAR-DC combination therapies for solid tumors, reflecting the increasing interest in myeloid-based cell therapies[12].

Cellular therapy combinations for improving patients' outcomes

Different strategies combine ACT with immune checkpoint blockade (ICB), radiotherapy, and oncolytic viruses to enhance efficacy. Combining TIL/CAR-T/TCR-T cells with ICB through monoclonal antibodies (*e.g.*, anti-PD-1) administration or engineered receptor modifications for impairing inhibitory signaling may restore their function and improve tumor clearance[13]. Furthermore, radiotherapy and oncolytic viruses are attractive alternatives[14,15], as they both can induce tumor immunogenic cell death via DNA damage or by direct cell lysis, respectively, leading to the release of tumor-associated antigens, neoantigens, and damage-associated molecular patterns that stimulate dendritic cell maturation, enhancing antigen presentation, and can also activate other immune cell subtypes. Moreover, both strategies also reduce tumor burden and could eliminate remaining tumor cells that lack expression of the targeted antigen. Engineered oncolytic viruses can even carry target-coding genes and induce tumor expression of new target antigens. Currently, there is a phase I clinical trial ongoing combining CAR-T and a binary oncolytic adenovirus for the treatment of Her2+ tumors (NCT03740256).

GENERAL CONCLUSIONS AND FUTURE DIRECTIONS

While ACT has reshaped the therapeutic landscape for hematologic cancers, translating similar success to solid tumors remains a significant scientific and clinical challenge. Tumor heterogeneity, antigen escape, and the complex TME collectively limit the efficacy of current strategies. However, the rapid evolution of cellular engineering, including synthetic biology, metabolic reprogramming, multispecific targeting, and genome editing, holds considerable promise for overcoming these barriers.

Future progress will require:

- Deeper understanding of TME-induced immunosuppression;
- Development of robust preclinical models that better recapitulate human solid tumors;
- Integration of ACT with complementary platforms (*e.g.*, checkpoint blockade, oncolytic viruses, radiotherapy);
- Scalable manufacturing solutions enabling allogeneic, off-the-shelf products;
- Systematic evaluation through well-designed clinical studies.

As the field advances, next-generation cell-based therapies are poised to play an increasingly central role in the treatment of solid tumors, moving closer to durable, clinically meaningful benefits for patients who currently have limited therapeutic options.

Key points

Most clinical trials evaluating engineered T cells for solid tumors remain in early phases, reflecting ongoing biological and translational hurdles.

The TME profoundly impairs T-cell trafficking, persistence, and cytotoxic function through physical, metabolic, and immunoregulatory mechanisms.

Future progress depends on integrating preclinical insights, innovative engineering strategies, and combination therapies to overcome immunosuppressive barriers and improve clinical outcomes.

CONFLICTS OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable.

AUTHORS' CONTRIBUTIONS

Substantive scientific and intellectual contributions to the study: Furtado IP, Esteves KS and Souza LEB. **Conception and design:** Furtado IP, Esteves KS and Souza LEB. **Acquisition of data:** Furtado IP, Esteves KS and Souza LEB. **Manuscript preparation:** Furtado IP, Esteves KS and Souza LEB. **Manuscript writing:** Furtado IP, Esteves KS and Souza LEB. **Critical revision:** Furtado IP, Esteves KS and Souza LEB. **Final approval:** Furtado IP, Esteves KS and Souza LEB.

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