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REVIEW OPEN ACCESS

The Impact of Extracellular Vesicles on Inflammation in the Tumor Microenvironment of Sarcomas: A Literature Review

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Abstract

Introduction: Sarcomas are a diverse group of tumours encompassing over 100 different subtypes occurring in bone, muscle, and cartilage. The sarcoma tumour microenvironment (TME) contains various immune modulators and is influenced by the specific sarcoma subtype. The sarcoma TME is modulated by secretion of cytokines, chemokines, and extracellular vesicles (EVs). EVs play a role in inflammatory and immune responses in the TME. EVs effects are attributed to their cargo, consisting of mRNAs, proteins, miRNAs, chemokines, and cytokines. Sarcoma cells release tumour-derived EVs, facilitating communication, tumour progression, and inflammation.

Methods: We conducted a literature search for keywords and concepts associated with EVs and inflammatory responses in sarcomas on the PubMed database. Keyword combinations included relevance to EVs, sarcomas and inflammation. Only studies from peer reviewed journals, written in English, and published between 2013-2024 were considered. Sarcoma subtypes viewed included: rhabdomyosarcoma, Ewing sarcoma, chondrosarcoma, liposarcoma, and osteosarcoma.

Results: Ewing sarcoma EVs carry miRNA and mRNAs including EWS/FLI-1 mRNA, and surface proteins causing upregulation of inflammatory pathways, and contributing to the release of pro-inflammatory cytokines. Rhabdomyosarcoma EVs carry miRNAs and PAX3/7-FOXO1 mRNA stimulating inflammatory pathways to release cytokines and chemokines. Chondrosarcoma's hypoxic TME causes increased EV secretion, favouring M2 polarisation, and the production of immunosuppressive markers. Liposarcoma EVs enriched with miRNAs and MDM2 induced an inflammatory response in macrophages. Osteosarcoma EVs contained TGF-β and miRNA cargo which influenced macrophage polarisation.

Discussion: Sarcoma-derived EVs contain a wide range of mRNAs and miRNAs, with Ewing sarcoma and Rhabdomyosarcoma also containing the fusion oncogenes *EWS/FLI-1* and *PAX3/7-FOXO1*, respectively. Surface proteins on Ewing sarcoma and osteosarcoma EVs were better understood compared to other sarcomas. Various sarcoma-derived EV cargo demonstrated potential to influence inflammatory pathways within macrophages. Macrophage polarisation is fundamental to immune function, determining pro-inflammatory and anti-inflammatory responses.

Conclusion: By understanding the role of EVs in the inflammatory process, a deeper insight in tumour progression and tumour cell-cell communication can be achieved. The uniqueness of EV cargo to certain sarcoma subtypes could potentially indicate a future as biomarkers for early cancer detection. Further research into inflammatory effects by EVs can provide potential as novel therapeutics.

Keywords: extracellular vesicles; sarcoma; Inflammation; tumour microenvironment; cytokines; chemokines

Introduction

Sarcomas are a diverse group of tumours that occur within mesenchymal structures such as bone, muscle and cartilage, with over 100 different subtypes [1–3]. In adults, sarcomas are quite rare, with 12,000 new cases of soft tissue sarcomas and 3,000 new cases of bone sarcomas each year in the United States, accounting for less than 1% of global adult malignancies [4]. However, the incidence of sarcomas in paediatric cancers is much higher, accounting for 12% of paediatric cancers [5].

The sarcoma tumour microenvironment (TME) generally contains lymphocytes, macrophages, fibroblasts, vasculature, and the extracellular matrix, but is more specifically directed by the tumour subtype [6]. The anticancer immune phenotype that the TME presents correlates with the specific sarcoma subtype. The components of a TME play a large role in its inflammation. Tumour-associated macrophages (TAMs) are an essential component of the TME, which can polarise into anti-oncogenic M1 or pro-oncogenic M2 subtype cells, playing a large role in tumour-associated inflammation [7]. Research has demonstrated that the TME of sarcomas contains a high abundance of M2 TAMs, which have been associated with poor prognosis [6]. B cells, natural killer

cells, and cytotoxic T-cells are typically implicated in the anti-cancer response, however, their implication in sarcomas highly varies based on the subtype [6]. While the TME of specific sarcomas can vary, cancer cells modulate the TME by secretion of extracellular vesicles (EVs), cytokines, chemokines, and soluble proteins [8].

EVs are lipid bilayer-enclosed particles released by cells to mediate intercellular communication and maintain homeostasis [9]. They also play a key role in other biological and pathological processes including the immune response, inflammation and tumorigenesis [10,11]. EVs carry a wide range of cargo including proteins, nucleic acids such as miRNA, DNA and mRNA, lipids, and metabolites [12]. EV's are also divided into subtypes with the most common being exosomes and microvesicles. Exosomes are 30-150 nm in diameter that have a singular outer membrane formed by inward budding of endosomes. Microvesicles range from 100 nm to 1 μm in diameter and are formed by the outward budding of the plasma membrane [13].

EVs play a pivotal role in the TME and contribute to a variety of cancer-related processes. In the context of sarcomas, tumour-derived EVs (TDEVs) facilitate communication and transport between sarcoma cells and surrounding stromal cells to promote tumour progression, angiogenesis, and metastasis [14]. EVs have demonstrated the ability to alter the immune milieu within the TME by promoting immune evasion via the transfer of immune-supressive molecules (eg. TGF-β) and pro-inflammatory cytokines (eg. IL-6, TNF-α) [15].

Inflammation is known to be an enabling factor for cancer, driving cancer hallmarks such as sustained proliferative signalling, evasion of growth suppressors, and enabling replicative immortality [16,17]. The term cancer-related inflammation highlights the relationship between inflammation and cancer; as inflammation becomes chronic and pathological, it fosters a pro-tumorigenic environment that promotes tumour cell proliferation and survival [18]. Although persistent pro-inflammatory signals lead to increased mutations, tumour cell proliferation, and angiogenesis, anti-inflammatory signals also contribute to tumour progression by creating an immunosuppressive microenvironment that shields tumour cells [19–21].

This review aims to investigate the impact of EVs on inflammation within sarcoma TMEs. Specifically, this review focuses on soft tissue and bone sarcomas including: rhabdomyosarcoma, Ewing sarcoma, chondrosarcoma, liposarcoma, and osteosarcoma.

Methods

To conduct this review, a literature search was conducted using the PubMed database. The search involved keywords including "extracellular vesicles" AND, "sarcoma", "inflammation", "chondrosarcoma", "Ewing sarcoma", "liposarcoma", "osteosarcoma", and "rhabdomyosarcoma". The search was limited to primary research studies published in the English language between 2013 and 2024. The eligible studies were reviewed and assessed and only papers found to provide research on the involvement of extracellular vesicles within the process of inflammation or the development of sarcomas were included.

Results

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is the most common paediatric soft tissue sarcoma, occurring in the muscle and/or connective tissues [22,23]. RMS is more specifically classified by histological subtype, with embryonal RMS (ERMS), and alveolar RMS (ARMS) being the most common [24]. ARMS is commonly characterised by the presence of the fusion oncogene, *PAX3-FOXO1* or *PAX7-FOXO1*, however approximately 10% of ARMS cases are fusion oncogene negative. ARMS typically occurs in the extremities and trunk. ERMS is considered fusion negative and occurs primarily in the head, neck and bladder area [25].

Exosomes released from fusion positive RMS cells differ from fusion negative cells, however the total amount of protein and miRNA content within the exosomes was similar [25]. It was also found that despite differences in miRNA cargo, the exosomes produced by both ARMS and ERMS cell lines increased recipient RMS cell proliferation [24]. The characterised ARMS and ERMS EV protein and miRNA cargo related to cellular pathways involving inflammation via cytokine and chemokine release, B-cell activation, and growth signalling [22,24]. When analysing ARMS specifically, it was observed that the *PAX3/7-FOXO1* fusion oncogene directly impacts the exosome miRNA content, providing a potential reason for the difference in exosome cargo between ARMS and ERMS [22,25]. A downstream effector of PAX3/7-FOXO1 in exosome-mediated paracrine signalling, miR-486-5p, is known to play a large role in inflammation and cell proliferation, and has a greater expression in ARMS exosomes [22]. Furthermore, Ghamloush et al., noted that the miR-486-5p in RMS plays a role in increasing cancer progression not only in fusion positive RMS but also fusion negative RMS, however its mechanism was not explored [22]. In a separate study, Ramadan et al. investigated miR-1246 in fusion negative RMS EVs. They found that miR-1246 caused dysregulation of the WNT pathway, causing an increase in β-catenin expression within fibroblasts and thus, increased cell proliferation and tumorigenesis [26]. β-catenin is also known to stimulate NF-κB activity and therefore increase inflammation via cytokines and chemokines [26].

Ewing Sarcoma

Ewing sarcoma (EWS) is a highly aggressive malignancy of the bone and soft tissue [27–29]. It primarily impacts children and young adults, being the second most common soft tissue or bone cancer in people under the age of 20 [27,30]. EWS is primarily characterised by the

presence of the *EWS/FLI-1* fusion gene, that is found in 95% of patients, minimal T-cell infiltration, and a large presence of immunosuppressive myeloid cells within the TME [31].

The first identification of EVs within EWS was in 2013, where Tsugito et al. and Miller et al. showed that microvesicles and exosomes released by EWS malignant tumour cells carried oncogenic EWS/FLI-1 fusion mRNA [27,30]. In 2016, Ventura et al. further investigated the high expression of CD99, a cell surface glycoprotein known to be a hallmark protein of EWS, on exosomes released from EWS cells [28]. An additional study on EWS EVs demonstrated a direct correlation between CD99 expression and the aggressive growth of ES [32]. Further literature has shown EWS EVs contain a wide variety of miRNAs. Most recently, Ruzanov et al. determined that repeat RNAs were the most prevalent RNA type housed within EWS EVs [29]. They observed that the repeat RNAs HSAT2,3 in EWS/FLI-1- or ERG-expressing cells resulted in failures at the G2/M checkpoint, DNA damage cascades, and increased inflammation in the TME [29]. Specifically, Ruzanov et al. identified the upregulation of various inflammatory pathways such as TNFA, KRAS, WNT/β-catenin, and IL-6-JAK-STAT3 within EWS cells that were recipients to the EWS EVs [29]. Furthermore, when myeloid cells take up EWS EVs containing the HSAT2,3 RNAs, the myeloid cells are induced to release proinflammatory and immunosuppressive cytokines IL-8, IL-10, IL-20, and IL-35 [29]. Gassman et al., further built on this research, noting that EWS EVs affect myeloid cells on the transcriptomic level, activating pro-inflammatory and type I/III IFN response gene expression cascades [31]. EWS EVs have also been noted to impair the differentiation of immune cells to monocyte-derived dendritic cells [31]. While the mechanism is not well known, Gassman et al., noted in the presence of EWS EVs, CD14+ T-cells are more proliferative [31]. The subsequent differentiation of CD14+ T-cells in the presence of EWS EVs inhibited CD4+ and CD8+ T-cell activation in the TME and IFNγ release, contributing to the characteristic immunosuppressive TME in EWS [31].

Chondrosarcoma

Chondrosarcoma (CS) is a malignant bone sarcoma typically arising in the axial bones such as the pelvis and scapula [33]. Higher grade CS have an increased risk for metastasis, and as such, higher grade tumours have worse prognosis [34].

While research on EVs in CS is limited, it has been noted that EVs secreted from CS cell lines in a hypoxic setting induce macrophage M2 polarisation. Hypoxia is a common characteristic of solid tumours, often found at their centre [34]. In hypoxic environments, secretion of CS-derived EVs increases, however, the molecular mechanisms behind the favouring of M2 polarisation and increased EV release are still unknown [33,34]. The M2 macrophages within the CS TME produce immunosuppressive markers such as arginase-1, TGF-β, and IL-10, and chemokines [34]. Arginase-1 causes feedback to the CS cells, increasing proliferation, and promoting migration and metastasis [33,34].

Liposarcoma

Liposarcoma (LPS) is the most common soft tissue sarcoma among adults [35]. There are four subtypes including well-differentiated LPS, de-differentiated LPS (DD-LPS), myxoid/round cell LPS, and pleomorphic LPS [36]. DD-LPS is the most common subtype, given its increased tendency to recur [35,36].

DD-LPS EVs have been demonstrated to carry *MDM2* DNA, which is known to be influential in tumour progression [37]. According to Casadei et al., when EVs contact preadipocytes in the surrounding TME, the presence of this *MDM2* DNA results in overproduction of MDM2 protein and mRNA in the recipient preadipocytes [37]. The MDM2 protein binds to tumour suppressor proteins such as p53 and p21, leading to their degradation [37]. The removal of these key regulatory proteins provides LPS cells the ability to proliferate uncontrollably, evade apoptosis, and accumulate mutations. Reduction in both p53 and p21 not only promotes tumorigenic activity, but also inflammatory responses due to increased *MMP2* production in spreading preadipocytes [37]. The enrichment of DD-LPS EVs with miR-25-3p and miR-92a-3p is also significant in developing an inflammatory response. Following DD-LPS EV uptake by surrounding macrophages, miR-25-3p and miR-92a-3p are delivered [38]. Casadei et al. observed that these miRNAs explicitly promote IL-6 secretion from macrophages in a TLR7/8-dependent manner [38]. Subsequently, chronic IL-6 secretion leads to an inflammatory environment that supports tumour growth. In fact, the presence of IL-6 is crucial to sustaining a positive feedback loop of continuous pro-inflammatory macrophage recruitment, amplifying IL-6 secretion such that a constant chronic inflammatory state is maintained [39].

Osteosarcoma

Osteosarcoma (OS), which frequently affects children and young adults, is the most common primary malignant bone tumour [40]. OS initiates from mesenchymal cells at the bone, and is also known to be highly metastatic [40]. OS has a complex genomic landscape, as there is significant somatic structural variations and copy number alterations, but a low frequency of recurring DNA point mutations [41].

OS EVs trigger pathways influencing inflammation via communication with recipient cells. Studies have reported the presence of TGF-β within OS EVs, which facilitates the production of pro-inflammatory cytokines (eg. IL-6 and TNF-α) upon interacting with mesenchymal stem cells [42]. This promotes inflammation and forms a pro-tumorigenic environment. The modulation of immune cell activity is a

key role of OS EVs. Specifically, TAMs initially beginning as a M1 pro-inflammatory phenotype are influenced by OS EVs towards an M2 anti-inflammatory phenotype. The M2 phenotype is characterised by secretion of TGF-β, IL-10, and CCL22 [43]. Wolf-Dennen et al. reported that OS EVs led to an upregulation of M2 phenotype expression, via identification of M2-related markers [44]. These anti-inflammatory signals create an immunosuppressive microenvironment. Araki et al. conducted *in vitro* osteoclastogenesis experiments and found that OS EVs inhibit osteoclast maturation by suppressing the NF-κB signaling pathway [45]. In particular, miR-146a-5p carried by OS EVs downregulates TRAF6, preventing the activation of the IKK complex and most importantly, reducing phosphorylation of IκBα and NF-κB, which inhibits the gene expression necessary for pro-inflammatory signalling and osteoclast differentiation [45]. The miRNA cargo of OS EVs is influential in modulating inflammatory responses. Notably, miR-21 in OS EVs has been shown to activate pro-inflammatory cytokines with macrophages [46].

Summary

A table encompassing the cargo and immune influence within the various sarcomas can be found in Table 1.

Table 1. Various Sarcoma Subtype EV Cargo and Their Respective Immune Influence

Sarcoma	Cargo	Immune Influence
Rhabdomyosarcoma	*PAX3/7-FOXO1*	Pro-inflammatory via cytokine and chemokine release, B-cell activation, and growth signalling
	miR-486-5p	Pro-inflammatory, mechanism unknown
	miR-1246	Pro-inflammatory via dysregulation of the WNT pathway and stimulation of NF-κB activity
Ewing sarcoma	*EWS/FLI-1*	Pro-inflammatory via cytokine release, and upregulation of TNFA, KRAS, WNT/β-catenin, and IL-6-JAK-STAT3 inflammatory pathways
	HSAT2,3 and EWS/FLI-1	Pro-inflammatory and via cytokines release, failures at G2/M checkpoint and DNA damage cascades Anti-inflammatory via immune suppressive cytokine release
Chondrosarcoma	Specific cargo is unknown	Anti-inflammatory via creation of immunosuppressive microenvironment via M2 polarisation
Liposarcoma	*MDM2*	Pro-inflammatory via *MMP2* production
	miR-25-3p and miR-92a-3p	Pro-inflammatory via chronic IL-6 secretion
Osteosarcoma	TGF-β, IL-10 and CCL22	Anti-inflammatory via creation of immunosuppressive microenvironment
	miR-21	Pro-inflammatory via pro-inflammatory cytokine activation
	miR-146a-5p	Anti-inflammatory via reduction of pro-inflammatory signalling

Discussion

Results from the primary research on EWS, RMS, CS, LPS and OS displayed some commonalities and variation between sarcoma subtypes. Based on the papers reviewed, EV cargo and composition played a large role in the subsequent inflammatory response for each of the sarcomas. The cargo of sarcoma-derived EVs contained a wide range of proteins, mRNA, miRNA, chemokines and cytokines. EWS and RMS EVs were found to carry mRNA of their driver fusion oncogenes, *EWS/FLI-1* and *PAX3/7-FOXO1*, respectively [22,27]. Surface proteins have also been noted on sarcoma-derived EVs, such as CD99 in EWS and TGF-β in OS [32,43]. In these studies, these surface proteins were shown to not directly induce their own mediated response, but rather work in tandem with other EV cargo, typically miRNA, to facilitate binding to other cells to mediate uptake. Nonetheless, these surface proteins play an important role, especially concerning EWS as without the CD99 surface protein present on the EV, the increased proliferation and inflammation within the TME ceases [28,32]. While LPS, CS, and RMS have not been noted to contain surface proteins to help in their facilitation, this can be attributed to a lack of research within the area. EVs can also carry cytokines and chemokines as cargo, supporting an inflammatory response within the TME [47]. Overall, the cargo present within sarcoma-derived EVs play an integral role in tumour progression, and while the sarcoma subtypes share similarities in that EVs alter the inflammation in the TME, the specific cargo and methods which produce a pro-inflammatory outcome varies by subtype [48].

Immune cell modulation is a crucial role of all TDEVs, as it heavily influences tumour progression and

inflammation by shaping the immunological landscape. Literature has demonstrated that M2 polarisation is a significant process that occurs following the internalisation of TDEVs into macrophages [49]. The macrophages are polarised towards a M2 phenotype that is anti-inflammatory and immunosuppressive, commonly characterised by its IL-10 and TGF-β production and modulation of cytotoxic T-cells [43]. Literature on EWS and RMS lacked evidence of association with M2 polarisation. On the other hand, LPS and OS followed a signalling mechanism where cargo within LPS and OS EVs led to M1/M2 polarisation, facilitating the production of pro-inflammatory and anti-inflammatory cytokines, respectively [38,44]. Expression of M2 markers were observed in CS EV studies, although specific initiators that resulted in a M2 shift were not identified. Both LPS and OS EVs share a common signalling mechanism, the TGF-β signalling pathway. OS studies have reported the presence of TGF-β within OS EVs, whereas LPS studies have only identified miR-193b, a target of the TGF-β signalling pathway in LPS cells [42,50]. While LPS studies related to the TGF-β signalling pathway lack substantial evidence, there remains abundant literature supporting the influence of miRNA on macrophages within the LPS TME. For instance, miR-25-3p and miR-92a-3p found in DD-LPS EVs were shown to promote IL-6 secretion from recipient TAMs [38]. Contrarily, OS EVs contained miR-146a-5p that suppressed pro-inflammatory signalling by inhibiting the NF-κB pathway [45]. RMS-derived EVs also carry miR-1246, affecting the Wnt and NF-κB pathway, resulting in a pro-inflammatory outcome via the release of cytokines and chemokines [26]. This highlights that miRNA cargo has versatile effects in driving both pro-inflammatory and immunosuppressive environments.

Inhibition of T-cell activation is a critical aspect of how EVs influence inflammation and immune evasion in sarcomas. In EWS, the uptake of EWS EVs by myeloid cells triggers the release of immunosuppressive cytokines [31]. This immunosuppressive environment not only impairs the body's ability to mount an effective defense against tumour cells, but also creates a feedback loop that supports chronic inflammation [51]. The broad scale inhibition of T-cell activation was not reported in other sarcomas, however, this could be due to the lack of research in this area.

The disruption of normal cellular functions by EVs is linked to their role in influencing inflammation, as the EVs not only carry oncogenic material but also induce inflammatory responses that exacerbate tumorigenesis. The presence of *MDM2* DNA in DD-LPS EVs leads to the degradation of the tumour suppressor protein p53 in recipient preadipocytes [37]. This degradation alters normal cell cycle regulation, facilitating uncontrolled cell proliferation and an inflammatory response. Similarly, EWS EVs containing HSAT2,3 repeat RNAs cause failures at the G2/M checkpoint, initiating DNA damage cascades [29]. These disruptions not only drive tumorigenesis but also contribute to an inflammatory TME, with the damaged cells releasing signals that attract immune cells and promote chronic inflammation.

Future directions in EV research involving sarcomas show promise in biomarker discovery and future therapeutics [52]. The use of biomarkers is especially relevant when considering EWS and RMS, which contain hallmark fusion oncogenes within their EVs, *EWS/FLI-1* for EWS and *PAX3/7-FOXO1* for RMS [22,27]. A study by Miller et al. reported *EWS/FLI-1* contained in EWS-derived EVs highlighting its potential as a sensitive biomarker [30]. In the cases of sarcomas without characteristic fusion oncogenes, surface proteins present on sarcoma-derived EVs could also potentially serve as biomarkers [53]. Unique miRNA present within EVs from certain sarcoma subtypes such as EWS and RMS could also be used as biomarkers for early stage detection [53]. For instance, specific miRNA (eg. members of miR-17–92 cluster) were detected in Kaposi's sarcoma-associated herpesvirus (KSHV) patient exosomes. KSHV is known to cause Kaposi's sarcoma, a cancer commonly associated with AIDS [54]. Moreover, research involving novel therapeutics can also be conducted in inhibiting certain inflammatory pathways mediated by EVs. Specifically, the inhibition of the encapsulation of specific cargos that play a role in pro-inflammatory outcomes, such as miR-1246 in RMS, miR-25-3p and miR-92a-3p in LPS, and TGF-β in OS [26,38,43]. EVs can also be used as carriers for established chemotherapies, as they can allow for better intercellular communication and transport of therapeutic agents or mRNA treatments [52,55]. To further gain a more holistic view of EVs and their role in biological processes, future research could compile and explore more sarcoma subtypes as well as their effects on tumour progression, metastasis, and cell to cell communication.

Conclusions

In conclusion, current literature on EVs derived from various sarcoma subtypes including EWS, RMS, LPS, CS, and OS reveals both commonalities and distinct variations in their abilities to induce inflammatory responses. A key finding is the significant role of EV cargo, predominantly miRNA, in modulating the TME by promoting immune modulation and inflammation.

EVs contribute to immune modulation by promoting M1/M2 macrophage polarisation, influencing cytokine and chemokine production, and disrupting normal cellular functions, thus exacerbating tumorigenesis and inflammation. The unique miRNA cargo of EVs from different sarcomas also demonstrates versatile roles in either promoting or suppressing inflammation.

The inhibition of T-cell activation, particularly noted in EWS, and the disruption of cellular functions through oncogenic EV cargo further underscore the complexity of EV-mediated inflammation and immune evasion in sarcomas. These findings highlight the need for continued research into the specific pathways and molecular mechanisms involved.

Future research directions should focus on leveraging the unique mRNA and miRNA profiles of sarcoma-derived EVs for early detection biomarkers and developing novel therapeutics targeting EV-mediated inflammatory pathways. Additionally, comprehensive studies encompassing a broader range of sarcoma subtypes and EV functions in cell-cell communication, tumour progression, and metastasis will provide a more holistic understanding of EVs in sarcoma biology. Such advancements hold promise for improving diagnostic and therapeutic strategies in sarcoma treatment.

List of Abbreviations Used
ARMS: alveolar rhabdomyosarcoma
CS: chondrosarcoma
DD-LPS: de-differentiated liposarcoma
ERMS: embryonal rhabdomyosarcoma
EVs: extracellular vesicles
EWS: Ewing sarcoma
LPS: liposarcoma
OS: osteosarcoma
RMS: rhabdomyosarcoma
TAM: tumour-associated macrophages
TDEVs: tumour-derived extracellular vesicles
TME: tumour microenvironment

Conflicts of Interest
The author(s) declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent
This study was a literature review that analyzed pre-existing research and therefore did not require ethics approval nor participant consent.

Authors' Contributions
BSY: Conducted independent literature search, collected and analyzed selected studies, drafted the manuscript, revised the manuscript critically, gave final approval of the version to be published.
EJS: Conducted independent literature search, collected and analyzed selected studies, drafted the manuscript, revised the manuscript critically, gave final approval of the version to be published.

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