**Review**

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# The Efficacy of Chimeric Antigen Therapy in Viral Infectious Diseases: A Systematic Review of Randomized Controlled Trials

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**Abstract**

Infectious diseases are among the most important global health problems, and their burden on society is wide. It is shown that chimeric antigen receptor (CAR) T-cell therapy can fight viral infectious diseases in many aspects. This systematic review investigated the efficacy of CAR T-cell therapy against viral infections. A comprehensive literature search was conducted in Medline, Scopus, Cochrane Central Library, and Embase up to May 2024. Keywords such as CAR T-cell therapy, viral, virus, and infection were used to identify relevant studies. In the identification stage, a comprehensive search across databases, including Medline, Scopus, Cochrane Central Library, and Embase, identified 12183 papers. Finally, 7 articles with total of 134 individuals were examined. Three studies investigated the efficacy of CAR T-cell therapy against human immunodeficiency virus (HIV), hepatitis B virus (HBV), and cytomegalovirus (CMV). The primary objectives of these trials were to assess the safety and feasibility of adoptive transfer of CAR T-cells in patients with viral infections. The aforementioned results demonstrate the efficacy of CAR T-cell therapy in targeting viral antigens and inhibiting viral replication, providing possible treatment options for long-term infectious illnesses like HIV, HBV, and CMV. These findings show the efficacy of CAR T-cell therapy in infectious diseases, but the data are limited. To maximize the efficacy of CAR T-cell therapy and clarify its long-term effectiveness in the treatment of infectious diseases, more investigation and clinical studies are required.

**Keywords:** Chimeric antigen therapy, viral infectious diseases, hepatitis

## Introduction

Infectious diseases are among the most important global health problems, and their burden on society is wide-ranging and complex. Infectious diseases can affect all ages, including children, the elderly, immunosuppressed individuals, and pregnant women (1). These diseases can be the main cause of other diseases, such as cardiovascular, respiratory, and clinical diseases (2). Because of these harmful effects, prevention, diagnosis, and management of infectious diseases are vital. The use of vaccines, compliance with public health standards, infection control, early diagnosis, and effective treatment can help eliminate the burden of these diseases on communities. Chimeric antigen receptor (CAR) T-cell therapy is a cutting-edge immunotherapy strategy that involves genetically engineering a patient's T-cells with a CAR. This engineered receptor enables T-cells to specifically target and eradicate cancer cells, as well as cells involved in immune-related diseases. This process involves extracting T-cells, genetically modifying them to express CAR, and then injecting engineered cells into the patient. This innovative treatment has shown significant success, especially in blood malignancies such as B-cell lymphoma and leukemia. CAR T-cells are designed to recognize specific molecules on the surface of cancer cells, offering a precise and targeted treatment approach (3).

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The challenges associated with the development of novel antiviral agents and the increasing significance of chronic viral infections within immunocompromised patient populations have redirected attention toward immunotherapy, drawing inspiration from the exceptional outcomes achieved in the field of oncology. In particular, CAR T-cell based therapies have emerged as a promising strategy for the treatment of infections. This review systematically examines the principal findings derived from clinical investigations that substantiate this potential, with a particular emphasis on CAR T-cells.

## Material and Methods

The present study aimed to explore the efficacy of CAR T-cell therapy against viral infections. The search strategy, screening, and data selection were all checklist-based. The Preferred Reporting Items for Systematic Reviews and Meta-analysis were also followed. The protocol for this systematic review has been submitted to Prospero (583352).

### Search Strategy

A comprehensive search was conducted in May 2024 in Medline, Scopus, Central Cochrane, and Embase. Keywords such as chimeric antigen receptor, CAR-T, T-cell therapy, viral, virus, and infection were used to identify relevant studies. The search strategy is summarized in Table 1. After eliminating duplicate entries, articles were screened based on their titles and abstracts. Only studies that met the established inclusion criteria were selected for further analysis.

### Inclusion and Exclusion Criteria

The inclusion criteria were as follows: 1) Studies investigating CAR-T in Epstein-Barr virus (EBV), cytomegalovirus (CMV), hepatitis B virus (HBV), or human immunodeficiency virus (HIV) infections. 2) Studies reporting outcomes such as viral load reduction, treatment efficacy, safety profile, and side effects. 3) Articles published in English. 4) Studies with available full-text articles. 5) Studies on adult population.

Exclusion criteria: 1) Studies that are not directly related to CAR-T in viral infections. 2) Studies that do not report relevant outcomes or lack sufficient data. 3) Non-English publications. 4) Observational studies. 5) Articles that were different from the majority of used articles in terms of materials and methods.

### Quality Assessment

The Cochrane risk of bias assessment tool (ROB-2) was used to assess the potential for bias in the selected studies. Two authors assessed the study quality, and in terms of disagreement, it was resolved by consensus and the opinion of the corresponding author.

### Data Extraction

We extracted the following data from the included articles: first authors' names, country of study, date of publication, pathogen, sample size, age of participants, male/female ratio, cell, method, target, receptor, and outcomes. The data extraction process was performed by two independent authors, and any differences were discussed.

**Table 1.** Search Strategy for the Pubmed, Scopus, Embase, and Cochrane Central Library databases

| Database | Search strategy | Date/results |
|---|---|---|
| Pubmed | ["Receptors, chimeric antigen" (mesh) or "chimeric antigen receptor*" (title/abstract) or "CAR-T" (title/abstract) or "T-cell therapy" (title/abstract)] and [viral (title/abstract) or virus (title/abstract) or "infecti*"(title/abstract)] | May 2024<br>2371 results |
| Scopus | Title-abstract-keywords (CAR-T or "chimeric antigen receptor*" or "T-cell therapy") and Title-abstract-keywords (virus or viral or infecti*) | May 2024<br>5890 results |
| Cochrane Central Library | #1: Chimeric antigen receptor (title)<br>#2: T-cell (title)<br>#3: CAR-T (title)<br>#4: virus (title)<br>#5: viral (title)<br>#6: infection (title)<br>#7: infectious (title)<br>#8: #1 or #2 or #3<br>#9: 4 or #5, or #6, or #7<br>#10: #9 and #8 | May 2024<br>1704 results |
| Embase | ("Chimeric antigen receptor"/exp. or "CAR-T": abstract, title) and [(virus or viral) near/5 (infection or infectious)]: abstract, title) | May 2024<br>2218 results |

CAR-T: Chimeric antigen receptor T-cell therapy

## Results

An initial search of several databases, including Medline, Cochrane Central Library, Embase, and Scopus, yielded 12,183 articles. After eliminating duplicates, 9,242 duplicates were retained. After examining the titles and summaries, 9,196 articles were determined to be irrelevant, leaving 46 potential candidates for full-text evaluation. After thorough examination of the full texts, 7 articles were deemed eligible for inclusion in the meta-analysis (Figure 1).

Seven clinical studies were conducted between 2000 and 2024 to evaluate the effectiveness and safety of CAR T-cell therapy for treating viral infections such as HIV (4-7), HBV (8,9), and CMV (10). A total of 134 patients participated in the study. Three of the trials used first-generation CARs that included the extracellular domain of human CD4 to target the viral envelope glycoprotein-120 (gp-120) found on infected cells. The other trials featured a fourth-generation CAR design, which consisted of a single-chain variable fragment (scFv) targeting gp-120, connected to the CD3ζ chain along with the CD28 and 4-1BB co-stimulatory domains. Additionally, two trials have incorporated the T-cell receptor (TCR). CARs were engineered into T-cells using lentiviral or retroviral transduction methods, except for one study that employed mRNA electroporation. The main goals of these trials were to evaluate the safety and feasibility of CAR T-cell therapy in patients with viral infections. A comprehensive overview of each study is presented in Table 2.

Upon assessing the quality of the studies, none exhibited high risk of bias. While most studies had some minor concerns, one study was found to have a low risk of bias (Figure 2).

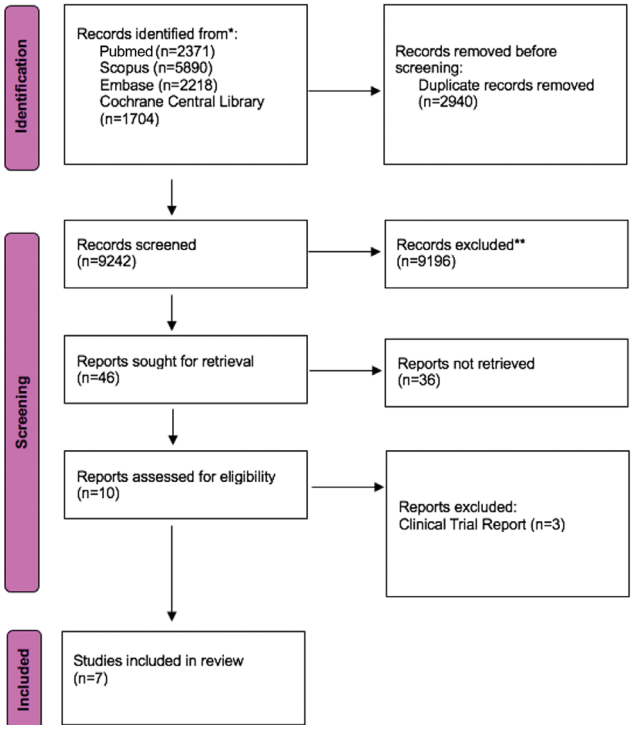


**Figure 1.** Study flow diagram.

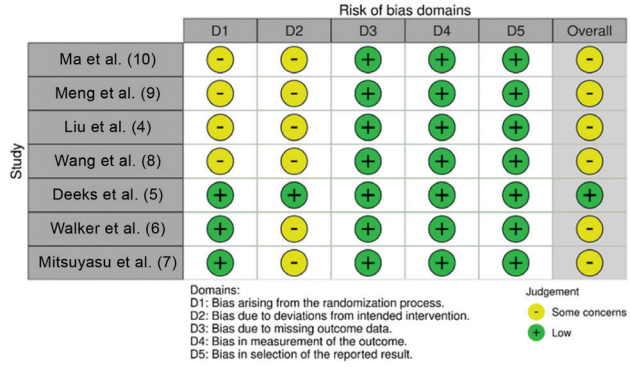


**Figure 2.** Quality assessment of included studies.

**Table 2.** Characteristics of included studies

| Authors' references | Year | Country | Pathogen | Participants | | | Intervention | | | | | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Number | Age | Male/ female | Cell | Method | Target | Receptor | Dose | |
| Ma et al. (10) | 2024 | China | CMV | 6 | 18-60 | NR | T-cells | Lentiviral transduction | CMV-specific TCRs | CD4 and CD8 | 1-3 doses (1×103 cells/ kg to 5×105 cells/kg) | Effective treatment of CMV reactivation in most patients, with minimal adverse events and long-term persistence, even in the presence of anti-GVHD therapy |
| Meng et al. (9) | 2021 | China | HBV | 8 | 53.5 (46-67) | 5/0 | T-cells | mRNA Electroporation | HBV-specific TCRs (TCR-A02/HBs or TCR-C08/HBs) | CD8 | Multiple doses ($1\times10^4$–$5\times10^6$ cells/ kg and $5\times10^6$ cells /kg) | Decreased and stabilized the circulating HBsAg and HBV DNA concentrations |
| Liu et al. (4) | 2021 | China | HIV | 14 | 31 (26-47) | 14/0 | T-cells | Lentiviral transduction | gp120 | scFv | Single dose ($5.00\times10^7$ to $1.00\times10^8$) | Decreased cell-associated viral RNA and intact proviruses |
| Wang et al. (8) | 2020 | China | HBV | 12 | 53 (33-69) | 9/3 | T-cells | Lentiviral transduction | CD19 | scFv | Single dose ($10^6$ cells /kg) | Chronic and resolved HBV infection did not significantly affect the safety or efficacy of CAR T-cell therapy, with similar responses, cytokine release syndrome, and neurologic toxicity observed across all cohorts |
| Deeks et al. (5) | 2002 | USA | HIV | 40 | 41 | 40/0 | T-cells | Retroviral transduction | gp120 | CD4 | 3 doses (Total of $3\times10^{10}$) | Decreased HIV burden in certain reservoir assays and a trend toward fewer recurrent viremia events |
| Walker et al. (6) | 2000 | USA | HIV | 30 | NR | NR | T-cells | Retroviral transduction | gp120 | CD4 | Single dose ($10^7$, $10^8$, $10^9$, or $10^{10}$) | Adoptive transfer of genetically modified HIV-antigen-specific T-cells was safe and well-tolerated, with sustained survival of both $CD4^+$ and $CD8^+$ T-cells observed after co-stimulation |
| Mitsuyasu et al. (7) | 2000 | USA | HIV | 24 | 40 | 21/3 | T-cells | Retroviral transduction | gp120 | CD4 | Single dose (2 to $3\times10^{10}$) | Gene-modified T-cells expressing CD4ζ demonstrated sustained persistence in the blood and rectal tissue of HIV-infected adults, leading to a significant reduction in rectal HIV RNA levels, suggesting the potential of *ex vivo* T-cell gene therapy as a promising approach for HIV treatment |

NR: No result, CMV: Cytomegalovirus, TCRs: T-cell receptors, GVHD: Graft-versus-host disease, HBV: Hepatitis B virus, HBsAg: Hepatitis B surface antigen, HIV: Human immunodeficiency virus, Gp120: Glycoprotein-120, ScFv: Single-chain variable fragment

## Discussion

By utilizing the application of T-cells that have been genetically altered to identify and eradicate contaminated cells, CAR T-cells have emerged as a potentially efficient means of battling infectious disorders. The aforementioned results demonstrate the efficacy of CAR-T in targeting viral antigens and inhibiting viral replication, providing possible treatment options for long-term infectious illnesses like HIV, HBV, and CMV. Our meta-analysis showed that CAR-T is a useful approach for treating infectious diseases such as HIV, HBV, and CMV.

### HIV

HIV was first recognized in 1984, following unusual and deadly pneumonia cases in men. Since then, millions have contracted the virus across both low- and high-income nations. HIV is a retrovirus that spreads through unprotected sexual intercourse, mother-to-child transmission, or through contaminated needles. The virus causes long-term immunosuppression by reducing $CD4^+$ T lymphocyte counts, which triggers a series of opportunistic infections (11).

Due to the need for lifelong antiretroviral therapy (ART) to maintain stable plasma viremia suppression, HIV infection has become a common focus of CAR T-cell therapy. The virus targets multiple cell types using the viral envelope gp-120, leading to various immunosuppressive mechanisms, such as the destruction of $CD4^+$ T-cells and the downregulation of major histocompatibility complex (MHC) expression in infected cells (12). These immunological perturbations have justified the significant interest in developing CAR-T therapies for HIV infection.

Initial studies on CAR-T therapy for HIV began in the 1990s, typically alongside ART. While preclinical research has shown encouraging early outcomes, later clinical trials have indicated only a limited effect on the persistence of the virus (7,13-15). Two main structural designs have been used to create anti-HIV CAR T-cells: CD4 receptors and broadly neutralizing antibodies that target the gp-120 protein, which are capable of neutralizing most circulating strains of HIV (16).

Between 2000 and 2002, three clinical studies were conducted to assess the efficacy of CD4ζ CAR T-cells in patients with active HIV viremia. The CD4ζ CAR method included the extracellular domain of human CD4 attached to the zeta chain and was expressed in T-cells. In 2000, two clinical trials were published, each enrolling a separate cohort of patients (6,7). One trial included 30 patients with HIV infection who received autologous CD4ζ-modified T-cells, while the other trial involved 24 patients who received syngeneic CD4ζ-modified T-cells from their identical twins (6,7). In 2002, a phase II clinical 40 patients with HIV receiving ART were randomized to receive either HIV-specific $CD4^+$ and $CD8^+$ CAR T-cells or unaltered T-cells. During the initial 24 weeks following infusion, a lower frequency of viral rebounds (viral blips or relapses) was observed in the CAR T-cell group (5). However, this trend did not continue over time. The results showed that gene-modified T-cells were safe and could survive long-term in the bloodstream. However, they did not observe any notable reduction in HIV levels in the blood or tissue reservoirs (5).

The restricted control of viral replication noted in earlier clinical trials using first-generation CAR T-cells, which lack co-stimulatory domains, may be due to the absence of these critical signaling molecules. In 2021, a clinical trial involving 14 patients was published that utilized a second-generation CAR design that integrated a high-affinity scFv linked with CD28 and 4-1BB co-stimulatory domains (4).

### HBV

HBV infection remains a significant global health burden, with limited treatment options. Recent advancements in immunotherapy, particularly CAR T-cell therapy, have shown promise in targeting and eliminating cancer cells. Given the similarities between cancer and virus-infected cells, CAR T-cells have emerged as a potential therapeutic strategy against HBV infection (11).

Multiple studies have explored the potential of CAR T-cells to target HBV-infected hepatocytes. A key focus for CAR T-cell development is the hepatitis B surface antigen (HBsAg), which is expressed on the surface of infected cells. Meng et al. (9) demonstrated that TCR cells engineered to recognize HBsAg could effectively target and kill HBV-infected hepatocytes. However, Wang et al. (8) did not find any difference in CAR-T efficacy between patients with chronic and resolved HBV infection. Therefore, further clinical studies are required to provide robust evidence of the potential of CAR T-cell therapy in combating HBV infection.

### CMV

CMV is a common pathogen that poses a significant risk to immunocompromised individuals. It can cause various organ-specific diseases and suppress the immune system, leading to additional infections. CMV is linked to transplant rejection and graft-versus-host disease (GVHD). Therefore, managing CMV viremia in solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) recipients is critical to prevent severe complications. Although antiviral drugs like ganciclovir and retrovir are used to treat CMV, their effectiveness is limited by drug resistance and potential side effects. Similar to other herpesviruses, CMV can escape T-cell immune responses by downregulating the expression of MHC molecules (17).

Adoptive cell therapy using CMV-specific T-cells has been extensively studied in patients undergoing HSCT. However, limitations such as the availability of compatible T-cell donors and insufficient research on SOT patients have hindered its widespread application (17-19). To address these challenges, researchers have explored the potential of CAR T-cells to prevent CMV infection. Preclinical studies in *in vitro* and humanized mouse models have demonstrated promising results for various CMV CAR T-cell therapies (20). Glycoprotein B, a crucial protein in the CMV envelope, has emerged as a key target for CAR T-cell therapy. A scFv-targeting glycoprotein B linked to CD28 and CD3ζ domains, has been successfully used to generate CAR T-cells. These cells exhibit high expression and functionality, as evidenced by cytokine production and degranulation (21). A recent study by Ma et al. (10) showed that TCRs effectively treated CMV reactivation in most patients, with minimal adverse events and long-term persistence, even in the presence of anti-GVHD therapy. Early studies highlighted a challenge in which CMV-infected cells showed resistance to being killed by CAR T-cells, even though there was significant degranulation. This resistance was linked to the expression of anti-apoptotic factors produced by CMV (22).

**Other Viral Infections**

**Coronavirus**

The coronavirus disease-19 (COVID-19) pandemic has had profound impact on CAR T-cell therapy, affecting both clinical trials and standard care practices. Early studies conducted during the pre-Omicron and pre-vaccination phases identified patients undergoing CAR T-cell therapy as one of the most vulnerable populations, with high risks of severe illness, prolonged infections, and mortality rates reaching up to 50% (23,24). Mathematical models have been developed to analyze the interactions between the virus, CAR T-cells, and memory cells, with theoretical findings indicating that CAR T-cells can delay viral replication. This delay is especially advantageous in the early stages of infection, suggesting a promising therapeutic role for CAR T-cells in the antiviral treatment of COVID-19 (25).

Since these initial reports, several key developments have occurred, including widespread population vaccination, the introduction of new COVID-19 therapies, and the emergence of novel SARS-CoV-2 variants. These factors likely contributed to the reduced mortality rates observed in patients with lymphoid malignancies and those undergoing allogeneic hematopoietic cell transplantation (4.5-7%) (26-28). A cohort study of 64 CAR T-cell recipients in 2022 that examined the impact of COVID-19 vaccination and monoclonal antibody use reported a COVID-19 specific mortality rate of 13% (29). In a retrospective analysis of 75 pediatric and young adult CAR T-cell therapy recipients, the mortality rate was 4.3% (30). Additionally, SARS-CoV-2 hospitalization rates were nearly 10-fold higher in the pre-Omicron period (40.4%) that of the Omicron period (4.3%), with 95.7% of patients experiencing asymptomatic or mild infections during the Omicron era (30). The largest cohort study of CAR T-cell recipients with SARS-CoV-2 infection revealed a substantial decline in COVID-19 related mortality over time (31). The COVID-19-attributable mortality rate decreased from 43.6% at the onset of the pandemic to 7.5% in 2022 (during the Omicron period) (31). Additionally, there was a marked reduction in the severity of COVID-19, as fewer patients experienced lower respiratory symptoms, required oxygen therapy, or needed hospitalization or intensive care unit care. Among the general population, advancing age has remained one of the most significant factors associated with poorer COVID-19 outcomes (32).

Despite these promising developments, the evidence remains evolving, and gaps remain in the understanding of the optimal integration of CAR T-cell therapy for COVID-19. Future clinical trials are essential to evaluate the safety, efficacy, and mechanisms of CAR T-cell therapy in the management of SARS-CoV-2 infections. These studies should also explore personalized approaches based on age, comorbidities, and vaccination status to maximize therapeutic benefits while minimizing risks.

**EBV**

EBV, a widely prevalent member of the gamma herpesvirus family, is linked to various lymphomas and lymphoproliferative disorders (LPDs), infecting over 90% of adults globally (33). EBV-associated post-transplant lymphoproliferative disease (PTLD) occurs in 1-25% of HSCT recipients, with its incidence influenced by donor and recipient serostatus, the extent of T-cell depletion in the graft, and the level of post-transplant immunosuppression (34).

EBV-LPDs express several B-cell antigens, such as CD19, CD20, and CD30, which are potential targets for CAR T-cell therapy. However, their application in treating EBV-associated LPDs is challenging because of the immunosuppressed state of patients, which hinders T-cell production, and the prolonged time required for CAR T-cell manufacturing. CD19-directed CAR T-cell therapy has been used in three adult SOT recipients with refractory PTLD (35). However, all patients experienced significant complications, including cytokine-release syndrome, neurotoxicity, and acute kidney injury, with none achieving a positive response. Ultimately, all three patients succumbed to their illness (35,36). Nikolaenko et al. (37) retrospectively analyzed patients with EBV-positive

diffuse large B-cell lymphoma, not otherwise specified [EBV+ diffuse large B-cell lymphoma (DLBCL), nitric oxide synthase (NOS)], treated with CAR T-cell therapy. Although the sample size was limited, the findings suggest that CAR T-cell therapy is effective for EBV+ DLBCL and NOS, with response rates comparable to those reported in the literature for other aggressive B-cell lymphoma subtypes. Notably, responses were more favorable when the EBV viral load was undetectable during CAR T-cell therapy. However, the study also revealed a significantly higher incidence of grade 3 immune effector cell-associated neurotoxicity syndrome in patients with EBV+ DLBCL, NOS. These outcomes suggest that although there are anecdotal reports of CAR T-cell therapy for PTLD, the broader application of this approach may depend on the development of an off-the-shelf CAR T-cell product.

The potential of CAR-T as a flexible and successful tactic for treating a range of infectious disorders is highlighted by our findings, which opens new possibilities for the creation of individualized and tailored medical interventions. To fully understand the therapeutic benefits of CAR-T and address issues like off-target consequences and long-term efficacy, more clinical studies and design optimization are necessary.

## Conclusion

Antiviral therapies have significantly extended lifespans in recent decades. The escalating complexity of pathogen resistance, the appearance of emerging pathogens, and the international spread of infectious diseases underscore the urgent need for new therapeutic solutions. In this regard, the progress made in innovative immunotherapies, such as CAR T-cell therapy, which has shown exceptional success in treating cancer, should be leveraged to combat viral infections. CAR T-cell therapy, a revolutionary cancer immunotherapy, involves genetically engineering a patient's T-cells with a CAR to specifically target and destroy cancer cells. The use of this cutting-edge therapy has demonstrated considerable potential, especially for blood cancers such as B-cell lymphoma and leukemia.

While preclinical research has shown the beneficial effects of CAR T-cell therapy for various infections, further research is warranted to confirm its suitability for clinical application in treating viral diseases. The potential application of CAR T-cell therapy in infectious disease treatment is a promising avenue that warrants exploration and additional investigation.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: H.H., Concept: H.H., Design: H.G., Data Collection or Processing: E.A., Analysis or Interpretation: M.N., Literature Search: E.A., Writing: H.G.

**Conflict of Interest:** No conflict of interest was declared by the author.

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