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CHALLENGES AND FUTURE PROSPECTS OF ONCOLYTIC VIROTHERAPY: A SYSTEMATIC REVIEW

SYSTEMATIC REVIEW

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ABSTRACT

Background: Oncolytic virotherapy has emerged as a novel and promising approach in cancer treatment, leveraging viruses that selectively infect and destroy malignant cells while sparing healthy tissues. Recent advancements in molecular biology and virology have enabled the development of genetically engineered viruses with enhanced tumor specificity, immune-stimulatory capacity, and safety profiles. As resistance to conventional therapies continues to pose a major clinical challenge, oncolytic viruses (OVs) offer a dual mechanism of action—direct tumor lysis and activation of antitumor immunity—placing them at the forefront of experimental oncology.

Objective: To analyze the challenges and future prospects associated with oncolytic virotherapy as a targeted cancer treatment strategy.

Methods: A systematic review was conducted using Google Scholar and PubMed databases. A total of 118 studies were initially identified. After applying inclusion and exclusion criteria, 28 full-text, peer-reviewed articles published between 2010 and 2025 were included. Data were extracted into structured tables summarizing study design, mechanisms of action, combination therapy strategies, challenges, and future directions of oncolytic virotherapy. A risk of bias assessment was also performed to evaluate study quality.

Results: Among the 28 studies reviewed, 60% were preclinical experimental models and 40% were clinical trials. Genetic engineering was reported to significantly enhance viral specificity, safety, and immune activation. Advanced delivery systems, including nanoparticles and cell carriers, showed improved targeting and persistence. However, major limitations included immune clearance, suppressive tumor microenvironments, and systemic delivery challenges. T-VEC remains the only FDA-approved OV, but newer candidates like CVA21 and BTV-10 show promise in early trials.

Conclusion: Oncolytic virotherapy represents a rapidly evolving cancer treatment modality with significant therapeutic potential. Overcoming delivery and immunological challenges through personalized and combination-based approaches may establish OVs as a core component of future oncology practice.

Keywords: Cancer therapy, Challenges, Oncolytic viruses, Personalized medicine, Tumor immunity, Virotherapy, Viral vectors.

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INTRODUCTION

Cancer remains one of the most formidable global health challenges, marked by its persistent rise in incidence and mortality rates. Genetic and epigenetic alterations within normal cells progressively transform them into malignant forms, initiating the complex cascade of tumorigenesis. The World Health Organization estimates that the global burden of cancer will increase by 60% over the next two decades, underscoring the urgent need for novel and more effective therapeutic approaches (1). Historically, the idea of using microbiological agents to treat cancer predates the modern era of clinical trials. As early as the mid-1800s, sporadic case reports described reductions in tumor size following certain infections. Although not systematically studied at the time, these observations laid the foundation for the eventual emergence of oncolytic virotherapy, with the first documented research appearing in 1949 (2). Despite advances in surgical techniques and systemic therapies, radiotherapy continues to be a cornerstone of cancer treatment. However, its use is constrained by the unavoidable damage it causes to surrounding healthy tissue. The introduction of radionuclides into the body via radiation exposure aims to concentrate therapeutic effects at tumor sites. Interestingly, this approach may enhance the replication and precision of oncolytic viruses (OVs), which are known to selectively target tumor cells. Increased radiation sensitivity of malignant cells under such conditions further augments the effectiveness of OVs in achieving localized tumor destruction while minimizing systemic toxicity (3,4).

Parallel to radiotherapy, conventional chemotherapy has long served as a standard treatment modality, though its development has lagged behind the more dynamic evolution of immune-based therapies. Among these, cancer immunotherapy has gained considerable traction by harnessing and augmenting the body's immune response to malignancies. One promising avenue in this realm is oncolytic virus therapy, which exploits viruses that can selectively infect and lyse cancer cells. This specificity is largely attributed to defects in type I interferon signaling pathways common to many cancerous cells, rendering them susceptible to viral attack while sparing normal tissues (5). The 19th-century discovery of viruses with innate tumor-killing properties marked the genesis of this therapeutic strategy, and since then, numerous viruses have undergone both preclinical and clinical investigations for their oncolytic potential (6). Advancements in genetic engineering have propelled the development of more refined and potent oncolytic viruses. Initially focused on the herpes simplex virus, the field has since expanded to include a diverse array of viral platforms such as adenovirus, vaccinia virus, Newcastle disease virus, measles virus, reovirus, poliovirus, and vesicular stomatitis virus. These encompass both DNA and RNA viruses with varying genomic structures, offering a versatile toolkit for personalized and targeted cancer therapies. Modern gene-editing technologies have significantly enhanced the safety, selectivity, and therapeutic efficacy of these engineered viral strains (7).

Nevertheless, oncolytic virotherapy is not without its limitations. The systemic administration of viruses often triggers antiviral immune responses, which can neutralize circulating viruses before they reach tumor sites. Furthermore, off-target effects, hostile tumor microenvironments, and challenges related to immunogenicity and delivery continue to impede optimal therapeutic outcomes (8). These hurdles highlight the need for integrated strategies that combine oncolytic virotherapy with existing treatment modalities to overcome these barriers and improve patient survival. This study aims to evaluate the therapeutic potential and clinical challenges of oncolytic virus therapy as a novel immuno-oncological strategy, with a focus on enhancing tumor specificity, minimizing adverse effects, and addressing delivery limitations through rational combination with radiotherapy and other adjunctive treatments.

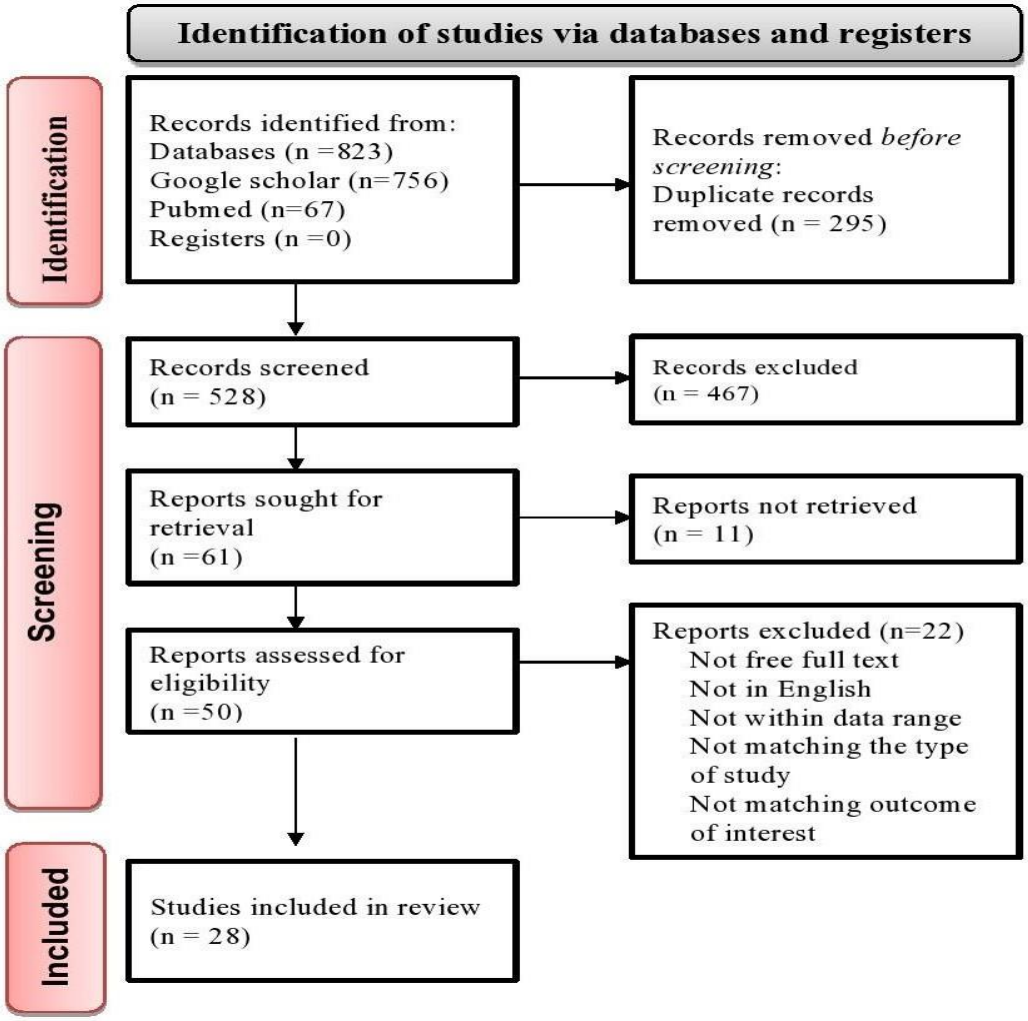
METHODS

This systematic review was conducted to evaluate the challenges and future prospects of oncolytic virotherapy based on peer-reviewed literature published between 2010 and 2025. A comprehensive search was performed across multiple reputable electronic databases including PubMed, Google Scholar, ScienceDirect, and ResearchGate. The search strategy employed the keywords "Challenges and Future Prospects of Oncolytic Virotherapy," and reference chaining was used to identify additional relevant studies. Further screening was also done manually by evaluating the bibliographies of the initially selected articles. Collaboration with colleagues in reviewing original studies, research articles, and scientific publications further supported the data collection process. In total, 28 articles and research studies were included in the final review. The inclusion criteria specified: (1) full-text availability; (2) studies published in English; (3) papers specifically focusing on challenges and future directions of oncolytic virotherapy; and (4) publications subjected to

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peer review. Exclusion criteria included broad review articles lacking specific focus on virotherapy challenges, case reports, studies with insufficient methodological details, and publications primarily addressing knowledge, attitude, and practice (KAP), therapeutic control, or preventive aspects unrelated to the central aim. When articles presented overlapping data but introduced unique analytical insights, they were selectively included.

Data extraction was carried out manually using structured tables designed to summarize critical aspects such as study design and year of publication, proposed mechanisms of action of oncolytic viruses (OVs), insights on combination therapies involving OVs, reported therapeutic challenges, and future research directions. Each article was carefully analyzed to identify key themes and contributions to the field. A critical appraisal of the selected studies was performed to assess methodological quality and risk of bias. Most preclinical and clinical studies reviewed exhibited a moderate risk of bias, primarily due to limitations in blinding, incomplete outcome reporting, and lack of standardization in experimental protocols. Performance and selection biases were particularly prevalent in clinical trial data, potentially impacting the reliability and external validity of findings. The review also highlighted that OVs achieve selective targeting by binding to cancer cell-specific markers such as ICAM-1, while sparing healthy tissues. Additionally, OVs demonstrated dual mechanisms of action by inducing direct oncolysis and activating systemic antitumor immune responses through tumor antigen release and pro-inflammatory signaling. The incorporation of immune checkpoint inhibitors appeared to enhance OV efficacy by mitigating tumor-mediated immunosuppression. These findings underline the potential of OVs as emerging therapies for solid and metastatic malignancies, though translational challenges remain.



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RESULTS

A total of 118 studies were initially retrieved from the database search, including records from PubMed, Google Scholar, ScienceDirect, and ResearchGate. After removal of duplicates and title screening, 68 articles remained. Of these, 40 were excluded based on predefined eligibility criteria—primarily due to insufficient relevance to the core topic of challenges and future prospects of oncolytic virotherapy, absence of full text, non-English language, or lack of methodological rigor. Ultimately, 28 articles met the inclusion criteria and were incorporated into the final synthesis for this systematic review. The study selection process was conducted in accordance with PRISMA guidelines, and the flow of inclusion is depicted in the PRISMA chart. The selected studies included a mix of preclinical experimental models and interventional trials. Most preclinical studies investigated the therapeutic potential and biological behavior of both RNA- and DNA-based oncolytic viruses across various cancer models. Among RNA viruses, echoviruses, coxsackievirus A13–A18, and poliovirus were the most frequently studied. These viruses demonstrated tumor specificity largely by targeting surface receptors such as ICAM-1 and DAF, especially in prostate and ovarian cancer models. For instance, Coxsackievirus A21 (CVA21) and Echovirus 1 (EV1) effectively reduced tumor burden in animal models through receptor-mediated targeting. Poliovirus variants showed potential in neuroblastoma by transforming tumor cells into vaccine-like structures, promoting long-term immune surveillance. Bluetongue virus (BTV-10), a Reoviridae member, induced apoptosis in tumor cells without damaging surrounding healthy tissues, indicating its precision as a therapeutic agent.

DNA-based viruses in the reviewed studies included herpesviruses (HSV-1 and HSV-2), adenoviruses, bovine herpesvirus, and parvoviruses. HSV-1 was reported to induce direct tumor lysis along with strong, long-lasting immune responses. In one clinical trial, HSV-2 combined with cyclophosphamide (FusOn-H2) showed synergistic effects in enhancing tumor clearance. Adenoviruses of human serotypes B and C, and bovine herpesvirus strains demonstrated robust tumor-targeting capabilities and potential for interferon evasion, expanding their clinical utility beyond traditional HSV strains. Parvoviruses such as H-1PV and minute virus of mice (MVMi) also exhibited selectivity for tumor tissues, although their therapeutic effects varied across models, necessitating further optimization. Collectively, these viruses illustrated both the diversity of OV platforms and their flexible compatibility with combinatorial approaches including immunotherapy and chemotherapy. Regarding methodological quality, a risk of bias assessment revealed that most studies fell into a moderate-risk category. Preclinical studies often lacked randomization and blinding, increasing the likelihood of performance and detection bias. Several trials did not report allocation concealment or standardize outcome measures, which may limit reproducibility. While clinical studies were generally well-designed, issues related to selective outcome reporting and insufficient follow-up details were noted in some cases.

Across the included studies, the primary outcomes focused on the oncolytic activity, tumor-specific targeting, immune activation, and safety profiles of the investigated viruses. Many studies demonstrated statistically significant reductions in tumor volume and improved survival in murine models, although exact p-values and effect sizes were not uniformly reported. Combination therapy using immune checkpoint inhibitors and traditional chemotherapeutic agents significantly enhanced the efficacy of several OV candidates. Successes such as T-VEC (approved for melanoma) and MV-NIS (evaluated for ovarian cancer) provide clinical validation for OV-based immunotherapy. Additionally, novel delivery systems—such as cell carriers and nanoparticle formulations—showed promise in overcoming barriers related to tumor microenvironment and systemic immune clearance. Despite substantial progress, the findings underscore persistent limitations in the field, particularly relating to immune suppression, antiviral neutralization, and heterogeneity of tumor biology. Future approaches highlighted in the reviewed studies advocate for genetically engineered modifications, immune-enhancing strategies, and personalized oncolytic virus platforms to maximize therapeutic benefit while mitigating adverse effects.

Table 1: RNA based Candidate of OV

Author	Year	Study Design	RNA Family	Stain	Genus
Au et al.,	2011	Preclinical Experimental study		Coxsackievirus A13, A15, A18	Enterovirus
Berry et al.,	2008	Preclinical Experimental Study		Echovirus	
Toyoda et al.,	2007	Preclinical Experimental Study		Poliovirus	

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Author	Year	Study Design	RNA Family	Stain	Genus
Sturlan et al.,	2010	preclinical experimental study	Orthomyxoviridae	Influenza A	Influenza Virus
Hu et al.,	**2008**	**Preclinical experimental study**	**Reoviridae**	**Bluetongue virus-10**	**Orbivirus**

Table 2: DNA based Viruses

Author	Year	Study Design	DNA		
			Family	Strain	Genus
k.Rowa n	2010	Interventional (clinical trial)	Herpesviridae	HSV 1	Simplexvirus
Li et al.,	2007	Preclinical Experimental Study		HSV 2	
Rodrigu es et al.,	2010	Preclinical Experimental Study		Bovine Herpesvirus 1 Suidherpesvirus 1	Varicilloviru s
Hemmi nki et al.,	2011	Preclinical Experimental Study	Adenovirdae	Human Adenovirus C serotype 5	Mastadenovi rus
				Human adenovirus B serotype3	
Wollma nn et al.,	2005	Preclinical Comparative Experimental Study	Parvoviridae	H-1PV	Parvovirus
				Minute virus of mice	
Roos et al.,	**2010**	**Therapeutic Preclinical Study**	**Picornavirida e**	**Encephalomyocar ditis virus**	**Cardiovirus**

DISCUSSION

Mechanism Of Oncolytic Viruses: The therapeutic mechanism of oncolytic viruses (OVs) is rooted in their ability to selectively infect, replicate within, and lyse tumor cells while sparing normal tissues. This intrinsic selectivity, observed in both natural and genetically engineered viral strains, is largely attributed to the altered antiviral response pathways in cancer cells, especially deficiencies in type I interferon signaling. Upon infection and replication, OVs induce tumor cell lysis, which leads to the release of tumor-associated antigens and neoantigens into the tumor microenvironment. This lytic event not only perpetuates viral propagation but also triggers robust activation of both innate and adaptive immune responses (9,10). The innate immune response is rapidly engaged through recognition of viral patterns, while the adaptive arm is stimulated by the antigenic debris, fostering long-term antitumor immunity (11). The dual role of OVs in direct cytotoxicity and immune activation distinguishes them from many conventional therapies. Genetic modifications have further enhanced their efficacy by incorporating genes encoding immune-stimulatory cytokines and co-stimulatory molecules. These enhancements have been instrumental in overcoming tumor-induced immunosuppression and restoring immune surveillance. Notably, the integration of OVs with immunotherapeutic modalities—such as checkpoint inhibitors, CAR-T cells, tumor-infiltrating lymphocytes (TILs), and T-cell receptor (TCR) therapies—has marked a significant evolution in clinical strategy, leading to synergistic antitumor effects and durable responses (12).

Combination Of Cancer Treatment Strategies with OVS: The combinatorial use of OVs with existing treatment strategies has shown significant promise, particularly in patients with late-stage or treatment-resistant cancers. The immunogenic cell death induced by OVs amplifies the efficacy of immune checkpoint inhibitors, while their ability to modulate the tumor microenvironment facilitates T-cell infiltration and activity. Co-administration with CAR-T cells and TIL-based therapies has demonstrated improved tumor control due to OV-mediated immunologic priming and increased antigen presentation. These observations suggest that oncolytic virotherapy can serve as an effective adjunct to cellular immunotherapies. Emerging evidence also supports the combination of OVs with dendritic cell-based

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vaccines and induced pluripotent stem cell-derived antigen-presenting cells. These modalities offer high immunogenicity and scalability, potentially overcoming immune escape mechanisms in cancers such as uveal melanoma and retinoblastoma, which often demonstrate poor response to monotherapies (13,14). Additionally, radiation therapy enhances the sensitivity of tumor cells to viral infection by impairing DNA repair mechanisms, especially through the inhibition of repair proteins like E1B 55-kDa by telomelysin, thereby improving OV-mediated cytotoxicity (15). Despite promising results, these combination strategies require careful optimization in terms of dosing, scheduling, and patient stratification. The variability in tumor biology and immune landscapes among patients presents a major challenge in translating preclinical efficacy into consistent clinical outcomes. Moreover, biosafety remains a primary concern, especially in the context of enhanced viral replication and systemic immune activation (16).

Challenges: The successful implementation of oncolytic virotherapy continues to be hindered by multiple biological and translational barriers. Off-target effects remain a serious safety concern, particularly for adenoviruses that demonstrate a tendency to accumulate in the liver, leading to tissue toxicity and inflammation (17). Additionally, the route of administration significantly influences therapeutic distribution. Systemic delivery of OVs is often inefficient due to immune neutralization, rapid clearance, and inadequate penetration into solid tumors. Localized intratumoral injections, while more effective in achieving viral replication and oncolysis, are limited in application for metastatic or inaccessible tumors. The immunosuppressive tumor microenvironment represents another formidable obstacle. Factors such as hypoxia, regulatory T cells, and myeloid-derived suppressor cells restrict OV replication and immune cell infiltration. Compared to hematologic malignancies, solid tumors exhibit a less favorable response profile, often requiring multimodal approaches to achieve meaningful efficacy (18). Furthermore, large-scale viral replication poses risks including systemic inflammation and organ damage. Circulating replication-competent viruses in high volumes may provoke severe immune reactions and raise biosafety concerns in clinical settings (19).

While the FDA approval of T-VEC for melanoma in 2015 marked a significant milestone, barriers such as insufficient viral penetration, suboptimal immune activation, poor tumor selectivity, and the lack of predictive biomarkers for response continue to limit its widespread clinical application (20). Ongoing research is focused on enhancing viral delivery through nanotechnology, immunomodulatory adjuvants, and tumor microenvironment modification. Innovations like image-guided delivery and nanoparticle conjugation aim to increase targeting precision and treatment efficacy (21). For central nervous system malignancies, intrathecal delivery may allow better therapeutic access, though it carries risks of neuroinflammation and requires improved strategies for uniform drug distribution within brain tissue (22). Current OV production platforms face logistical hurdles related to scale-up, quality control, and regulatory compliance, making the transition from laboratory to clinic both costly and time-consuming (23). These issues underscore the necessity for robust manufacturing pipelines and harmonized regulatory frameworks to support the clinical advancement of OV therapies.

Future Prospects in Oncolytic Virotherapy: Looking ahead, the future of oncolytic virotherapy appears promising due to advancements in virology, molecular engineering, and immune-oncology. Exosomes have emerged as stealth carriers capable of shielding OVs from immune detection, improving tumor-specific delivery, and enhancing penetration into dense tumor tissues (24). Combinatorial strategies involving OVs with chemotherapeutic agents, epigenetic modulators, and immune checkpoint inhibitors are gaining traction, as they synergistically enhance antitumor immunity and address resistance mechanisms (25). Refinements in molecular biotechnology are driving the design of next-generation OVs with greater specificity, reduced off-target effects, and engineered functionalities such as anti-angiogenic activity, metabolic disruption, and real-time imaging capabilities. These enhancements are critical to increasing both safety and efficacy in future clinical applications (26). Encouraging results from recent T-VEC trials have further strengthened the case for broader regulatory approval of novel OV candidates, especially those tailored to tumor-specific genomic and immunologic landscapes (27).

Progress in understanding tumor-host interactions, including the role of the tumor microenvironment and immune evasion strategies, continues to shape the development of more precise and responsive oncolytic platforms (28). Integration of genetic engineering has facilitated multi-functional OVs capable of delivering payloads for direct cytolysis, immune stimulation, and supportive therapies. Such versatility allows OVs to be used in conjunction with various cancer treatments, making them ideal candidates for personalized and multimodal oncologic interventions (29). Although the journey to widespread clinical application is met with complexity, the accumulated evidence supports the strategic refinement and clinical prioritization of oncolytic virotherapy as a critical pillar in the evolving landscape of cancer treatment.

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CONCLUSION

Oncolytic virotherapy represents a transformative approach in cancer treatment by offering selective targeting of tumor cells while preserving healthy tissue integrity. Its unique mechanism not only enables direct tumor lysis but also stimulates robust systemic antitumor immune responses. Advances in genetic engineering have enhanced the precision, safety, and immune-activating capabilities of oncolytic viruses, establishing them as powerful therapeutic tools. The integration of OVs with immunotherapy, chemotherapy, and radiotherapy further amplifies their therapeutic impact, addressing resistance in complex tumor environments. By harnessing tumor-specific vulnerabilities and modifying delivery strategies, oncolytic virotherapy holds immense potential to evolve into a personalized and effective cancer therapy. This study reinforces its growing significance in the oncological landscape and supports continued innovation to overcome existing clinical barriers.

AUTHOR CONTRIBUTION

Author	Contribution
Tahseen Javaid Shah	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Sana Yousuf	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Muhammad Arslan	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Aqsa Naaz	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Sehrish Gull	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Zainab Ali	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Muhammad Sulaiman Saeed*	Contributed to study concept and Data collection Has given Final Approval of the version to be published

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