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# Immunosuppression in Medulloblastoma: Insights into Cancer Immunity and Immunotherapy

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## Opinion statement

Medulloblastoma (MB) is the most common pediatric brain malignancy, with a 5-year overall survival (OS) rate of around 65%. The conventional MB treatment, comprising surgical resection followed by irradiation and adjuvant chemotherapy, often leads to impairment in normal body functions and poor quality of life, especially with the increased risk of recurrence and subsequent development of secondary malignancies. The development and progression of MB are facilitated by a variety of immune-evading mechanisms such as the secretion of immunosuppressive molecules, activation of immunosuppressive cells, inhibition of immune checkpoint molecules, impairment of adhesive molecules,

downregulation of the major histocompatibility complex (MHC) molecules, protection against apoptosis, and activation of immunosuppressive pathways. Understanding the tumor-immune relationship in MB is crucial for effective development of immune-based therapeutic strategies. In this comprehensive review, we discuss the immunological aspect of the brain, focusing on the current knowledge tackling the mechanisms of MB immune suppression and evasion. We also highlight several key immunotherapeutic approaches developed to date for the treatment of MB.

## Introduction to medulloblastoma

### Definition and epidemiology

Brain and other central nervous system (CNS) tumors are the most common form of solid tumors in infants and children [1] and are the leading cause of cancer-related deaths in childhood [2]. Medulloblastoma (MB) is the most common malignant childhood brain tumor, accounting for around 20% of all pediatric CNS tumors [3], and 63% of childhood embryonal tumors [1]. MB is a heterogeneous group of embryonal tumors that affect children more frequently than adults, with an incidence of 0.55 per 100,000 population in children aged 0-4 years and 0.16 per 100,000 population in adolescents aged 15–19 years [4]. Most MBs are known to arise from the cerebellar vermis in children; however, the cerebellar hemispheres are more common sites of origin among adults [5]. Males are more frequently diagnosed with MB than females in the children populations, with no racial or ethnic predisposition [6]. The 5-year overall survival (OS) rate of MB patients is 64.7%, although the prognosis varies greatly among the different tumor subgroups [4].

### Classification of MB

In its most recent update of tumor classification, the WHO recognized four main histologic types of MB, namely classic MB, large cell/anaplastic MB (LC/A-MB), desmoplastic/nodular MB (D/N-MB), and MB with extensive nodularity (MBEN) [7], which are differentiated according to cellular and histological criteria [8, 9]. Nevertheless, this update requires the integration of histological classification with molecular classification in MB diagnosis [7].

Four main molecular subtypes of MB were identified based on genotyping results: WNT-activated, sonic hedgehog (SHH)-activated and *TP53*-mutant, SHH-activated and *TP53*-wildtype, and non-WNT/non-SHH MB [7]. Wnt-activated subtype comprises about 10% of all MB cases, and is characterized by mutations rendering the Wnt pathway constitutively active [3, 10]. Almost all WNT-activated MB cases exhibit classic histology [11], and patients have the most favorable prognosis, with nearly 90% surviving more than 5 years [12, 13]. SHH-activated MB is the most common subtype in infants and adults. It exhibits a favorable prognosis (77% 10-year OS rate in infants) that worsens with the increase in age [11]. This subtype is associated with mutations in genes critical for the SHH pathway [14]. This subtype is further subdivided according to the presence of mutations in *TP53* gene, which has profound prognostic implications [7]. *TP53*-mutant subtype is associated with a 5-year OS rate of 41% as compared to 81% in *TP53*-wildtype subtype [15]. Non-WNT/non-SHH subtype comprises Group 3 and Group 4 MB, which affect males twice as often as females, and have no identified alterations in specific signaling pathways. Group 3 has the highest metastasis frequency and the worst prognosis among all subtypes, with a 5-year OS rate of 45% and 58% in infants and children, respectively [11]. On the other hand, Group 4 MB represents the most common subtype overall among the different age groups, with an intermediate prognosis (50% 5-year OS rate in infants and children) [11].

### Treatment strategies in MB

The current standard of care for MB includes surgical resection followed by craniospinal irradiation and adjuvant chemotherapy. However, although 5-year OS is approximately 80% for patients older than 3 years with no metastasis and with gross total tumor resection, it declines to around 60% in children with metastatic

disease and/or having subtotal tumor resection [16–19]. Moreover, treatment options in MB have been shown to be neurotoxic especially on infants, with studies demonstrating a decrease in intellectual functions among this patient group [20, 21], besides deficits in processing speed, broad attention, and working memory [22, 23] and increased risk of postoperative cerebellar mutism syndrome [24]. Therefore, there is a dire need for improving the conventional therapy and introducing safer and more effective alternatives. Recently, immunotherapy has gained much attention as an attractive approach to target cancer cells while sparing the adjacent non-tumor tissues. Clinical evidence has shown benefits of immunotherapy in many cancers including melanoma and leukemias among others [25–27]. Nevertheless, to develop safe and effective immunotherapies for MB, we need to better understand the normal and tumor immunology of the brain.

# Brain-immune interaction

## Aspects of immunity in the brain

The brain was originally described as an immune-privileged site, due to the restriction of immune cell entry by the blood-brain barrier (BBB), the absence of conventional lymphatic vessels, the inability of microglia to present antigens to T cells, and the low expression of major histocompatibility complex (MHC) molecules [28]. Nevertheless, it is now accepted that the brain shows persistent immune surveillance. Trafficking of immune cells across the BBB has been observed to be low and tightly controlled under normal physiological conditions, which increases when neuroinflammatory reactions develop [29, 30]. The cerebral-spinal fluid (CSF), which drains in the cervical lymph node, is also considered as a pathway for trafficking immune cells and macromolecules, providing a continuous and highly regulated communication between the brain and the immune system [31–34]. Moreover, functional lymphatic vessels have been recently discovered to line the dural sinuses, assisting in the drainage of macromolecules and enabling immune cells to enter the cervical lymph nodes [35–37].

Another unique feature of the brain-immune microenvironment is the unique population of immune cells. The brain immune cell population is composed of microglia (80% of brain immune cells), dendritic cells (DCs), macrophages, T cells, B cells, and natural killer (NK) cells [38]. Microglia are considered as the first line of response to pathological insults by which they show morphological [39] and molecular changes [40], exhibit phagocytic ability, express MHC molecules (although at low levels), release proinflammatory cytokines, and activate other immune cells [41–43]. On the other hand, DCs, which are the antigen-presenting cells (APCs) of the brain, have the ability to capture, process, and present foreign antigens, and also express different molecules such as CD11c, CD205, and MHC class II molecules. In the cervical lymph nodes, they encounter naïve lymphocytes and induce T cell activation and recruitment into the brain [44–46]. Recent studies have shown that B cells as well migrate to the infected brain area and aid in functional recovery after a focal stroke [47, 48].

## Immunity in brain tumors

Brain tumors have evolved multiple mechanisms to escape and inhibit the antitumor activity of immune cells [49]. Brain tumor cells secrete a number of chemokines, cytokines, interleukins, and growth factors that stimulate the

infiltration of immune cells such as microglia, macrophages, myeloid-derived suppressor cells (MDSCs), and T cells [50–54] into the tumor niche. Nevertheless, this microenvironment reprograms attacking immune cells by releasing cytokines and interleukins such as interleukin (IL)-10, tissue growth factor (TGF)-β, prostaglandin E2 (PGE2), and vascular endothelial growth factor (VEGF) that promote anti-inflammatory responses [55–57]. Furthermore, microglia acquires an M2-like phenotype by the influence of IL-4, IL-10, and IL-13 released by glioblastoma (GB) cells. In turn, microglia promotes glioma growth and survival by secreting growth factors such as TGF-β [58], VEGF, and members of fibroblast growth factor (FGF) family [59]. Besides, NK cells are functionally suppressed by the inflammatory molecules secreted by glioma cells such as cyclooxygenase (COX2), PGE2 [60], and TGF-β [61]. Furthermore, glioma stem cells have been shown to secrete cytokines that are known to reprogram tumor-associated macrophages (TAM) to become immunosuppressive [62].

Lymphocyte apoptosis is another immune-escape mechanism. GB cells were shown to contribute to lymphocyte apoptosis via interaction of CD70 expressed on glioma cells with CD27 expressed on T- and B-lymphocytes [63]. T cell apoptosis is also mediated by Fas-Fas ligand (FasL) interaction, which directly induces T cell apoptosis [64]. Another study revealed that FasL-positive microglia also mediate apoptosis of Fas-positive T cells [65].

Furthermore, intracranial tumors frequently display low numbers of tumor-infiltrating lymphocytes (TILs). Instead, naïve T cells are sequestered in large numbers in the bone marrow [66]. TILs that successfully infiltrate are exposed to further suppression [67]. This "cold tumor" phenotype is usually associated with immune checkpoint molecules [68, 69], such as programmed cell death-ligand 1 (PD-L1). Binding of PD-L1 with PD-1 on lymphocytes mediates T cell inactivation. Studies showed that the expression of PD-L1 on glioma cells and PD-1 on T cells is correlated with tumor progression into high-grade glioma [70]. Microglia also express PD-L1 and impede T cell activation [71].

## Mechanisms of immunosuppression and resistance in MB

Tumor microenvironment (TME) is a specialized niche in which dynamic interactions between malignant cells and host cells occur [72, 73]. These interactions are mediated by junctions, receptors, secretions, and signals of different cell types encased in a three-dimensional (3D) extracellular matrix (ECM), which promotes tumor progression and invasion [74]. MB exhibits a cold immune microenvironment which is largely attributed to the low levels of pro-inflammatory cytokines and T cell infiltration [75]. Besides MB cells, the main players in this malignant tumor are the innate and adaptive immune cells along with stromal cells including fibroblasts and vascular endothelial cells [76]. Immune cells within the MB TME include immunosuppressive cells such as TILs [77], TAMs [73, 75, 78], MDSCs [79], regulatory T (Treg) cells [80], tumor-associated astrocytes (TAA) [81], as well as NK cells [76] (Fig. 1). To enhance the aggressive impact of MB TME, MB cells secrete immunosuppressive molecules including cytokines such as TGF-β [82], ILs [83], chemokines [84], PGE2 [85], VEGF [86], immune checkpoint inhibitors [87], and gangliosides [88], to evade the immune recognition and promote tumor progression [89] (Fig. 2).

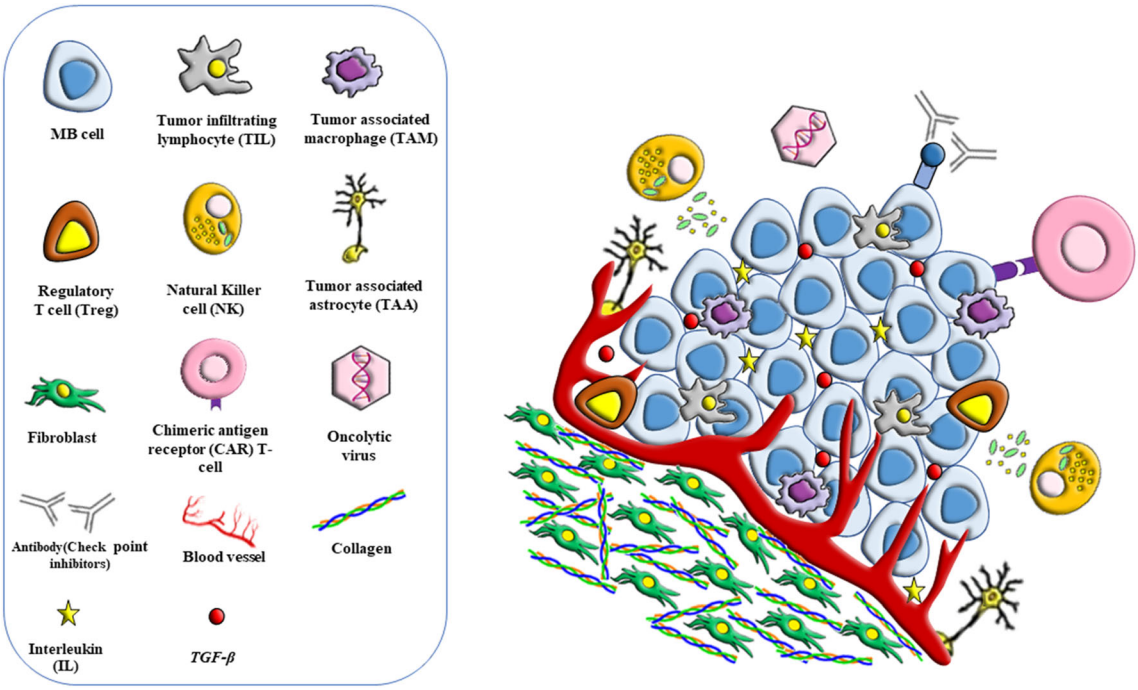


**Fig. 1.** MB microenvironment and immunotherapeutic strategies. MB exhibits an immunosuppressive microenvironment that involves the extracellular matrix including fibroblast and collagen as well as the immunosuppressive cells such as NK cells (NKs), tumor infiltrating lymphocytes (TILs), tumor-associated macrophages (TAMs), regulatory T cells (Treg), and tumor-associated astrocytes (TAA). MB is targeted via several immunotherapy approaches including the chimeric antigen receptor (CAR) T cell therapy, oncolytic virotherapy, immune checkpoint inhibitors, and cytokine inhibitor/administration.

## Immunosuppressive cells in MB microenvironment

### Tumor-infiltrating lymphocytes (TILs)

In MB, T-lymphocytes can only migrate to TME by the influence of a plethora of secretions. Once they migrate to TME, T-lymphocytes known as tumor infiltrating lymphocytes (TILs) play a critical role in promoting the survival and the progression of tumor cells as well as sustaining the tumor niche [77]. Notably, MB is characterized by a higher neutrophil-to-lymphocyte count ratio which reflects a poor prognosis in patients and is considered a feature of immunosuppression [76]. Several studies showed that MB induces the systemic immune suppression in the patients due to significant reduction in the absolute lymphocyte count and elevation in the neutrophil-to-lymphocyte count ratio in different MB subgroups [90•, 91].

### Tumor-associated macrophages (TAMs)

Macrophages in TME exhibit the anti-inflammatory M2 phenotype [92]. Recent studies showed that monocyte-derived TAM2 are immunosuppressive cells responsible for suppressing the anti-tumor immunity within the TME and mediating poor clinical prognosis [92, 93]. In this context, TAMs are considered as a major player in the MB microenvironment, where they modulate the immune response through the secretion of cytokines, chemokines, and growth

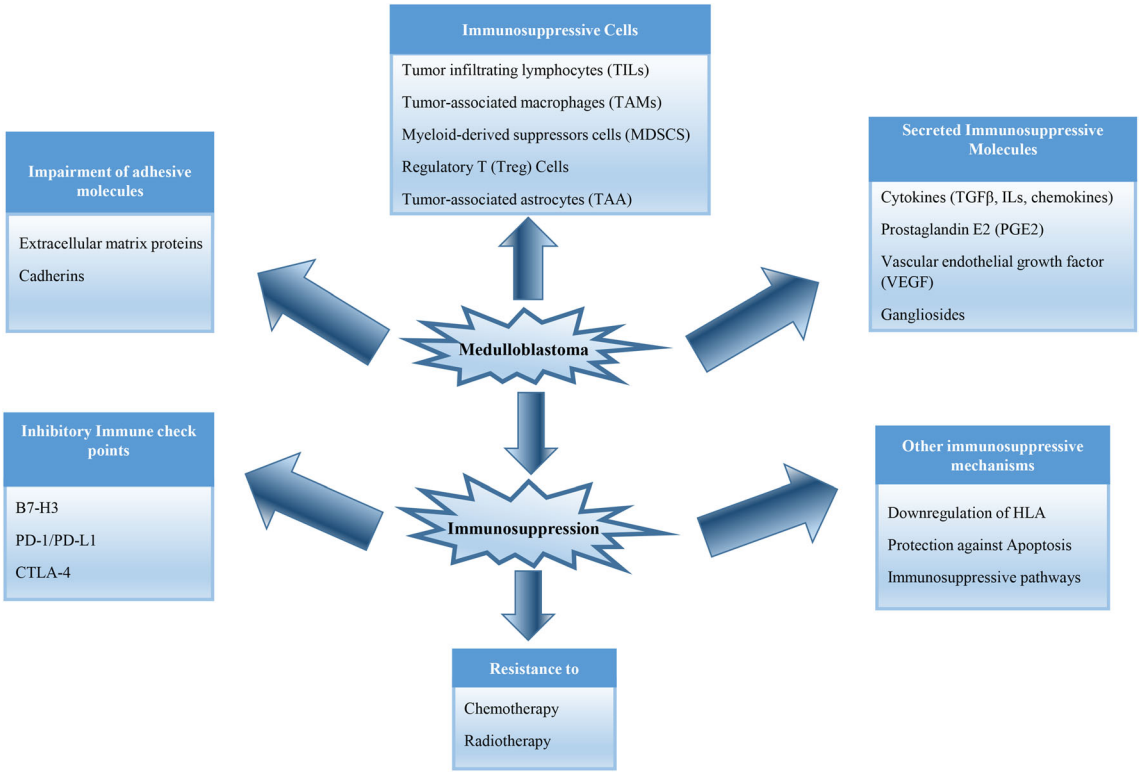


**Fig. 2.** Schematic representation of major immunosuppressive mechanisms of MB. Key mechanisms of MB immunoresistance are briefly described in the figure, including immunosuppressive cells, secretion of immunosuppressive molecules, impairment of adhesive molecules, inhibition of immune checkpoints, downregulation of HLA molecule, protection against apoptosis, and activation of immunosuppressive pathways. These mechanisms are also involved in chemoresistance and radioresistance.

factors [75] to promote tumor progression, survival, invasion, metastasis, angiogenesis, and inflammation [94], as well as resistance to chemotherapy [92].

## Myeloid-derived suppressor cells (MDSCs)

MDSCs are immature myeloid cells that act as a potent suppressor of anti-tumor immunity within the TME [79]. Under pathologic conditions, MDSCs promote tumor growth and invasion [95] through the suppression of T cells within MB TME in response to secreted IL-6 cytokines [79]. A recent study showed that the activation of CD200R on MDSCs by its ligand (CD200) leads to the negative regulation of immune response and promotes tumorigenesis [96].

## Regulatory T (Treg) cells

Treg cells are a subgroup of CD4+ T-lymphocytes which serve as potent inhibitors of anti-tumor immunity through the suppression of T cell activation and progression by the production of nitrogen-oxygen species (NOS) under the control of MDSCs [97], downregulation of IL-2, and induction of the cytokine secretion by T-helper type 2 (Th2) cells. Several studies revealed the role of STAT3 in myeloid cells to maintain the Treg populations in MB [79].

### Tumor-associated astrocytes (TAAs)

In the normal brain, astrocytes are responsible for maintaining homeostasis, however, in the pathological state, they adapt the "reactive state" through a specialized transition called "astrogliosis" to impact the immune surveillance and promote inflammation [98, 99]. In MB, TAAs enhance MB cell proliferation and growth through the expression and secretion of the mitogen SHH in the TME in response to nestin expression [100]. Moreover, TAA-derived C-C ligand 2 (CCL2) chemokine has been shown to trigger the stemness in MB stem cells (MBSCs) through the activation of the Notch signaling pathways, in addition to inducing necroptosis (programmed necrosis) [101].

## Secreted immunosuppressive molecules

### Cytokines

*Transforming growth factor (TGF-β)*

TGF-β is a pleiotropic cytokine [102] secreted by MB cells. It is considered as a potent immune suppressive factor that helps evade the cytotoxicity of the T cell populations [82] and mediates the negative effect on NK cells [103] either directly through the disruption of IFN-γ secretion, or indirectly through the inhibition of IL-12 production by DCs [104]. Previous studies showed that the expression of TGF-β1 and TGF-β2 promotes autoregulation in MB [105].

*Interleukins (ILs)*

In the early stage of tumorigenesis, the elimination of cancer cells is mediated by the activation of pro-inflammatory and Th1-associated factors including IL-1, IL-12, and IL-15. However, in the advanced stages of tumor progression, the prolonged inflammatory state in the TME promotes the activation of the suppressive response of Th2-associated factors such as IL-4, IL-5, IL-8, IL-10, and IL-13 [83].

IL-6 is a paracrine growth factor that triggers development, proliferation [106], inflammation, and immune regulation of MB cells [106, 107]. In MB cells, IL-6 activates the oncogenic JAK/STAT pathway [107–109], leading to MB cell viability, proliferation, glycolysis, clonogenicity [107], as well as the chemoresistance in Group 3 of MB cell lines [108]. In addition, Th17 cells produce a repertoire of interleukins that promote tumor growth and impair immune surveillance. Accumulated evidence revealed the high levels of Th17 and IL-17 both in the patients' peripheral blood and among MB-infiltrating T cells [109, 110]. Besides, IL-8 has been attributed to the survival, growth, and immunosuppressive and pro-angiogenic properties of MB cells [111].

*Chemokines*

Chemokines are chemoattractant cytokines that control the migration of immune cells via the interaction with their cell surface receptors [84]. C-C motif ligand 2 (CCL2), is one of the chemokines that is highly expressed

in MB and considered as a pro-inflammatory mediator that has the potency to promote the spreading and proliferation of the tumor cells and is sufficient to drive the leptomeningeal dissemination through the interaction with its C-C chemokine receptor type 2 (CCR2) [112, 113]. To add, the overexpression and activation of the chemokine receptor CXCR4 may be essential for the maximal growth of the SHH-driven MB [114].

### Prostaglandin E2 (PGE2)

Prostaglandin E2 (PGE2) is bioactive lipid compound [115] that plays a role in many human cancers including MB [85, 116]. It mediates cellular proliferation, angiogenesis, inhibition of apoptosis, invasion, and suppression of immune responses via the interaction with four distinct G-protein coupled receptors (EP1, EP2, EP3, and EP4). Notably, MB cells express high levels of PGE2 and its receptors in a way that promotes their proliferation [85].

### Vascular endothelial growth factor (VEGF)

VEGF is a pro-angiogenic growth factor that serves as one of the most potent mitogens in CNS malignancies [86, 117] Among the immunosuppressive factors released by malignant cells, VEGF-A plays an essential role in the induction of immunosuppressive microenvironment through a cascade of events including the impedence of DCs maturation and differentiation, aggregation of MDSC, and induction of Treg cells proliferation [118].In MB, VEGF-A mediates the invasion and metastasis through the CSF and reflects a poor prognostic status [119, 120]. Besides, the soluble and receptor isotypes of VEGF are found in most MB patients [121].

### Gangliosides

Gangliosides are sialic acid-containing glycosphingolipids [122] and one of the tumor cell surface molecules. They contribute to the immunosuppression in MB cell lines through the inhibition of the leukocytes' response, enhancement of platelet activation, angiogenesis, and tumor cell invasion. MB cell lines are characterized by a rapid shedding rate of gangliosides in CSF [123], which serves as a prognostic factor in MB patients [88].

## HLA class I defect

HLA class I molecules play a pivotal role in anti-neoplastic immune response [124] by either presenting a range of self and foreign antigens to cytotoxic T-lymphocytes (CTL), or serving as ligands for killer immunoglobulin-like receptors (KIRs) on NK cells [125]. Nevertheless, MB tumor downregulates the HLA class I molecules to evade T cell-mediated immunity and NK cell recognition [89]. This deregulation and structural alteration in the MHC class I antigen presenting machinery results in facilitating MB expansion, aggression, and metastasis. Furthermore, several studies reported the co-expression of the negative prognostic markers such as c-MYC and HLA class I molecules in MB [126]. They have shown the interaction of β2 microglobulin (β2m) that is produced and secreted into the extracellular matrix of MB tissues with the MHC class I molecules on adjacent cells leading to the enhancement of the migratory potential and invasiveness of MB cell lines [126, 127].

## Impairment of adhesive molecules

### Extracellular matrix (ECM) proteins

The key proteins in the ECM include fibronectin, collagen, tenascin, and laminin, which bind to integrins [128]. Integrins are multifunctional cell surface heterodimers, expressed in tumor cells and are responsible for promoting tumor growth, stemness and metastasis. [129]. In vivo and in vitro studies reported the interaction of cell surface integrins with ECM tenascin mediating the adhesion, survival and proliferation of MB cells [128]. Another ECM protein, known as type I collagen, plays a role in MB angiogenesis and vasculature [130].

### Cadherins

Cadherins are $Ca^{2+}$-dependent hemophilic cell-cell adhesion molecules [131] that maintain homeostasis [132] through the interaction with β-catenin. In this sense, the dysfunctional expression of these classical cadherins seems to be related to cell differentiation, proliferation, tumor invasion, and metastasis. Moreover, mutations in β-catenin have been associated with MB development. Accumulated evidence has shown the immunoreactivity of most MBs and high grade-gliomas for N-cadherin and β-catenin, which are responsible for dissemination, proliferation, and poor prognosis [131].

## Immune checkpoint molecules

B7-H3 is an inhibitory immune checkpoint ligand [87], which plays a critical role in promoting MB angiogenesis, progression, tumor cell signaling and chemoresistance [133]. Notably, B7-H3 is highly expressed in MB tumor tissues compared to other immune checkpoints, like the PD-1/PD-L1 and the cytotoxic T-lymphocyte antigen (CTLA)-4 [87]. Besides, the persistent expression of PD-1/PD-L1 immune checkpoint in MB shows a worse prognosis in patients [89].

## Protection against apoptosis

Apoptosis is induced in response to different anti-neoplastic agents [134, 135•, 136–139]. Notably, MB mediates the resistance to apoptosis [140] through the expression of intracellular apoptotic inhibitor (IAP) and the caspase inhibitors to escape from death receptors-induced apoptosis and granzymes-mediated killing pathways [89, 141]. Besides, MB cells undergo a high mitotic activity under the cIAP1 expression [142]. In addition, MB has the potency to express the anti-apoptotic genes including Bcl-2 and c-FLIP, resulting in the resistance to TNF-related apoptosis-inducing ligand (TRAIL) [141]. Another anti-apoptotic molecule, known as microRNA 21 (miR-21), is widely upregulated in all MB subgroups [143]. Moreover, glioma transcription factor (Gli1) binds directly to the Bcl-2 promoter, resulting in the regulation of the MB cell survival [144].

## Novel immunosuppressive pathways in MB

Several studies have demonstrated the role of tumor's intrinsic signaling pathways in mediating the resistance to the immune aggression including the activity of STAT [145], PI3K/Akt/mTOR [146], MAPK [147], and ERK pathways [148]. In MB, PI3K/Akt/mTOR pathway is activated to trigger cell development,

proliferation, migration, angiogenesis, and chemoresistance [146–153]. Furthermore, STAT3 is a master cell survival protein that plays an important role in anti-apoptosis, angiogenesis, and cell evasion of the immune cells in many brain tumors, but its elevated level is noticed mainly in MB for its maintenance and development [145]. Recent studies reported the implication of cyclin-dependent kinase (CDK) inhibitor, known as P27, in MB cell migration [154].

### Subgroup-specific immune microenvironment in MB

Understanding the immune microenvironment of MB subgroups is essential in order to develop strategies for immunotherapies in pediatric populations. These subgroups have distinct immune profiles that exploit several mechanisms to facilitate immunosuppression and evasion [155]. Recent studies showed a significant difference in immune and stromal cell populations that reside in the MB subgroups-related microenvironment except for NK cells and B cells. First, SHH-derived MB is characterized by more macrophages, DCs, T cells and myeloid cells compared to Group 3 MB, which reflects a better prognosis [76, 89, 155]. On the other hand, SHH-derived MB expresses high levels of inflammation-related genes including TAM-related genes such as *CD163* and colony-stimulating factor-1 receptor (CSF1R) and the inhibition of this receptor can arrest the protumor effects in the TME [94].

Moreover, SHH- and Wnt-derived MBs exhibit a monocytic/macrophage and Treg supported pro-tumorigenic microenvironment, while most Group 3 and Group 4 MBs belong to a pattern of tumors that suppresses the infiltration of lymphocytes by immunosuppressive cytokines and checkpoint pathways. Such differentiation of immunological characteristics among the different MB subtypes supports the development of subtype-specific immunotherapeutic strategies [76].

## Immune biomarkers in MB

To identify the heterogeneous phenotypes of distinct MB subtypes, several studies highlight the characterization of novel cell surface markers expressed by these tumor cells. Based on the cancer stem cell (CSC) theory, some tumors including MB contain a subpopulation of cells that exhibit stem cell-like properties, responsible for tumor initiation and maintenance [134, 135•, 156–159••]. CSCs in brain tumors express neural precursor cell surface markers such as CD133 (prominin1) which is responsible for the resistance against apoptosis, drugs, and ionized radiations, and for enhancing the self-renewal capacity [156, 160, 161]. Another cell surface marker, CD271, is a member of the tumor necrosis factor receptor family and is commonly referred to as p75 or p75NTR. It plays a critical role in neurodevelopment including growth cone elongation, axon guidance, cell survival, and cell death depending on neurotrophin ligands as NGF, BDNF, NT-3, and NT-4 [156, 160]. Furthermore, MB exhibits an inverse relationship among the cells that express both cell surface markers (CD133 and CD271). Higher self-renewing cells capacity exhibits an increased expression of CD271 and a decreased expression of CD133 to maintain tumorigenesis, while the opposite expression pattern of these cell surface markers exhibits a highly motile displayed cell [160]. To add, matrix metalloproteinase (MMP) triggers the MB invasion. MB tissues express MMP-9

and membrane type-1 (MT1)-MMP, which is likely responsible for invasion, radio-resistance, and triggering the hypoxic status [161]. Moreover, tumor propagating cell (TPC) expresses another marker, known as CD15, which was found on progenitors and stem cells in the embryonic and adult CNS, plays an essential role in the maintenance and growth of human MB [162]. Interestingly, recent studies highlight a critical immune marker that mediates the immune response in both normal brain and brain tumors, known as MHC class I. In addition, aggressive types of MB are associated with a negative prognostic marker which is c-myc gene. As a result, MHC class I is expressed in aggressive MB with poor prognosis, which in turn induces ERK1/2 phosphorylation and mediates MB metastasis [126]. Besides, all MB cells express a potent CD146 marker, which is responsible for the growing tumor rate and metastasis in the pediatric population [163].

# Immunotherapy in medulloblastoma

MB patients usually benefit from different therapeutic paradigms of maximal safe resection, radiation, and adjuvant chemotherapy [18, 164] that can lead to long-term limitations in behavioral, social, cognitive, and physical functions [165, 166]. In the last few decades, there has been a significant progress in the field of immunotherapy that aimed to improve the host immune response against tumor cells [167, 168]. In MB, various experimental approaches in immunotherapy have highlighted the increasing potential for MB treatment (Fig. 1).

## Adoptive cellular therapy/cellular immunotherapy

Adaptive cellular therapy involves the direct isolation and modification of host immune cells to enhance their cancer-fighting capabilities, followed by their subsequent infusion back into the host for direct targeting of cancer cells [169]. This approach can be deployed in different ways: NK cell therapy, chimeric antigen receptor (CAR) T cell therapy, engineered T cell receptor (TCR) therapy, and TIL therapy.

### NK cells therapy

NK cells can effectively target MB cells mainly through activation of different NK cell receptors (NKG2D, DNAM-1, NKp30, and NKp46) upon the binding of specific MB cell ligands [163]. Blocking of NKG2D receptors on the NK cells and specific ligands expressed on HTB-186 MB cell line, major histocompatibility complex class I-related chain A (MICA) and UL16 binding protein (ULBP-2), have increased the resistance to NK cells lysis in vitro [170], indicating the impact of appropriate stimulation of NK cells for potential targeting of MB cells. However, blocking of HLA class I on MB cells and stimulation of NK cells with IL-15 increased the cytotoxicity against MB cells in vitro [170]. Accordingly, stimulation of NK cells via IL-15 could be a valuable strategy for MB treatment, as has already been suggested for other pediatric solid tumors [171]. Modification of cord blood NK cells to express a dominant negative TGF-β receptor II (DNRII) by retroviral transduction proved an effective therapeutic intervention for brain tumors through evading TGF-β [172]. An in vitro study reported that

MB cells were rendered susceptible to NK cells expressing DNRII receptors and also suggested that DNRII can restore the function of NK cells by neutralization of TGF-β [103]. Another study showed that the intracranial injection of human NK cells resulted in a remarkable regression of orthotropic human MB xenografts in NOD/SCID mice, suggesting that NK cells alone were able to significantly delay MB growth [173]. One clinical study has shown the safety of autologous NK cell therapy in patients with recurrent malignant gliomas [174]. A phase I clinical trial conducted on children with recurrent MB and ependymoma showed no dose-limiting toxicities of the intraventricular infusion of autologous ex vivo expanded NK cells, with one out of nine patients showing a stable disease for one month at the end of study follow-up [175]. Another phase I clinical trial has focused on the side effects and the accurate dose of NK cell in pediatric patients with recurrent/ refractory brain tumors including MB, but the results have not been released yet (ClinicalTrial.gov; Phase I clinical trial; NCT02271711) (Table 1).

## Chimeric antigen receptor (CAR) T cell therapy

CAR T cell therapy represents a new era of personalized cellular cancer therapy. It is based on genetically engineering patient's own T cells to express a particular receptor that specifically binds a tumor antigen [176]. CAR T cell treatment holds great promise in the treatment of brain malignancies [177, 178]. It has also been translated clinically and showed an effective therapeutic potential in GB patients [179]. Since HER2 is overexpressed in MB, it can be targeted by CAR T cell therapy. HER2 CAR T cells were able to proliferate and secrete IFN-γ and IL-2 in a HER2-dependent manner. They recognized and attacked MB cell lines and autologous primary MB cells ex vivo and reduced the growth of MB in the orthotopic xenogenic SCID mouse model [180]. Nellan et al. showed that HER2-BBz-CAR T cells therapy effectively cleared MB that was implanted in the posterior fossa of NSG mice via both regional and intravenous delivery in a xenograft mouse model without causing any considerable treatment-related toxicity [181]. Similar results were obtained for NKG2D-specific CAR T cells (KD-025) where KD-025 eliminated MB xenograft in NSG mice without any noticeable safety issues [182]. Another study showed a remarkable antitumor activity B7-H3 CAR T cells in vivo where they mediated MB regression in NSG mice model [183]. Given these data, advances in CAR T cell therapy allow this approach to be translated clinically into patients with MB. Two phase I clinical trials, (ClinicalTrial.gov; Phase I clinical trial; NCT03500991) and (ClinicalTrial.gov; Phase I clinical trial; NCT03638167), are currently evaluating the feasibility, safety, and tolerability of CAR T cell therapy in CNS tumors including MB (Table 1).

## Engineered T cell receptor (TCR) therapy

Like CAR T cell therapy, engineered TCR therapy involves targeting tumors via new T cell surface receptors. However, in engineered TCR therapy, the artificial receptor relies on the TCR-peptide/MHC to mark cancer cells with recognizable antigens [184]. MB cells are characterized by a high expression level of several

**Table 1. Immunotherapy clinical trials for MB patients (ClinicalTrials.gov)**

| Clinical Trial | Treatment | Feature | Phase | Delivery | Number of Participants | Combination | Estimated completion date |
|---|---|---|---|---|---|---|---|
| **NK cell therapy** | | | | | | | |
| NCT02271711 | Expanded NK cell infusion | ex vivo propagated autologous NK cells with aAPCs | I | IV | 12 (Brain tumors including MB) | | August 2020 (completed without posted results) |
| **CAR T-cell therapy** | | | | | | | |
| NCT03500991 | HER2 specific CAR T-cells | HER2 specific CAR T-cells autologous CD4 and CD8 T cells lentivirally transduced to express HER2 and EGFRt | I | Indwelling CNS catheter | 48 (Brain tumors including MB) | | July 2036 |
| NCT03638167 | EGFR806 specific CAR T-cells | EGFR806 specific CAR T-cells autologous CD4 and CD8 T cells lentivirally transduced to express EGFR806 and EGFRt | I | Indwelling CNS catheter | 36 (CNS tumors including MB) | | March 2037 |
| **Immune checkpoint inhibitors** | | | | | | | |
| NCT03173950 | Nivolumab | Anti PD-1 antibody (human IGg4 mAb) | II | IV | 180 (CNS tumors including MB) | | December 2024 |
| NCT02359565 | Pembrolizumab | Anti PD-1 antibody (humanized mouse IgG4 isotype mAb) | I | IV | 110 (Brain tumors including MB) | | December 2023 |
| NCT03130959 | Nivolumab | Anti PD-1 antibody (human IGg4 mAb) | II | IV | 170 (CNS tumors including MB) | Ipilimumab | June 2021 |
| NCT00089245 | Omburtamab | 131I-8H9 radiolabeled mAb (anti-B7-H3 mAb) | I | intrathecal | 120 (CNS tumors including MB) | | July 2020 (completed without posted results) |
| NCT02502708 | Indoximod | IDO pathway inhibitor | I | IV | 81 (primary malignant brain tumors including MB) | TZM, radiation, cyclophosphamide, and etoposide | February 2020 (completed without posted results) |
| NCT04049669 | Indoximod | IDO pathway inhibitor | II | IV | 140 (Brain tumors including MB) | TZM, radiation, cyclophosphamide, etoposide, and lomustine | October 2026 |
| **Vaccination** | | | | | | | |
| NCT01326104 | DC vaccine and tumor-specific immune cell vaccine | TTRNA-xALT; TTRNA-DCs | I and II | IV for TTRNA-xALT vaccine and ID for TTRNA-DCs vaccine | 17 (Recurrent MB and primitive neuroectodermal tumors) | | July 2021 |
| NCT02332889 | Autologous DCs | Autologous DCs pulsed with peptide mixes derived from full-length MAGE-A1, MAGE-A3, and NY-ESO-1 | I and II | IV | 1 (Brain tumors including MB) | | May 2018 (terminated due to a serious adverse event and disease progression) |
| NCT01171469 | Autologous DCs | Autologous DCs loaded with allogeneic brain tumor stem | I | ID | 8 (Brain tumors including MB) | Imiquimod | December 2017 |

**Table 1.** (Continued)

| Clinical Trial | Treatment | Feature | Phase | Delivery | Number of Participants | Combination | Estimated completion date |
|---|---|---|---|---|---|---|---|
| | | | | | | | (terminated without posted results) |
| **Oncolytic virotherapy** | | | | | | | |
| NCT02962167 | MV-NIS | Attenuated strain of measles virus; expressing NIS | I | LP | 46 (patients with recurrent MB or AT/AR) | | November 2022 |
| NCT03615404 | CMV RNA-pulsed DC | Expression of pp65 | I | IM with tetanus-diphtheria toxoid vaccine | 11 (recurrent MB, grade IV glioma, and recurrent malignant glioma) | | August 2022 |
| NCT03299309 | PEP-CMV | SLP | I | ID | 30 (recurrent MB and malignant glioma) | TMZ or bevacizumab | December 2023 |
| NCT03043391 | PVSRIPO | Attenuated strain of poliovirus; IRES replaced by IRES from HRV2 | I | IT | 12 (malignant glioma and MB) | | March 1, 2022 |
| NCT02444546 | Reolysin | Wild-type reovirus | I | IV | 6 (High-grade relapse or refractory brain tumors including MB) | Sargramostim | January 1, 2025 |
| NCT03911388 | HSV G207 | γ-34.5 and ICP6 genes deletion | I | Catheters | 15 (Recurrent or refractory cerebellar brain tumors including MB) | 5 Gy dose of radiation | September 2024 |

Abbreviations: *aAPCs* artificial antigen presenting cells; *AT/AR* Atypical Teratoid/Rhabdoid Tumor; *CAR* chimeric antigen receptor; *CMV* cytomegalovirus; *DC* Dendritic cells; *EGFR* epidermal growth factor receptor; *HER2* human epidermal growth factor receptor 2; *HRV2* human rhinovirus; *HSV* herpes simplex virus; *ID* intradermally; *IM* intramuscular; *IRES* internal ribosome entry site; *IT* intratumorally; *IV* intravenously; *LP* Lumbar puncture; *mAb* monoclonal antibody; *MB* Medulloblastoma; *MV* Measles virus; *NIS* sodium iodide symporter gene; *NK* natural killer cells; *PD-1* programmed cell death protein 1; *SLP* synthetic long peptide; *TMZ* Temozolomide; *TTRNA-DCs* total tumor RNA loaded dendritic cells; *TTRNA-xALT* total tumor RNA- ex vivo expanded Autologous Lymphocyte Transfer

immunogenic antigens that belong to an expanding family of immunogenic cancer testicular antigens (CTAs) [185–187]. PRAME, an immunogenic CTA, is frequently expressed in various cancers including MB with a limited expression in normal tissues [186, 188]. Orlando et al. targeted MB by using genetically modified T cells with PRAME-specific TCR (SLL TCR T cells) [189]. Engineered SLL TCR T cells have effectively destroyed MB HLA-A*02$^+$ Daoy cells. Besides, orthotopic MB NSG mice showed a dynamic tumor regression after injection of SLL TCR T cells [189]. These data suggest that engineered TCR therapy could be an effective strategy for targeting MB and should be tested in early-stage clinical trials for MB patients.

### TIL therapy

TIL therapy depends on harvesting naturally occurring lymphocytes that have already infiltrated into the tumor site, followed by their activation, expansion, and subsequent infusion back into patients. This approach was initially established by Eberlein et al. in which the injection of lymphocytes expanded in IL-2 has mediated the cure of mice with syngeneic lymphoma [190]. Regarding MB, tumor-reactive T cells were generated and adoptively transferred into MB-bearing mice. These TIL clones have retained their antitumor activity against MB and exhibited a considerable in vivo clonal expansion and persistence within the peripheral blood [191].

## Immune checkpoint inhibitors

Immune checkpoint inhibitors have been approved for the use in various types of cancers due to their potential in producing durable tumor regression [136, 137, 192, 193]. These drugs are predominantly monoclonal antibodies that are developed to block immune checkpoints on the surface of immune cells, preventing the interaction with the respective checkpoint ligands, reducing the suppression of T cells, and thereby restoring the function of immune cells [138]. Several studies have discussed the activity of checkpoint inhibitors on MB. Pham et al. demonstrated that the molecular subtypes of murine MB possess distinct immunologic profiles that differentially respond to immune checkpoint inhibitors in mice bearing intracranial MB tumors [155]. Murine group 3 MB contained a higher percentage of PD-1$^+$ CD8$^+$ cells than the SHH MB group, whereas no appreciable difference was detected for the CTLA-4$^+$ CD4$^+$ T cells between the two MB groups. This further suggested that group 3 MB has a more pronounced response to PD-1 blockade [155]. However, another study has demonstrated a complete absence of PD-L1 expression in pediatric MB, and correspondingly PD1/PD-L1 blockers might be inappropriate for MB treatment [89]. While Vermeulen et al. has recognized limited PD-L1 level in MB [89], Martin et al. showed higher PD-L1 expression level in SHH compared to group 3 and 4 MB [139]. The uncommon PD-L1 expression and rare PD-1$^+$ T cell tumor infiltration inferred that MB may not be a suitable candidate for immune checkpoint inhibitors [194]. Several clinical trials, (ClinicalTrials.gov; Phase II clinical trial; NCT03173950), (ClinicalTrials.gov; Phase I clinical trial; NCT02359565), (ClinicalTrials.gov; Phase II clinical trial;

NCT03130959), (ClinicalTrials.gov; Phase I clinical trial; NCT00089245), (ClinicalTrials.gov; Phase I clinical trial; NCT02502708) and (ClinicalTrials.gov; Phase I clinical trial; NCT04049669) are investigating checkpoint inhibitor drugs in MB patients (Table 1). However, many of those results have not been released yet.

## Vaccination

The expression of tumor-specific antigens holds immunotherapeutic potential, as they have been successfully targeted by vaccination for cancer patients [195, 196]. A series of tumor-specific antigens could render MB amenable to vaccine therapy [197]. Monocyte-derived DCs were generated to be used as a source of tumor-associated antigens. DC-based vaccination showed a more favorable response in high-grade glioma and atypical teratoid-rhabdoid tumors than that in MB patients [198]. Nair et al. have investigated the potential to generate DCs to evaluate ex vivo-generated DCs-RNA based vaccination approach in MB patients [199]. This study is currently in phase I and II clinical trial (ClinicalTrials.gov; Phase I and II clinical trial; NCT01326104). Another autologous DC vaccination based on targeting peptides derived from NY-ESO-1, MAGE-A1, or MAGE-A3, was administrated to MB patients (ClinicalTrials.gov; Phase I and II clinical trial; NCT02332889). However, the study was terminated due to a serious adverse event and disease progression. Furthermore, a Phase I clinical trial was organized for patients with malignant brain tumors including MB using vaccination with brain tumor stem cells-loaded DC. Nevertheless, this trial was terminated without any posted results (ClinicalTrials.gov; Phase I clinical trial; NCT01171469) (Table 1). The use of MB vaccines seems, at least at present time, to be limited and not considered as a therapy of choice mainly for MB patients.

## Oncolytic virotherapy

Oncolytic viruses (OVs) are biotherapeutics that have been genetically engineered to selectively infect and kill tumor cells, gaining attention for the treatment of several types of cancers [200–202]. An in vitro study has reported the ability of rhinovirus, a recombinant form of poliovirus, to inhibit the proliferation and subsequently kill MB cells [203]. The oncolytic virotherapy with myxoma virus was also studied in MB where it prolonged the survival of tumor-bearing mice. The combinational therapy with rapamycin further enhanced the oncolytic potential of the myxoma virus and reduced tumor metastasis [204]. Another study has reported that the intracerebellar MB xenograft was eliminated after a single intravenous injection of picornavirus SVV-001, resulting in a significant increase in survival [205]. Studebaker et al. evaluated the oncolytic therapeutic potential of herpes virus eRp450 using orthotopic xenograft group 3 and 4 MB, in which eRp450 therapy displayed a significantly prolonged survival following a single intratumoral injection. It also revealed the enhanced efficacy of rRp450 upon the combination with chemotherapeutic drug cyclophosphamide [152]. This is in-line with another study supporting the role of engineered herpes simplex virus therapy for infecting and killing pediatric MB cells [153]. These results underline the potent preclinical antitumor activity of oncolytic virotherapy against MB. To date, various oncolytic viruses are currently under clinical evaluation, (ClinicalTrials.gov; Phase I clinical trial; NCT02962167), (ClinicalTrials.gov; Phase I clinical trial; NCT03615404), (ClinicalTrials.gov; Phase I clinical trial; NCT03299309), (ClinicalTrials.gov; Phase

I clinical trial; NCT03043391), (ClinicalTrials.gov; Phase I clinical trial; NCT02444546) and (ClinicalTrials.gov; Phase I clinical trial; NCT03911388) (Table 1).

### Cytokine inhibitors/administration

Targeting cytokines and their receptors have been investigated in many studies due to their critical role in several aspects of cancer biology. An in vitro study demonstrated that the blocking of pro-inflammatory IL-6 signaling by the FDA-approved drug bazedoxifene inhibited cell proliferation and colony formation, and decreased cell viability and glycolysis in Daoy and UW288 MB cell lines [107]. Another study reported that targeting IL-13 receptors by IL-13 cytotoxin induced cytotoxicity in UW228 MB cell lines [206]. Additionally, CXCR4 inhibitors (AMD3100 and AMD3465) have shown significant antitumor effects by inhibiting MB cell line growth and migration, inducing apoptosis in MB tumors, and reducing MB allograft growth in mice [114, 207, 208].

In contrast to the therapeutic role of cytokine inhibition, contradictory results have been obtained upon chemokines and ILs administration. Zhou et al. reported a considerable reduction in MB growth in IL-17-injected mice suggesting its antitumor properties [109]. Regarding chemokines, treatment with chemokine CXCL3 elicited a complete disappearance of MB lesion, and further forced the migration and differentiation of pre-neonatal precursor cells (pGCPs) in *Ptch1*$^{+/-}$ /*Tis21*$^{-/-}$ mice [209]. These results were consistent with other findings that confirmed the role of CXCL3 in reducing lesion size and promoting pGCPs migration [210].

## Conclusions

Medulloblastoma is one of the most devastating pediatric tumors in which long-term survival is achievable nonetheless with significant morbidity from current therapeutic strategies. There has been a great advance in the knowledge of MB immunology over the last few decades. Substantial research work focused on the immunosuppressive mechanisms of MB has been performed providing an initial understanding of how MB can improve its own immunosuppressive mechanisms and evade the immune responses. Standard chemotherapy and radiotherapy are both profoundly immunosuppressive regimens. On the other hand, numerous studies concentrated on the promising potential of various immunotherapeutic approaches to target MB. However, intrinsic immunosuppressive properties, antigenic heterogeneity, physical barriers, the most suitable immunotherapeutic strategy, the dose for each case, and the route of drug delivery are some of the challenges for successful immunotherapy. Novel immunotherapeutic strategies including combination therapy should be developed to overcome the aforementioned obstacles and to achieve the most favorable results.

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## Code Availability

Not applicable.

## Author Contribution

H.F.Bahmad and S.Nabha conceived the concept and idea of the present
review. H.F.Bahmad and S.Nabha worked on the study design strategy and selected the topics to be discussed. Z.Audi, Z.Saker, and M.Rizk did literature searches and screened titles and abstracts for relevance, abstracted the data from the eligible full text articles, analyzed and interpreted the data, and drafted the manuscript. H.Harati and Y.Fares critically revised the manuscript. H.F.Bahmad and S.Nabha critically revised the manuscript with input from the entire team. All authors have read and approved the final draft.Data AvailabilityNot applicable.

## Declarations

**Ethics Approval**
Not applicable.

**Consent to Participate**
Not applicable.

**Consent for Publication**
Not applicable.

**Conflict of Interest**
Zahraa F. Audi declares no conflict of interest. Zahraa Saker declares no conflict of interest. Mahdi Rizk declares no conflict of interest. Hayat Harati declares no conflict of interest. Youssef Fares declares no conflict of interest. Hisham F. Bahmad declares no conflict of interest. Sanaa M. Nabha declares no conflict of interest.

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- • Of importance
- •• Of major importance

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