Nanomedicines in the pediatric therapy: Tribulation and road ahead

Keywords
cancer, Nanotechnology, Nanomedicine, pediatric diseases, pediatric cancer

Abstract
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Explanation letter
Review 1:

The article entitled “Nanomedicines in the pediatric therapy: Tribulation and road ahead” has been written well and can be accepted for publication after some changes/modifications in my point of view. I have some minor comments on this paper.
The article entitled “Nanomedicines in the pediatric therapy: Tribulation and road ahead” has been written well and can be accepted for publication after some changes/modification in my point of view. I have some minor comments on this paper.

1. The introduction is not aligned with the aim and abstract of the paper. It can be modified.
Response: We have revised the introduction section and aligned with the aim and abstract of the paper.

2. Line no 240, figure 2, the quality of the figure is extremely awful. Improve or replace.
Response: We have improved the quality of figure 2 in the revised manuscript.

3. Line no 399, figure 3, there is description of the figure within the text, add proper description of the figure within the text. Moreover, the quality of the figures is too low, improve of replace.
Response: We have added more is description of the figure 3 in the revised manuscript, as well as improve the quality of the figure.

4. Figure 5, there is no information about text citation, clarify that should there no reference? If not then add the related references.

Response: Figure 5 is the brief summary from various literates that summarize the various breakthrough in nanomedicine for the cancer treatment in pediatric.

5. The quality of scientific English is not good enough, it is recommended to revise the paper

language by a native English speaker.
Response: We have improved the quality of English with an expert native speaker editor and corrected all the language related issue.

Review 2:

I have read the paper entitled “Nanomedicines in the pediatric therapy: Tribulation and road ahead” by Chen Lia-Na et al, with great interest. I think it is a very valuable paper because there is little known about this subject in the field of pediatrics. The content and organization of the article are well planned. I have some minor
We are thankful to the reviewer for reading our manuscript and his/her positive comments that improve the quality of our manuscript. Below we provide point-by-point response to the reviewer suggestions and made changes in manuscript (highlighted with red text) accordingly.

suggestions
- Subheading arrangements of the article should be reviewed again
Response: We have reviewed the subheadings and made correction accordingly.

- The ocular nanomedicine section disrupts the integrity of the manuscript, so it would be appropriate to remove it from the manuscript
Response: The reviewer suggestion are well taken and we removed the section of ocular nanomedicine in our revised manuscript.

- I think adding the use of nanomedicine in the neonatal period to the article will increase the value of the article.
Response: This is a very good suggestion and to our interest. However, the studies on the nanomedicine in the neonatal period in still in infancy and very immature. Moreover, no research group have achieved any promising results yet. There are few studies that study that phenomenon, we have added some details for the interested readers in the future perspective section about that.

Finally, there are too many spelling and grammatical errors in the article. In this respect, it would be appropriate to revise the article once again.
Response: We have improved the quality of English with an expert native speaker editor and corrected all the spelling and grammatical errors. We have highlighted the changes with yellow colour.

Review 3:

The role of nanomedicine in children is although in infancy; however, it is interesting and hotspot research topic recently. There are currently no authorised paediatric nanomedicines since the development of paediatric therapies; however, numerous research group from all around the world are actively devoted to investigate new avenue in this arena. The author put their effort in to provide an overview of the many initiatives to utilise nanotechnology to cure illnesses in children. they highlight discuss basic in vitro research through preclinical and clinical trials aimed at treating children infectious illnesses and paediatric solid tumours using nanotechnology. I have below some suggestion,

comments and question, after that I will able to take some decision on the manuscript.
1. First the language of manuscript need to improve, there are many grammatical and typo mistake that make sentence and concept difficult to understand.
Response: We have improved the quality of English with an expert native speaker editor and corrected all the spelling and grammatical errors.

2. the introduction part need to be thoroughly revised and author should link the progress of nanomedicine in adult with the pediatric and try to figure out the factors that halt or slow the progress of nanomedicine in children.
Response: We have revised the introduction section and also explain the progress of nanomedicine progress in adult and compare them with the paediatric population.

3. the section “Challenges of the pediatric population” should be moved to the end of paper before the future perspective.
Response: We have moved the section Challenges of the paediatric population before the future perspective.

4. the author mention the HIV prevalence and numbers, I would suggests to also add that number in the specific population, i.e., pediatric population.
Response: We have added the recent the HIV prevalence and numbers of the kids in our revised manuscript.

5. some references are outdated, especially when explaining the various Diseases
Response: We have updated all the outdate reference with up to date recent references in the revised manuscript.

condition, their patho and background, please update them with recent references.
6. at the end of the paper, I would suggest to add concluding remarks within a single para.
Response: The reviewer suggestion is well taken and we have added a single para that conclude the current paper.

response letter.docx

Nanomedicines in the pediatric therapy: Tribulation and road ahead

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Abstract

Nanotechnology has emerged as a critical technique for overcoming medicines' primary (bio)pharmaceutical disadvantages and enabling active or passive targeting of certain cells and organs. Majority of pediatric treatments are based on adult clinical experience. However, a solid concept that medication pharmacokinetics and therapeutic outcomes differ in children and adults. The interaction of certain medicines with their target receptors, varies with the maturity of various organs and systems. Usual observations are seen for toxic-side and adverse effects. Implementing innovative technologies in the pediatric population (e.g., nanotechnology) becomes exceedingly difficult in this environment. The article aims to deliver an overview of numerous initiatives to utilise nanotechnology to cure illnesses in children. We first discuss basic in vitro research through preclinical and clinical trials aimed at treating children infectious illnesses and paediatric solid tumours using nanotechnology, despite little existing literature on this subject. Finally, future perspectives of nanomedicine for pediatric population are elaborated.

Keywords: Nanotechnology, Nanomedicine, pediatric diseases, pediatric cancer, cancer.

1. Introduction

Nanotechnology has emerged as a critical technique for overcoming fundamental (bio)pharmaceutical issues like decreased physicochemical stability, low aqueous solubility and inadequate bioavailability [1, 2] . Nano-drug delivery systems can specifically target the cells and tissues, thereby augmenting the total drug payload at the intended location of the body and limiting the adverse effect by reducing the direct systemic exposure[3, 4] . Moreover, nano-formulations have been demonstrated to enhance localized medication delivery in areas protected by physiological or anatomical barriers, using alternate administration methods (e.g., inhalation). The ability of nanomedicine to enhance illness detection and therapy has been well proven, regardless of its level of complexity. Consequently, despite regulatory requirements, many nanomedicines have already reached the market[5, 6] . All of them, however, are intended for adult usage. Still, there is no nanomedicine-based therapy approved for the pediatric population.

There are currently no authorized pediatric nanomedicines since the development of pediatric therapies has typically relied on prior experience in adults, which is still limited to the majority of the nanotechnology approaches. The use of recently developed regulatory initiatives, for example the pediatric investigation plan, which promotes particular studies in pediatric in order to get the required data in order to gain clearance for a new medicinal product will make it easier to get medicines approved for children. Because of the progressive growth and maturation of the many organs, children have differences from adults[7, 8] . In the event of illnesses that affect children and adults, nanomedicines must first be modified for pediatric usage, which may need the development of a new pharmacological formulation, before being clinically tested in children.

Furthermore, nanomedicines must be created specifically for illnesses unique to children or that have significantly higher morbidity in children[9] . Despite the rapid success of nanomedicine for adults, these realities, unfortunately, clash with the complexity of the segmented paediatric market and the difficult clinical studies that deter academic and industrial researchers from investigating nanomedicine for pediatric population.

Cancer is the 2nd most common cause of mortality among children population less than 14 [10]. Pediatric cancer has been a prominent study area since the mid-1970s, and new research on the issue emerges often. In children under the age of 19, the death rates for a variety of malignancies have decreased significantly during the past three decades [11]. Nevertheless, despite current advancements, the 5-year mortality rate for youngsters with tumor remains as high as 26%, and several lives endure long-term unfavourable consequences that diminish their standard of living [12]. Presently, chemo is frequently used to treat juvenile cancer, despite its potential for adverse effects and damage to normal tissues. Due to their varying metabolic rates and undeveloped organs, children and adults have different tolerable doses, making it more difficult to determine the ideal dosage. The combination of two or more chemotherapeutic medicines has remained mostly unchanged over the past two decades, to prevent the drug resistance frequently induced by monotherapy. However, because organs and tissues develop fast in kids, they may respond differently to the medicine at various stages of development. Consequently, the childhood cancer survival rate remains poor.

This article aims to offer an outline of the many initiatives to utilise nanotechnology to cure illnesses in children. We first discuss basic in vitro research to preliminary and clinical studies to

treat juvenile infective illnesses and solid tumours using nanotechnology, despite the scant accessible literature on the subject. The future of pediatric nanomedicine is then explored.

2 . Nanomedicine for the Infectious diseases in the pediatric population

Even though a wide range of anti-bacterial agents are available, the management of infections has become a growing problem for contemporary medicine as resistant bacteria arise. Because of the reasons stated above, the condition is considerably more severe in the event of poverty-related illnesses and much more so in the case of the paediatric patients. The early advances made at the intersection of nanomedicine and paediatric HIV, tuberculosis, and malaria treatment, three diseases that take the most lives each year, will be reviewed in advance.

2.1. HIV/AIDS

With about 2.5 million fatalities each year, HIV/AIDS is the most devastating illness of current time [13] . In 2020, around 150,000 kids (0-9) were newly infected with HIV, with a total of 1.03 million kids who have HIV [14] . Due to the difficulty of clinical studies, the amount of antiretroviral drugs (ARVs) approved for use in children is smaller than that of adults, although the pharmacokinetic information is relatively inadequate [15] . The absence of approved liquid, chewable[16] , dispersible[17] , and orodispersible formulations[18, 19] , as well as the creation of pediatric fixed dose combinations (FDCs)[20] , are further disadvantages. Nevertheless of the approach chosen, the manufacturing procedure must be counterbalanced to keep medicine prices within reasonable bounds for patients[21] . Because the disease affects both adults and children, the progression of Nanomedicines for HIV prevention might be useful to all patient

subpopulations. Despite this, there are surprisingly few research projects aimed at developing nanotechnology-based anti-HIV medications overall, and for kids specifically.

Nanosuspensions are pure drug nanomaterials dispersions in a liquid pharmaceutical carrier maintained by emulsifiers. [22, 23] . They are the simplest basic nano-formulation, and because of the continuous increase in the surface area due to the smallest particle diameter, they may achieve a significant increase in dissolution rate and oral bioavailability. Despite the promise of this technology to generate liquid solutions that would allow for simpler dosage adjustment and ingestion, In HIV, only just a small number of ARV nano-dispersions have been examined, none of which have been tested in children[24]. Polymeric micelles (PMs) are a form of self-assembly nanomaterials created by complexing polymeric amphiphiles [25] , have been evaluated by various administering routes for instance parenteral[26] , oral[27] , intranasal[28, 29], and ocular[30] to augment the aqueous solubility of lipophilic drugs. A variety of PM-based medicines for treating various malignancies are now undergoing clinical trials[31] . To develop a sustainable and cost-effective water-based paediatric formulation, our group assessed the entrapment of the very first ARV efavirenz (EFV) included in PMs comprised of pristine and chemically changed poly (ethylene oxide)-b-poly(propylene oxide) block copolymers (PEO-PPOs)[32-34] . In mixed micelles, the drug's solubility was improved from 4 g/mL to 34 mg/mL, reflecting an 8430-fold increase [34-36] . Physical stability of EFV-loaded PMs was shown under a variety of storage settings, including severe dilution in gastrointestinal-like medium [34-36] . The pharmacokinetics of oral EFV were first evaluated in rats and matched to those of a typical extemporaneous simple syrup suspension and an oily solution that replicated the sole commercialized paediatric dosage of EFV in medium-chain triglyceride (MCT), Miglyol [33, 34][69,70].

Regardless of nanotechnology's potential to develop pediatric HIV therapy, other issues appear to be more pressing. For example, EFV causes a condition known as burning mouth syndrome (BMS), which can be alleviated by using a mix of tastes, sweeteners, and essences [35] . As a result, nanotechnologies must address other problems just as important in ensuring patient compliance and treatment regimen compliance.

Three factors that may influence the clinical translation of novel medications should be discussed at this time. The continual training of individuals assigned to assess clinical procedures is required for therapeutic innovation. Otherwise, the evaluation would be insufficiently rigorous, putting the participants' safety at risk. In contrast, patients may be denied access to potentially beneficial and safe products if the "Precautionary principle" occurs due to the regulatory agency's lack of competence.

2.2: Tuberculosis

Tuberculosis (TB) is the 2nd most lethal illness after HIV, with 1.5–1.7 million people dying each year[37, 38] . Although TB generally affects the airways, untreated or resistant strains have been seen to spread the illness to other organs [39]. Isoniazid, pyrazinamide, rifampicin and ethambutol are used in the first 60 days of conventional TB treatment, while RIF and INH are used in the last four months[40] . The effectiveness of TB treatment is closely linked to strict adherence to treatment approaches.

Even though ordinary tuberculosis infection can be treated, it nevertheless accounts for more than 25% of avoidable deaths and 2.4 percent of all fatalities worldwide[41] . Pediatric tuberculosis accounts for just 5% of all infections in industrialized nations, but it causes 20–40% morbidity in underdeveloped countries, with 130,000 children dying each year[42] . Because of the difficulty of diagnosis and the absence of commercially accessible preparations with enhanced (bio)pharmaceutical efficacy[43] , containing RIF/INH FDCs, children constitute a high-risk subpopulation, similar to HIV. Indian firms have established a variety of double and triple FDCs, but none have completed clinical studies [44] . Furthermore, some of these advancements ignore the fact that the gastrointestinal 284 tract's circumstances may accelerate the breakdown of several first-line medicines when they are taken orally. For example, in gastric acid fluids, Rapid hydrolysis of RIF results in 3-formyl RIF SV, a compound with little anti-TB action in vivo because of the low oral bioavailability[45] . INH catalyzes this route, resulting in a 30–50% increase in degradation rate[46, 47] . As a result, INH-mediated decrease oral bioavailability of RIF is a major worldwide issue[48] , and novel nanomedicines may be able to help.

Only a limited research organizations worldwide, mostly in poor countries, have focused on the progression of nanotechnology-based pediatric anti-TB medications[43] . Khuller and Swai's groups explored the entrapment of anti-TB medicines into nanomaterials and evaluated their efficacy in murine TB models via oral administration[49, 50] . Due to the preclinical testing done on infected TB animals, these findings were extremely reliable. These nanomedicines show great promise in replacing the present daily delivery routine with a single 7–10 day administration. Despite the fact that these advancements were not designed specifically for children, any effective bench-to-bedside therapy could benefit the paediatric population. In order to adhere to PIP regulatory regulations, further clinical trials in children are required. Our group has spent the

previous five years looking on the RIF encasement inside various forms of PMs[51] . The drug's aqueous solubility was enhanced by up to 5.4 times after encapsulation, however RIF-loaded PMs suffered progressive subordinate grouping, as a result of which physical stability deteriorates with time. As a result, a cryo-protected lyophilization method[52] was devised. In vitro, PMs not only chemically stabilised RIF in the presence and absence of soluble INH, but they also lead to considerably higher RIF bioavailability when taken orally (up to 3.3 times) than a drug solution mixed with INH in a 3/2 weight ratio[52] . This type of nanotechnology approach might be used to create the 1st RIF/INH liquid pediatric FDC.

2.3 Malaria

Malaria is the parasite illness that causes the most morbidity and mortality worldwide[53] . In 2011, nearly 3.3 billion population were having an incidence of getting malaria, with 80 percent of cases and 90 percent of fatalities occurring in Sub-Saharan Africa[54] . The most severely affected subpopulations are children under the age of five, as well as pregnant mothers. Malaria can be prevented and cured, though it result in the death of more than 6 million kids in 2010[54] and it results in 20 percent of the pediatric deaths ratio in Africa[55] . Artemisinin-based combination treatments (ACTs) are the 1st line therapy for simple falciparum malaria in children, which come in difficult-to-swallow tablets [56] . The WHO has recommended novel formulations of oral ACT pediatric products in this context . The creation of suspensions, rapidly dissolving tablets, and granules comprising lumefantrine/artemether [57,58], pyronaridine/artesunate [59], and mefloquine/artesunate is among the most significant advances [Various nano-formulation have been researched for the development of novel antimalarial agents in which only a few focused on the pediatric population[60] . CDs most likely focus on the utilization of the vast use of

nanotechnological approach, specifically the masking of bitter taste of antimalarial agents. Shah et al., for instance, enhanced the delectableness of an artemetherin liquid formulation [61] . Complexes of primaquine phosphate were utilised in a similar manner to create powders for resuspension [62]. As a result, reduction in RIF oral bioavailability caused by INH is a huge global concern [63] , and novel nanomedicines may be able to help.

3. Recent Developments in Nanomedicine for Pediatric Cancer

Nanomedicine plays a critical part in the anti-tumor tumor activity of Pediatric Cancer. Figure 1 highlight the various therapeutic strategies of Nanomedicine in cancer, and below we explain them in detail.

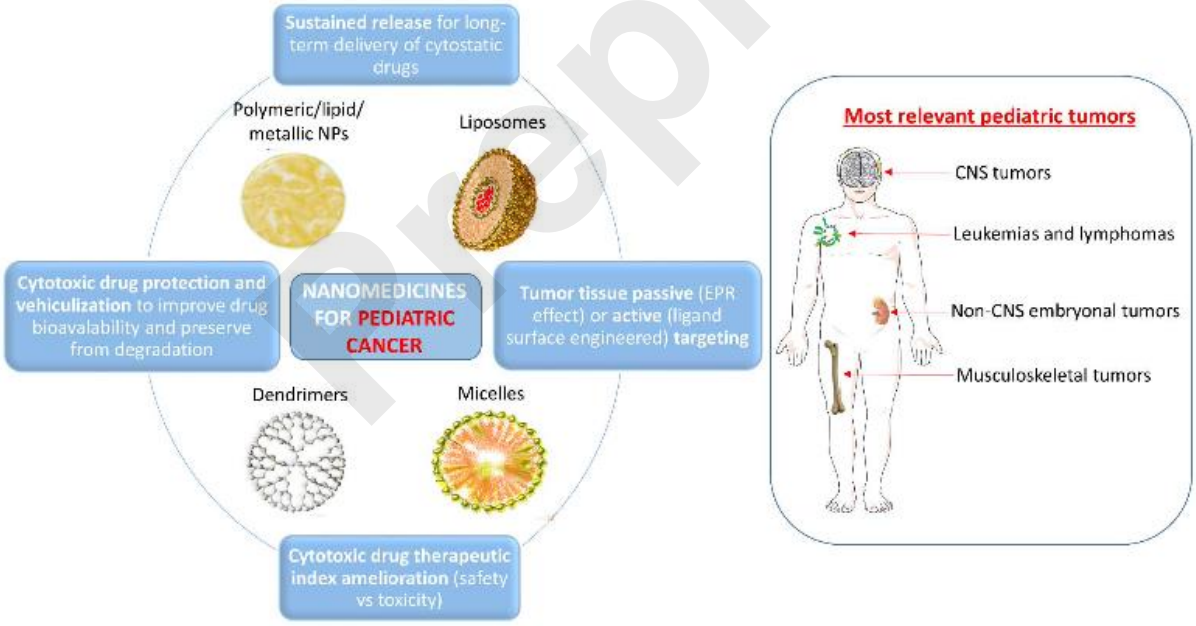

Figure 1. Nanomedicines as treatment options for paediatric malignancies.

3. 1 Blood Cancers

3.1.1. Leukemia

Leukemias are the most prevalent tumours in children, accounting for roughly 28% of all malignancies in children . White blood cells that are abnormal, which come from organs that generate blood cells, are the hallmark of the illness.

Leukemia has been treated with nanomaterials made of lipids. To combat multidrug resistance, In one study, solid nanoparticles based on lipids were employed to transfer mitoxantrone and a P-glycoprotein (P-gp) suppresser-element [64]. Overexpression of P-gp is thought to disrupt the multidrug resistance mechanism. As a result, combining the P-gp and mitoxantrone inhibitors can have a synergistic impact on inhibition and therapeutic effects. This nanocarrier, which has a negative surface charge and a size of 120 nm, was successfully loaded with the medication mixture and remained colloid stable after delivery.

Immunotherapy is another cancer treatment method that involves activating or improving immune cells' capacity to recognize and destroy tumor cells. One research group investigated the utilisation of ionizable nanomaterials for mRNA transport in CAR T cell therapy [65] . T cells are extracted from the individual and modified by inserting DNA or RNA into them in order to create CARs on their surfaces, an FDA-approved treatment for acute lymphoblastic leukaemia (ALL).

3.1.2 Lymphoma

Lymphoma is a lymphatic system cancer that lymph glands and spreads to certain other tissues through lymph fluid. Lymphoma is the 3rd most recurrent kind of tumor in youngsters, behind brain cancers and leukaemia. Every year, 2200 individuals under the age of 20 in the United States are diagnosed with lymphoma. Lymphoma and non-Hodgkin lymphoma account for around a quarter

of all pediatric cancers [66]. Adults with lymphoma are frequently treated with the anti-CD30 antibody-drug combination brentuximab and the anti-CD20 antibody rituximab. However, no targeted therapies are authorized for use in lymphoma patients under the age of 18[66] .

ALCL, the most frequent form of T-cell lymphoma in children, comprises an activated hazardous ALK oncogene and elevated amounts of CD30 cell surface expression. Nanoparticles treated with doxorubicin and ALK oncogene-specific siRNA and generated using RNA-based CD30-specific aptamers were used to treat ALCL with precision. Thanks to the aptamers that are conjugated, the nanomaterial accurately target ALCL cells, and the loaded gene curing agent siRNA and chemotherapeutic drug doxorubicin enhance their tumor-killing potential [67] .

3.2 Bone Cancers

3.2.1. Osteosarcoma

Bone tumours primarily affect older children and teenagers, accounting for around 3percent of all pediatric malignancies . Osteosarcoma is the most prevalent kind of bone tumor, and it has a disproportionate impact children. It affects young individuals (10 -30 years) accounts for 2% of all pediatric malignancies[68] . In this group, most osteosarcomas are very malignant tumours with a dismal diagnosis [68]. A distant tumour that has migrated beyond surrounding tissue has a 5-year rate of survival of 27 percent throughout all ages, according to American Cancer Society data [69] .

As with previous cancer therapies, Nanoparticles administration to osteosarcoma cancers is an developing area of study that aims to improve targeted medicine delivery while minimising cellular as wll as dosage damage. This is accomplished via either passive transport, which depends on the

EPR outcome, or active distribution, which employs the acidic pH of the osteosarcoma cancer environment and nanoparticle surface modification.

Due to their biocompatibility and surface alteration capabilities, Liposomes seem to be the most thoroughly examined vehicle for osteosarcoma treatment [70] . As doxorubicin was integrated into liposomes, it improved permeability of cells and cancer death of cell associated to when it was administered free [71] . Some investigations have demonstrated that liposome nanocarriers may be optimised to release drugs at an osteosarcoma tumor's particular temperature and pH [72] . Others have investigated liposome PEGylation, which decreases nanomaterial re-absorption by the reticuloendothelial system, resulting in a prolonged half-life and a lesser optimum dose [73] . In a recent in vitro investigation, the combination of gemcitabine and clofazimine in nanoparticles was discovered to have synergistic effects. This double loading was accomplished by inserting the gemcitabine hydrophobic into the liposome core and the clofazimine hydrophilic between the lipid bilayers. [74]

Inhibiting the synthesis of proteins by osteosarcoma cells using RNAi treatments, for instance siRNAs and microRNAs, has exposed potential and may be useful when combined with chemotherapies [75]. In contrast, the bioavailability and cellular absorption of potential nucleic acid carriers are hampered by their poor physicochemical qualities. Some study on prospective biocompatible carriers, including Amy-g- PLLD [76], has been reported. Both alone and in combination with doxorubicin, PEGylated liposomes have been evaluated for siRNA delivery [77, 78]. In 2017, a research demonstrated that using chitooligosaccharides to improve drug delivery enhanced tumour cell engulfment, anti-cancer implications, and rate of continued existence in mice models [79]. Curcum ininduced apoptosis with a rise of the concentration of markers for instance

sliced caspase and poly(ADP-ribose) polymerase and autophagy in vitro. Outcomes in vivo tailed a like pattern (Figure 3) [80]. Dhule et al. created a human OS tumour and cured it with conventional, HPCD-curcumin liposomes and empty liposomes. They performed hematoxylin-eosin staining and the DeadEndTM Colorimetric TUNEL test (Terminal deoxynucleotidyl transferase dUTP nick end labelling). Figure 2A illustrates nuclei stained in dark blue hematoxylin and cytoplasm in pink eosin, while nuclei are lost in dead cells in tumours treated with liposomal curcumin (Fig 2C and E), as shown by the black arrow, indicating that curcumin liposomes and curcumin itself cause cell death. Compared to Figure 2B, the arrows in Figure 3D and F suggest a substantial increase in apoptosis (brown regions). The brown spots designate the DNA-fragmented apoptotic area [80].

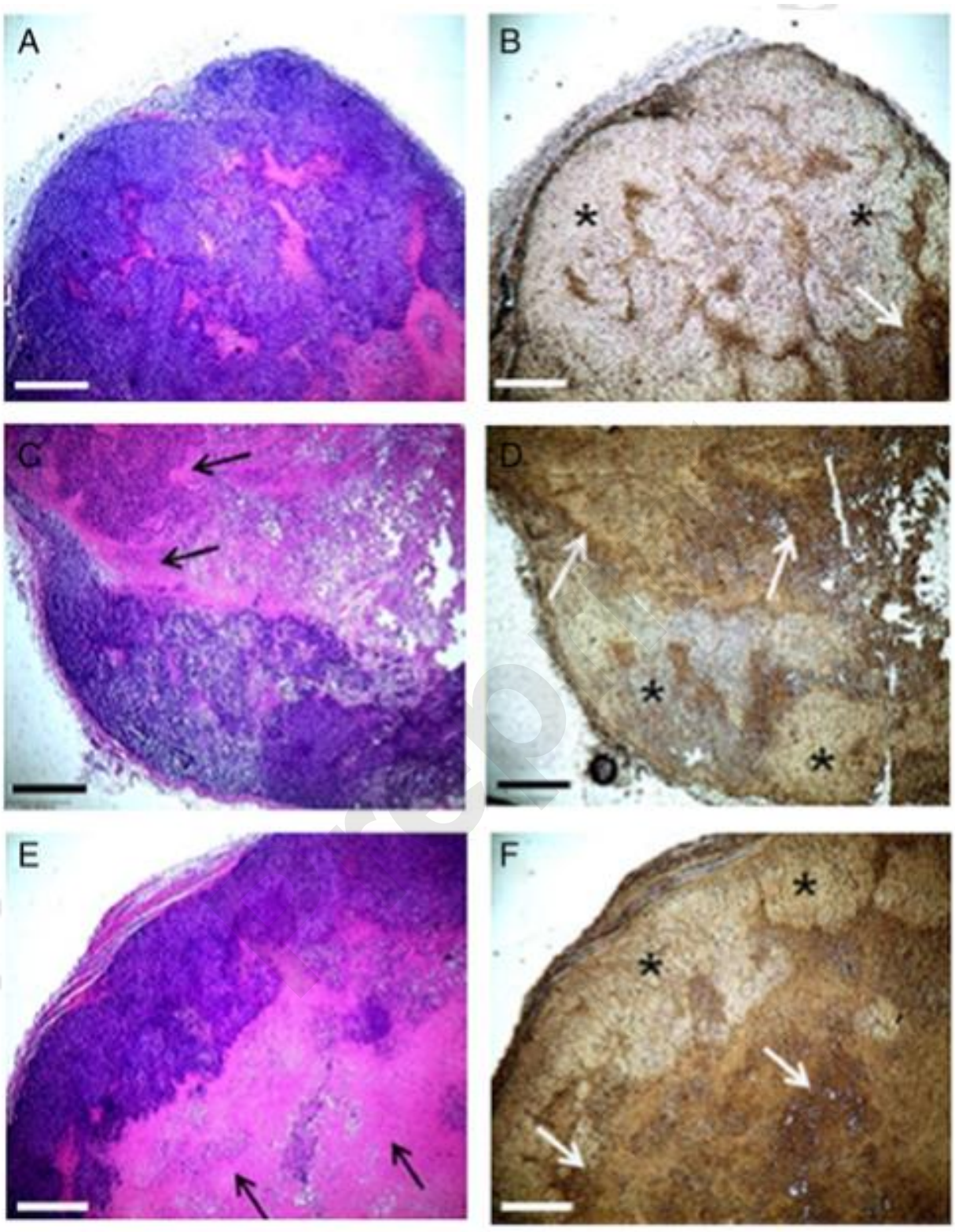
A
B
C
D
E
F

Figure 2: Liposomes containing curcumin cause cell death caused by apoptosis in an xenograft osteosarcoma model. Cancer cured with vacant liposomes (A,B), standard curcumin liposomes (C,D), and hydroxypropyl—CD-curcumin liposomes (E,F). Hematoxylin and eosin staining for tumour histology is shown in subfigures A, C, and E, while TUNEL staining for apoptosis detection is shown in subfigures B, D, and F. reproduced with permission from [80].

3.3 Cancers of the Central Nervous System

3.3.1 Brain Cancer

Brain malignancies are the second most prevalent malignancy in children, accounting for roughly 26% of all cancers in children. Brain malignancies are called for the cell type that gave rise to cancer and the location of the tumour in the brain. Surgery, radiation, and chemotherapy are used to treat them. However, brain tumours might make operation and the delivery of therapeutic medicines difficult depending on their location.

5.3.2. The Blood Brain Barrier

The blood brain barrier (BBB) is a compact barrier between the brain and the vascular system that protects the brain from potentially hazardous substances and infections while also regulating the flow of vital nutrients to keep a steady microclimate [81]. Endothelial cells with tight junctions, astrocytes, pericytes, and a persistent basement membrane make up the BBB. It is a semipermeable barrier with a strong expression level of many transporter protein sets that allows only essential small molecules such as oxygen to flow freely. Because the BBB is so effective, fewer medicines are effective, and the prognosis for paediatric patients with brain cancer is poorer[82]. Figure 4 illustrates the various approaches adapted by the nanomedicine for crossing BBB.

Molecular size appears to have a critical role in BBB penetration, according to the research. However, the size of molecules does not always affect BBB permeability[83]. The BBB prevents several tiny compounds with a molecular weight of approximately 100 Da from entering the brain, such as histamine[84]. Nevertheless, candidates may be able to pass if they interact with the BBB's primary transporters. It is believed that the activity of ATP-binding cassette (ABC) efflux carriers, for instance the (BCRP) breast cancer resistance protein, prevents many drugs from entering the brain [83].

The use of nanotechnology has aided in the delivery of medicinal drugs across the BBB. Gold, proteins, in the therapy and diagnostics of brain cancer, Lipids are being researched for use as cytostatic agents or medication transporters. The capacity to penetrate the BBB is influenced by two primary factors: nanoparticle size and surface. It tends to inhibit large particles, but a slightly positive surface charge might encourage particle–endothelial cell interaction[82]. Antibodies with a molecular weight of more than 500 kDa, such as intact IgG, commonly employed to cure malignancies, have poor BBB penetration[82]. Smaller antibody chains, for instance single-chain mutable segments or fragment antigen-binding (Fab), can reach the CNS more effectively.

In addition to diffusion, transcytosis mediated by ligands is being studied to transport drugs passing through the BBB. Despite the fact that the BBB is an extremely selective, Endothelial cell barrier that is semipermeable, the specific protein carriers produced on its membrane that permit critical nutrients to be delivered to the brain are optimal objectives.

The transferrin receptor (TfR) is in charge of iron delivery into the parenchyma of the brain, which is required for brain metabolism, neuronal conductance, as well as general brain task [98]. TfR is a remarkable and one-of-a-kind target because it is only produced on endothelial cells lining brain

capillaries rather than endothelial cells lining the arteries of other organs [85]. Transferrin receptor antibody is an appealing idea for medication delivery across the BBB because to its singular property. When combined to nanoparticles for instance liposomes, penetration and BBB targeting would be greatly increased [86-88].

Similarly, to cross the BBB, cell-penetrating peptides (CPPs) have been used. CPPs enable the cellular absorption of materials ranging from nanoparticles to tiny chemical compounds to big pieces of DNA. Wang et al. investigated the effectiveness of Tf-LPs and CPPs loaded with doxorubicin in the treatment of glioblastoma. In two kinds of glioma cells, this 120 nm nanoparticle with a zeta potential of 6.81 mV demonstrated increased cellular absorption and decreased toxicity when compared to free doxorubicin[89].

Amplification of the EGFR expression, which occurs in roughly half of all malignant gliomas[90, 91], is another potential marker. Human epidermal growth factor receptors are all members of the ErbB family of receptor tyrosine kinases[92]. The use of EGF, EGFR's natural ligand, might be a way to target all types of tumour cells, including those that express wild-type and mutant EGFR. The coupling of EGF to the nanoparticle may allow for targeted glioma therapy[93, 94].

Due to the brain's distinctive environment, which may be considered an immune-privileged zone distinct in comparison to the rest of the body, immune cells are prevented from accessing the brain [95, 96], immunotherapy is becoming more often utilised for brain tumours than for other tumour forms. As a result, microglia occupy a prominent position inside the brain. They are pro-tumorigenic under certain conditions, such as excessive synthesis of growth factors and lack of T-cell regulation. In addition, the majority of brain tumours contain an extracellular structure that

inhibits the migration and activation of T cells, hence preventing their movement and proliferation [97].

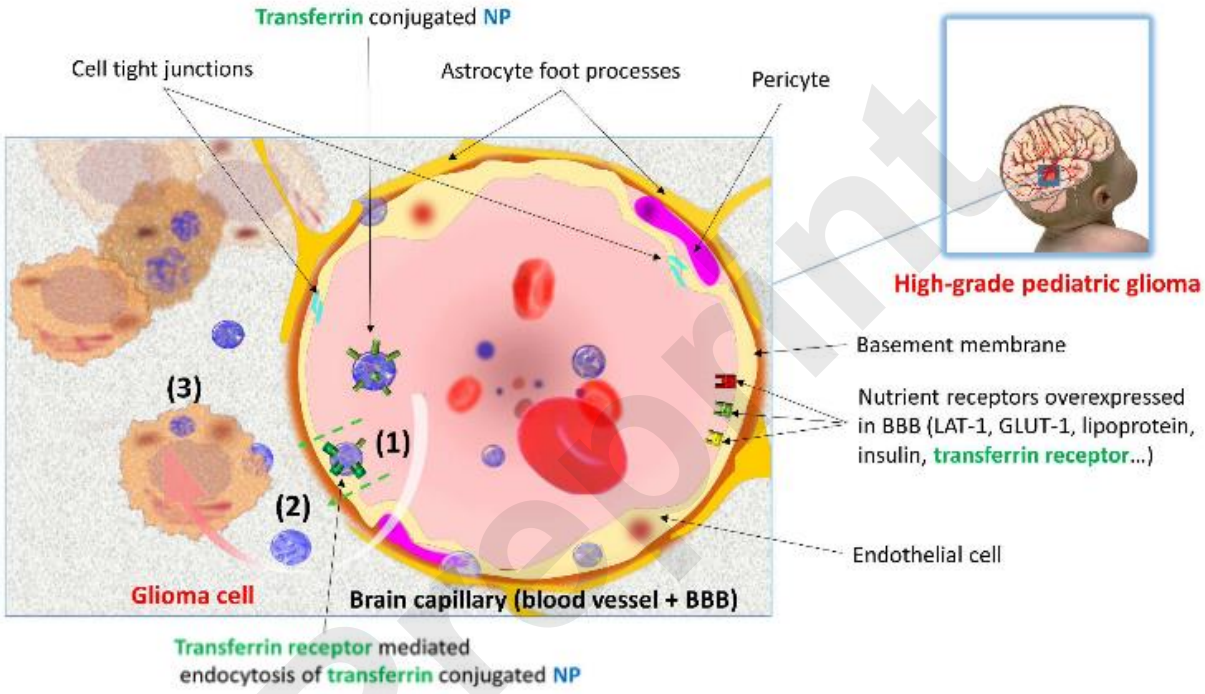

Figure 3: Nanomedicine crossing BBB in pediatric cancer. (1) Nanomedicine ligands are recognized by receptors (2) (2) NPs extravasate into CNS (3) Internalized NPs release their cytotoxic drug cargo, resulting in the demise of tumour cells. Reproduced with permission from [98]

3.3.3 Glioma

Glioma is a kind of childhood brain cancer formed by glial cells, which maintain and feed the neurons in the brain [99]. In order to treat glioblastoma, a micelle of folacin-modified poly(e-caprolactone) was created to transport luteolin, a vegetable-derived xanthone with broad-spectrum anticancer effects [100]. Folate acids have been conjugated to the nanoparticle's surface so that it could bind to the folate receptor, a glycoprotein that is overexpressed in numerous tumour tissues. In glioma tissues, luteolin-enriched folate acid -refined micelles induce much more cell inhibition and death than free luteolin and micelles devoid of folacin alteration [100].

Endothelial cells have an increased expression of TfRs of the BBB and gliomas. Fan et al. proposed a trans-BBB supply approach using protein-coated iron oxide with human H-Ferritin and L-Ferritin nanomaterials (HFns) to target BBB endothelial cell TfRs and cause transcytosis [101]. The nanomaterial exhibited sufficient drug-loading capacity and double cancer-targeting capability. TfR-mediated transcytosis carried them beyond the BBB in the endosome, where they were identified and entered glia cells through human H-ferritin receptor-mediated tumour targeting.

Radiotherapy is an essential element of tumor treatment. Though, radiation-induced side effects and confrontation pose clinical constraints. Uniting irradiation with various therapeutic drugs that obstruct certain DNA reparation pathways might provide greater therapeutic success than monotherapy with a lesser radiation dose that minimises possible side effects. By employing nanomaterial-based transfer of siRNA to inhibit the appearance of Ape1, an enzyme that

participates in the excision of the base restoration pathway, Kievit et al. discovered a policy to sensitise paediatric cancer cells, such as ependymoma and medulloblastoma cells, to radiation [102]. This chitosan, PEG, and polyethyleneimine-coated superparamagnetic iron oxide nanomaterial may bind to siRNA to prevent its deprivation. The medulloblastoma and ependymoma cells treated with siApe1 showed a 75percent decrease in Ape1 expression and an 80% suppression of Ape1 activity, indicating that siApe1 may be an efficient delivery strategy. Figure 4 summarizes the various breakthroughs in nanomedicine for pediatrics cancer treatment.

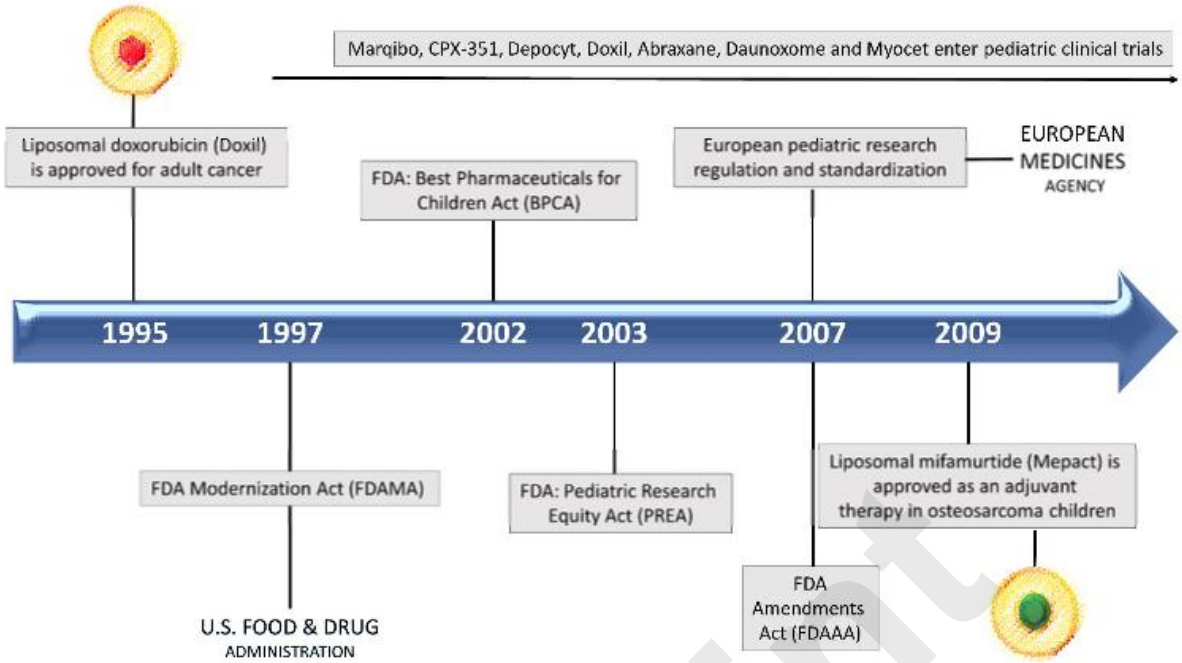

Figure 4: Timeline of nanomedicine development for pediatric cancers.

4. Challenges of designing nanomedicine for the pediatric population

Children are not merely little adults, according to doctors throughout the world[103]. This is not a cliche of demagogy; it is founded on scientific research that shows that children and adults have different medication absorption, biodistribution, metabolism, and excretion patterns[104] . Children also have varied pharmacodynamics as a result of the various interactions of medicines with their biological targets[105] . . In this perspective, it is obvious that treating illness in children cannot be reduced to a simple dosage modification based on body weight/surface[106] . The paediatric subpopulation is also divided into subgroups based on biological and metabolic differences, includes premature baby newborns, term newborn babies (0–27 days), preschool

children (2–5 years), toddlers and infants (28 days-23 months), school-aged children (6–11 years), and teenagers (12–16/18 years)[107] . Various gastric pH and passage, motility of intestine, and bile salt conjugation and transport are shown in each sub-category[107] . In addition, cognitive development may influence formulation suitability (for instance, in the case of inhalars)[108] and clinical trial possibility[109] . Children's clinical studies, for example, are more difficult because of clinical, scientific, ethical, technological, and logistical issues that have hampered the progression throughout time[110, 111] . Furthermore, toxicological implications of nanoparticle exposure, particularly by inhalation, should be extensively studied, because children have higher particle accumulation in the lungs than adults [112] . For instance, Various liposome compositions have proven biocompatibility, and some nano-DDS have been evaluated in adults [113] . However, there is comparatively little information on the safety in youngsters. Other methods, for example, carbon nanotubes, are more contentious, and their therapeutic use appears implausible [114] . All of these issues diminish the fragmented paediatrics market's flexibility and proximity, placing children at the top of the vulnerability scale [115] .

5. Future perspective

6. The global nanomedicine sector was valued $72.8 billion in 2011, as per BCC investigation, with anti-tumor medications leading the way. The market is projected to grow at an annual pace of 12.5% until 2016, when it will be valued $130.9 billion. In this globalized world, nanomedicine looks to be a auspicious tool for enhancing the treatment of paediatric disease [116]. In 2008, the Mattel Children's Hospital of the University of California, Los Angeles established the groundbreaking NanoPediatrics Programme, and

in 2011, Children's Healthcare of Atlanta and Emory University School of Medicine established the Center for Pediatric Nanomaterials, are examples of this potential and foresight. Other specialized institutes, such as the University of Novel South Wales' Australian Centre for Nanomedicine (Sydney, Australia), have dedicated one of their revolutionary initiatives to discovering new treatments for neuroblastoma, the utmost prevalent tumor in children under the age of five. Everything designates the significance of this avenue of investigation. At the same time, we should be persuasive and underline that translation from the laboratory to the bedside is a long and complicated process. Associated to the amount of research funds assigned to this area, there are fewer nanopharmaceutical materials available on the market. The PIP is a government initiative in the United States that funds research on paediatric therapies [117, 118] and also in Europe[119], which may increase advances in pediatric nanomedicines. Formation of the Pediatric Committee-Formulation Working Group of the European Medicines Agency is an exciting way to stimulate the creation of novel paediatric formulations and, in this example, the use of nanotechnologies to enhance efficiency. In recent years, it has been gratifying to see the emergence and consolidation of programmes that address fundamental barriers to paediatric therapy, for instance the Pediatric Formulation Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development [120], and the European Pediatric Formulation Initiative (EuPFI). GRIP (Global Research in Pediatrics – Network of Excellence), as well as the Global Research in Pediatrics – Network of Excellence (GRIP)[121] . These organisations examine and improve the taste and palatability of medications, which is a key problem in paediatric treatment [121]. Unrequited is if these creativities will be willing to support (or not) the development of

multi-disciplinary groups to solve the myriad challenges associated with the use of nanomedicine to children. Due to commercial constraints, we believe that the future of paediatric nanomedicine is inexorably linked to advances in the use of these advanced medications in adults. This is reinforced by nanomedicine's due to the lack of a reliable regulatory regime [122], which, from an ethical position, encourages the usage of the " Principle of precaution," limiting the use of nanotechnology on youngsters to the long term and only after lengthy and painstaking studies [123]. In contrast, many illnesses have a very high morbidity rate among youngsters, necessitating particular care and dedication that transcends commercial considerations in order to offer better treatment for everybody. The creation of research groups in academia and business that focus on the targeted and interdisciplinary treatment of each illness appears to be the most successful method for them. Instead, the present gap between adults and children would become much wider, placing paediatric patients even farther behind.

The role of nanomedicine in the neonatal period is of extreme interest and various research groups are actively investigating the potential role of nanomedicine in the neonatal period. However, a previous study suggests that early age exposure to the nanomedicine may induce inflamations and other pathological conditions [124]. Another study investigating the use of nanoparticles in the lungs of babies discovered that alveoli develop through secondary septation, alveolar flow becomes turbulent, and chaotic mixing sets in, considerably boosting particle deposition [125]. Despite the keen interest, there are no encouraging results. The researchers are actively investing the optimized kind of nanoparticle and understanding the interaction of nanomedicine with the different organs and physiological changes in the infant.

Concluding remarks

Nanotechnology has emerged as a critical technique for overcoming fundamental (bio)pharmaceutical issues like low aqueous solubility, reduced physicochemical stability, and limited bioavailability. Nanomedicine brings sustainable results for treating infant illness ranging from infection to various cancers and HIV. However, there are still many obstacles in translating those therapies and conducting clinical trials. Moreover, designing appropriate nanoparticles and minimize their toxicity is still a challenge that need to be solved. Although the success rate and growth of nanomedicine in the pediatric population is slower than the adult; however, it hold a great potential and will revolutionize the field.

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Conflicts of interest

None

Availability of data and material

All the data can be requested from the corresponding author upon reasonable request.

Code availability

Not applicable

Ethics approval

Consent to participate

Not applicable

Consent for publication

None

Author contribution statement

All authors contributed to the work fulfilling the criteria adopted from ICMJE. Acquisition of data: LC, ZS and XJ. Analysis and interpretation of data: LC, ZS and XJ. Drafting of the manuscript: LC, ZS and XJ. Critical revision: LC, ZS and XJ. Study conception and design: LC and XJ: Financial support: XJ. All authors read and approved the submitted version of the manuscript. Each author has agreed both be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even those in which the author was not personally involved, are appropriately investigated and resolved and that the resolution is documented in the literature.

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