Gelsolin and Related Proteins in Vertebrate Model Organisms

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Review

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Gelsolin, a protein of 82-84 kDa, is an actin-binding protein regulated by calcium (SILACCI et al. 2004). In mammals, gelsolin superfamily proteins comprise gelsolin, adseverin, CapG, flightless I, advillin, villin, villin-like and supervillin (LI et al. 2012; NAG et al. 2013; SHEKHAR et al. 2016). This conserved protein superfamily, widely expressed in eukaryotic cells, exists as cytoplasmic, plasma/secreted and brain isoforms. In mammals, gelsolin is encoded by a single gene and expressed through alternative splicing. The basic functions of gelsolin are binding, severing, and capping actin filaments (SUN et al. 1999; FELDT et al. 2018). A common sequence of all isoforms contains 730 amino acids. Gelsolin has six subunits (S1–S6), organized into two domains: on the N- (S1–S3) and C-terminal (S4–S6) halves, linked through 70 amino acids called a linker sequence (Fig. 1) (KWIATKOWSKI et al. 1986, 1988, 1989; BOLLATI et al. 2019). It was proposed that the six gelsolin subunits (S1–S6) evolved from a single domain prototype through gene triplication, followed by a duplication event (WAY & WEEDS 1988). In mammals, differences between gelsolin isoforms arise from the presence of a disulfide bond between Cys188 and Cys201 in plasma gelsolin, and 11 additional amino acid residues on the N-terminal domain in brain gelsolin. Furthermore, contrary to cytoplasmic gelsolin, the plasma isoform contains a signal peptide and 23-25 amino acid residues more on the N-terminal domain (BUCKI et al. 2008).

It has been shown that gelsolin has three different actin binding regions: a calcium-independent monomer binding fragment (S1), a calcium-independent...
filament binding fragment (S2-3), and a calcium-dependent monomer binding fragment (S4-6) (Bryan 1988). Besides Ca$^{2+}$ promoting gelsolin activity, intracellular pH, phosphoinositides, and tyrosine phosphorylation affect gelsolin regulation (Silacci et al. 2004). Gelsolin also binds to phosphatidylinositol 4,5-bisphosphate (PIP2). PIP2 inhibits the actin filament, severing activity of a proteolytic fragment of gelsolin encompassing its N-terminal half (Janmey & Stossel 1987).

The gelsolin cytoplasmic and plasma isoforms are produced by skeletal, smooth, and cardiac muscles, whereas the brain isoform is observed in oligodendrocytes, lungs, and testis. Differences in the structure of individual isoforms also modulate their functions. Cytoplasmic gelsolin is responsible for the regulation of cell actin dynamics, takes part in cytoskeleton structure reorganization, and influences cell shape changes and cell movement. The main function of plasma gelsolin, is participation in the removal of G-actin and F-actin from the bloodstream after cell damage. It is noteworthy that actin in the extracellular environment has toxic effects (Li et al. 2012). The third isoform, brain gelsolin, is involved in myelin sheath formation and central nervous system development (Vougiouklis & Brophy 1997; Mazur et al. 2016).

In gelsolin, the substitution of A sp187A sn or A sp187Yr causes familial amyloidosis of the Finnish type (FAF), a rare hereditary amyloid polyneuropathy characterized by corneal lattice dystrophy, progressive cranial, and peripheral neuropathy, and skin changes (Solomon et al. 2012). Gelsolin could be potentially used for the

Fig. 1. Cross-species comparison of the gelsolin protein structure. The upper part of the figure shows a comparison of the gelsolin protein’s architecture in various organisms: human (Homo sapiens), mouse (Mus musculus), chicken (Gallus gallus), African clawed frog (Xenopus laevis), and zebrafish (Danio rerio). Conserved functional domains and binding sites are highlighted by different color boxes. The proportions between individual sequences of proteins, domains, and binding sites have been preserved. On the lower part of the figure, a phylogenetic tree based on a protein sequence comparison of the gelsolin family from the various organisms is shown. Sequence alignment and phylogenetic tree: ClustalW2, www.ebi.ac.uk.
treatment of Alzheimer’s disease, caused by the accumulation and deposition of amyloid beta in the brain. Plasma and cytoplasmic gelsolin have the ability to connect with amyloid beta, thus limiting the aggregation of this protein (Isaacson et al. 1999; Huff et al. 2003; Antequera et al. 2009; Zorgati et al. 2019).

In our review, we focused on the role of gelsolin and related proteins in vertebrate model organisms such as zebrafish (Danio rerio), a frican clawed frogs (Xenopus laevis), chickens (Gallus gallus), and mice (Mus musculus). We present fundamental findings and new scientific data to show the main direction in research and future possibilities.

Our goal was to present the diverse and specific advantages of each animal model in the field of research related to gelsolin and gelsolin-family proteins. Our summary also underlines the enormous multifunctionality of gelsolin and its specific role in numerous biological processes such as development, morphogenesis, and pathogenesis, which makes gelsolin a potential candidate for diverse therapeutic applications.

**Zebrafish (Danio rerio)**

Based on the gelsolin domains in zebrafish, phylogenetic analysis revealed that there are six genes encoding gelsolin-like proteins: the gsnA and gsnB group with the vertebrate gelsolin gene, scinA and scinB with the scinderin (adseverin) gene, and scinLA (C/L-gelsolin) and scinLB scinderin-like genes as a diverged paralog of scin (Ružička et al. 2019). JIA et al. (2007) reported that the scinL of the zebrafish cornea is more closely related to scinderin than to gelsolin (JIA et al. 2007). It has been reported that the closest homolog of gelsolin is scinderin (Kwiatkowski 1999).

In zebrafish, the most investigated gene/protein of the gelsolin superfamily was scinderin-like (scinLA and scinLB) (JIA et al. 2007; 2009). Scinderin-like (scinL) is a unique gelsolin family gene, found only in fish. Besides zebrafish, this gene has been investigated in Anableps anableps (Kanungo et al. 2003), Paralichthys olivaceus (Hur & Hong 2013), and Takifugu rubripes (CA F89482.1). Similarly to mammalian gelsolin family members, in fish, scinL has the six conserved domains, S1 to S6. However, the fish scinL amino acid sequences show the C-terminal latch helix of gelsolin is missing in scinderins of other species, including mammals, chickens, and Xenopus.

It was reported that although scinLA and scinLB are situated on different zebrafish chromosomes (6 and 2, respectively), their gene structure and protein sequences are similar. The genes have almost identical exon-intron structures containing 17 similarly sized exons (JIA et al. 2009). Like scinLA, scinLB is expressed in the adult cornea, although at lower levels than scinLA (JIA et al. 2007). Both scinLA and scinLB belong to a distinct branch that clusters with, but is separate from, the scinderin vertebrate cluster. Thus, scinLA and scinLB are fish-specific paralogs of scinderin (JIA et al. 2009). ScinLA, scinLB, and gsnA are preferentially expressed in the adult cornea, whereas gsnB is expressed to a similar extent in the cornea, lens, brain, and heart (JIA et al. 2007). The authors reported that two zebra fish scinLA genes are involved in cornea crystallization. In addition to its accumulation in the cornea, the scinLA gene is expressed at low concentrations during early zebrafish development, where it appears to have a signaling role in dorsal-ventral patterning. Overexpression of scinLA dorsalizes the embryo and can lead to axis duplication, while the interruption of scinLA expression with a specific morpholino oligonucleotide ventralizes the embryo, and interferes with brain and eye development (Kanungo et al. 2003, 2004; JIA et al. 2007).

In contrast to the effect of knocking down scinLA expression, it has been shown that reducing scinLB expression does not affect dorsal-ventral signaling (JIA et al. 2009). However, the phenotypes with low scinLB expression exhibited a subtle change in the structure of the developing brain that was associated with increased cell death, reduced sonic Hedgehog b (Shhb) expression in the floor plate, and reduction in the distance between the eyes at 3 dpf. These investigations confirmed that scinLA and scinLB have distinct developmental roles (JIA et al. 2009).

Zebrafish is a valuable non-mammalian vertebrate model widely used to study development and disease. The evolutionary conservation of many metabolic pathways, and advantages such as relatively low-cost maintenance, the external development, and transparent body at the early stages of development is leading to a constantly increasing number of research endeavours involving this model (Howe et al. 2013; Plantie et al. 2015; Dubinska-Magiura et al. 2016; Bradford et al. 2017; Keenan & Currie 2019). Despite at least six of the genes encoding the gelsolin-like proteins, existing due to genome duplication during zebrafish evolution (Pasquier et al. 2017), there are many interesting research directions, since they are involved i.e. in developmental and cornea physiology.

**African clawed frog (Xenopus laevis)**

Studies on the gelsolin superfamily in amphibians were rarely undertaken. Research from the last century was focused on gelsolin expression during...
Among vertebrates, amphibian oocytes are an excellent model to study oogenesis, fertilization, and embryogenesis. It has been shown that in *X. laevis* oocytes, gelsolin is the most prominent actin-binding and actin-modulating protein (Ankenbauer et al. 1988). In *X. laevis* oocytes, a relatively high amount of gelsolin was present in the ooplasm, and it was also detected in the nucleus (Ankenbauer et al. 1988). The gelsolin identified in amphibian oocytes and eggs is more acidic than that reported for mammalian cells. Determination of the amino-terminal sequence of the *Xenopus* oocyte excludes plasma gelsolin (Ankenbauer et al. 1988). The gelsolin in oocytes is spread over the ooplasm. A small amount of gelsolin was also observed within the confines of the nuclear envelope. The authors believe that oocyte gelsolin plays a crucial role in various Ca$^{2+}$-dependent gelation and contractility processes characteristic for oogenesis and early embryogenesis in amphibians.

During amphibian embryonic and larval intestinal development, morphological, immunocytochemical, and immunoblotting analyses revealed an expression of villin (Heusser et al. 1992). For the first time, villin expression in *X. laevis* was observed just before hatching in the apical domain of endodermal cells bordering the primitive cavity, at a time when few surface microvilli were visible by TEM. In hatched larva, villin expression continued to increase in endodermal cells as they differentiated into intestinal epithelial cells. In pre-metamorphosis, villin was concentrated in the brush border of the intestinal epithelium. Villin was not detectable in the fertilized eggs, during gastrulation, or neurulation (Heusser et al. 1992).

Gelsolin, one of the proteins maintaining actin dynamics, is present in the *X. laevis* oocytes in high amounts. One should not be surprised, since the *X. laevis* oocytes are known i.e. because of their large size (Courjaret & Machaca 2016), so the actin cytoskeleton and associated proteins are crucial for its shape and function.

**Chicken**

Chicken (*Gallus gallus*) has been used to investigate the properties of gelsolin since the 1980s. Hinssen et al. (1987) isolated a gelsolin-like protein from chicken erythrocytes. The authors revealed that the mechanism of its binding to the erythrocyte membrane is dependent on calcium ions, and observed changes in the expression level of this protein during the differentiation and maturation of erythrocytes (Hinssen 1987).

Northern blot analysis showed a high level of gelsolin in the inner ear of chicken embryos and the presence of gelsolin mRNA in other tissues: heart, skin, and, in a lower amount, in the cerebellum, forebrain, eye, and muscles (Hellier et al. 1998). Something interesting is that, only one transcript of the gene encoding for gelsolin is present in the chicken genome. The amino acid sequence of the protein found in the chicken is 77% identical to human plasma gelsolin (Azur et al. 2016).

Proteomic studies have shown the role of gelsolin in the development of chicken' bursa of Fabricius (the birds' hematopoietic organ) (Korte et al. 2013). The highest concentration of gelsolin was noted in 18-day-old embryos, when the bursa of Fabricius was at the bursal stage. Both earlier and later stages showed a lower level of gelsolin. This suggests that gelsolin may play an important role during chicken' bursa of Fabricius development (Korte et al. 2013).

Gelsolin expression was examined at both the mRNA and protein level in the developing chicken embryo (Azur et al. 2016). Gene expression was observed in the early stages of development of the embryo, but its level differed in particular types of cells. A comparatively high gelsolin expression level was observed in different organs: the eye, brain vesicles, midbrain, neural tube, heart tube, and splanchnic mesoderm. A higher level of mRNA was observed in the cranial ganglia and dorsal root ganglia in older embryonic stages. The authors did not observe the expression of gelsolin in somites in the early stages of development. However, the results indicated a large role of gelsolin in the development of the chicken brain. Studies on 10-day-old chicken embryos showed the presence of gelsolin transcripts in cells of ectodermal origin in the head, such as cells of the optical system, nervous meninges, muscles, presumptive gland, and pericytes. Moreover, silencing the gelsolin expression resulted in a shorter mesencephalon in further development stages. In older embryos, gelsolin mRNA was present in all tissues of the body, but the highest expression was observed in all cranial and dorsal roots. A high level of gelsolin mRNA was observed in ganglia and the sympathetic trunk, suggesting that gelsolin has an important role in the development of the peripheral nervous system (PNS). These results were also confirmed at the transcript level using immunohistochemical methods (Azur et al. 2016).

Besides mice, other members of the gelsolin superfamily have not been investigated in detail. Villin was first studied in chicken intestinal epithelial cells and later was described in mammals (Drenckhahn et al. 1983). During early embryonic chicken development, villin was observed in...
cells of the primitive gut which are precursors of adult intestine (Drenckhahn et al. 1983; Ezzell et al. 1989). Shibayama et al. (1987) examined the assembly of the intestinal microvillus cytoskeleton during chick embryogenesis. The authors showed that villin is the first microvillar core protein to display a restricted apical localization. The presence of villin when the density of microvilli on the apical surface is quite low, suggests that villin may play a crucial role in microvillus assembly (Drenckhahn et al. 1983; Shibayama et al. 1987; Ezzell et al. 1989).

The gelsolin exact function in normal and pathological conditions is not well studied in chicken. However, detailed data regarding gelsolin expression at the early stages of development are a solid base for the further research.

Mouse

The house mouse (Mus musculus) is a common vertebrate animal model frequently used to conduct research on the role of gelsolin superfamily members in normal and pathological states (Witke et al. 1995).

Experiments concerning the role of gelsolin in mice were first performed using gelsolin-null (Gsn-) mice generated by Witke et al. (1995). Gsn- animals express neither cytoplasmic nor plasma gelsolin, but have normal embryonic development and longevity, although prolonged bleeding time was observed (Witke et al. 1995). Gelsolin plays an important role in the rearrangement of the actin cytoskeleton in different cells during a fast stress response, i.e. platelet activation, inflammation, leukocyte motility, and apoptosis. The prolonged bleeding time observed in Gsn- mice was probably caused by the reduced severing of actin filaments in blood platelets and therefore, slower cell shape change response (Witke et al. 1995). Gsn- animals also respond more slowly to inflammatory stimuli due to a decrease in the leukocyte migration rate. The presence of other proteins with a function similar to gelsolin may be the reason that knockdown of such an important protein is not lethal for mice (Witke et al. 1995). Gelsolin and proteins with similar actin-severing functions are not expressed during the early stages of development, suggesting that this mechanism of actin cytoskeleton rearrangement is not necessary for embryogenesis (Witke et al. 1995; Arai & Kwiatkowski 1999). Further analysis showed that when Gsn- mice are crossed with inbred lines, such as BALB/c and C57/black (commonly used laboratory lines), almost all animals die between postnatal days 17 and 21 (Kwiatkowski 1999). This finding indicates that in lines with multiple gene defects, gelsolin is necessary for survival.

Gsn- mice have defects in mammary gland morphogenesis (Crowley et al. 2000). The lack of gelsolin expression results in the failure of mammary anlage elongation and a lack of terminal ductal branching. After pregnancy, Gsn- mice undergo lobulo-alveolar development, although it is delayed. The mammary gland tissue structure of lactating mice was normal when compared to wild-type animals. Moreover, the mammary glands of Gsn- mice undergo normal gland restructuring during involution (Crowley et al. 2000). The important role of gelsolin in the mammary stroma in proper ductal morphogenesis could shed light on the significance of the reduction in gelsolin expression in breast cancers (Ach et al. 1996).

The role of gelsolin was also shown to be important in the pathological rearrangement of dendritic spine morphology following the hyperactivation of mTOR (mechanistic target of rapamycin) kinase (Nie et al. 2015). This process is often associated with epilepsy and autism. Gelsolin, as a target of A tf3 (transcription factor 3) transcriptional activity, was also up regulated. A tf3 activity inhibition prevents gelsolin overexpression and corrects the loss of dendritic spines in neurons (Nie et al. 2015). The cell process consisting of the stress-induced A tf3-gelsolin cascade could be a potential therapeutic target in mTORopathies (Nie et al. 2015).

Gelsolin may be involved in the pathogenesis of neuroinflammatory diseases (Gonçalves et al. 2010; Zhang et al. 2013). It has been reported that its expression level increased in mouse brain (corpus callosum and anterior commissure) after thermal injury. Gelsolin, as a regulator of actin cytoskeleton reorganization, was engaged in glial cell and monocyte activation, and possibly directly affects neural apoptosis in primary cell culture; therefore it plays an important role in inflammation-associated degeneration processes in the brain after skin burns (Zhang et al. 2013). Gelsolin is also required in Schwann cells to perform the re-myelination of the sciatic nerve following a crush injury in the brain (Gonçalves et al. 2010).

Gelsolin plays a dual role in apoptosis in different cells. One mechanism is based on caspase-3 cleavage leading to the generation of a constitutively active gelsolin fragment, which has pro-apoptotic properties, causing actin depolymerization and cell death (Harms et al. 2004).

The anti-apoptotic effect of gelsolin was observed in neurons. It was demonstrated that gelsolin protects cells from excitotoxic cell death (Harms et al. 2004). Neurons in mice lacking gelsolin have an increased apoptosis rate after expo-
sures to toxins. Loss of mitochondrial membrane potential and the activation of caspase-3 were especially apparent (HARMS et al. 2004). Similar observations were made of fulminant hepatic failure, where gelsolin shows an anti-apoptotic effect (LEIFELD et al. 2006). In the pathogenesis of ventilation-induced lung injury, observed during life-supporting mechanical ventilation of patients with acute lung injury, the absence of gelsolin leads to disease protection (MANNIATIS et al. 2009).

Experiments performed on mature cardiac myocytes isolated from gelsolin-null mice have shown that gelsolin plays an important role in the excitation-contraction coupling process (WEISSER-THOMAS et al. 2015). Gelsolin deficiency improves systolic function, without affecting diastolic function, in isolated cardiomyocytes (WEISSER-THOMAS et al. 2015). Gelsolin is expressed at a high level in murine and human hearts after myocardial infarction, and plays an important role in the progression of heart failure (LI et al. 2009). It acts through DNase I activation and down-regulation of anti-apoptotic survival factors. Gelsolin deficiency reduces apoptosis, hypertrophy, and mortality in the murine post-myocardial infarction model (LI et al. 2009).

An interesting role of gelsolin was described in the etiology of idiopathic pulmonary fibrosis (IPF) (OIKONOMOU et al. 2009). The development of this disease involves apoptosis in alveolar epithelial cells. Gelsolin, a key actin-binding protein, is necessary for actin cytoskeleton rearrangement during apoptosis. Indeed, in tissues obtained from patients with IPF, the gelsolin expression level was increased. On the other hand, the absence of gelsolin in the mouse model leads to attenuated epithelial apoptosis and therefore protects animals from IPF development (OIKONOMOU et al. 2009). This may have important implications for therapy in patients with asthma and pulmonary fibrosis, because regulation of actin cytoskeleton rearrangement in airway smooth muscles and alveolar epithelial cells may be a way to treat human diseases (OIKONOMOU et al. 2009).

It has been reported that in some pathologies, the level of gelsolin is increased while in others it is reduced (ONDA et al. 1999). A higher level of gelsolin was observed in renal cystadenomas and carcinomas in the murine model of tuberous sclerosis (ONDA et al. 1999). However, a reduction of gelsolin expression was observed in more than 70% of human, mouse, and rat breast cancers (ASCH et al. 1996). Having a detailed knowledge regarding gelsolin level, function, and mechanism of action in different cells and diseases allows us to find a new therapeutic target (ASCH et al. 1996; ONDA et al. 1999).

The mouse model is also used to develop therapies for human diseases connected with alterations in gelsolin structure and function (VERHELLE et al. 2017). Familial amyloidosis of the Finnish type (FAF) is caused by a single point mutation in the gelsolin gene (SOLOMON et al. 2012). This modification results in the loss of a calcium binding site, and the structural change of the molecule, which leads to the exposure of new cleavage sites. Mutant plasma gelsolin is first, intracellularly, cleaved by furin. Secondly, when it is secreted into the plasma, the additional cleavage site becomes exposed to MT1-MMP (membrane-type 1 matrix metalloproteinase) activity. As a consequence, two amyloidogenic peptides are produced. The aggregation, formation of cross-beta-sheet amyloid fibrils and plaques, lead to disease development (SOLOMON et al. 2012; ZORGATI et al. 2019). Gene therapy with AAV9 nanobodies may be a way to treat patients suffering from FAF disease (VERHELLE et al. 2017).

It has been reported that other members of the gelsolin superfamily have been investigated in mice. It was evidenced that villin in vertebrates is an epithelial cell-specific regulatory protein. This protein works as an actin-capping, actin-bundling, and actin-severing protein in epithelial cells (BRETSCHER & WEBER 1980; KHURANA & GEORGE 2008). Studies on villin knock-out mice revealed that this protein plays a crucial role in actin dynamics regulation, cell morphology and migration, epithelial-to-mesenchymal transition, and cell survival. In developing mice, villin was found at the apical surface of enterocytes as the first major actin-bundling protein (EZELL et al. 1989). In villin knock-out mice, significant changes in the microvillar structure have been noted, which are not well organized (FATH & BURGESS 1995). Studies on villin knock-out mice and villin and gelsolin double null mice also revealed the anti-apoptotic function (KHURANA et al. 2005).

Advillin (an actin regulatory/binding protein) was found in the adult murine brain (MARKS et al. 1998). A d Advillin is also expressed in the uterus endometrium, the intestinal lining, and at the surface of the tongue. In murine embryonic development, a strong expression of this protein was observed in the dorsal root ganglia and trigeminal ganglia. It was suggested that advillin has unique functions in morphogenesis and may play an important role in regulating actin organization and the motility of each tissue where it is expressed (MARKS et al. 1998).

Studies conducted by LUECK et al. (1998) revealed that during mouse and human development, adseverin (actin-severing protein) was highly expressed in the kidneys and intestines at all developmental stages. A dseverin was expressed in...
the cytoplasm of peripolar cells, thin limbs, thick ascending limbs, and in the principal cells of the cortical and medullary collecting ducts in the kidneys. Furthermore, in mouse and human intestines, adseverin was found in enterocytes with a gradient of increasing expression from the duodenum to the colon, and from the crypt to the villus. It is postulated that the adseverin found in resorptive epithelial cells has an important role in exocytosis (Lueck et al. 1998).

The gelsolin family of actin-binding proteins also contain Filil, a homolog of the Drosophila melanogaster flightless I protein (Kopecki & Cowin 2008). The Filil protein is essential for early fruit fly and mouse development. It was shown, using knock-out mice, that Filil together with CapG and villin, play a crucial role in actin cytoskeleton dynamics. In addition, studies by Archer et al. (2004) indicated that supervillin, gelsolin, and Filil are involved in intracellular signaling through nuclear hormone receptors including the androgen, estrogen, and thyroid hormone receptors (Archer et al. 2004, 2005).

Gelsolin gene knock-out (Gsn-) mice are a very useful animal model for studying gelsolin functions. Thanks to this line, researchers have found that gelsolin is not a crucial protein during development, but rather in processes involving rapid and dynamic actin cytoskeleton rearrangement, such as stress responses. Gelsolin plays very interesting function during apoptosis, as well as in other pathological processes such as cancer, in some cases as an activator and in others as a suppressor.

Conclusion and future directions

Our knowledge about the gelsolin protein superfamily in vertebrates is still poor. However, data obtained on model organisms has shed new light on the multifunctional roles of gelsolin. Gelsolin, an actin-binding protein, plays a crucial role in processes connected with actin cytoskeleton rearrangement. These processes include cell shape changes during differentiation, growth, forming protrusions, stress response, cancer, and apoptosis. Deregulation of gelsolin expression levels may lead to severe changes in different tissues and organs during development and in adults.

Gelsolin plays an important role in various diseases and potentially, could be a therapeutic target (Feldt et al. 2018; Piktel et al. 2018; Parr et al. 2019). However, we have to keep in mind that its role is different case by case. There is more than one mechanism of action, for example, in different kinds of cancer. In some diseases, gelsolin acts as a pro-apoptotic and in others as an anti-apoptotic factor. Therefore, further detailed research regarding gelsolin and its superfamily members is required.

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Research concept and design: M.M.-P., M.D.; Writing the article: M.M.-P., J.B.N.-T., A.G., M.D.-G., M.D.; Critical revision of the article: M.M.-P., J.B.N.-T., A.G., M.D.-G., M.D.; Final approval of article: M.M.-P., J.B.N.-T., A.G., M.D.-G., M.D.

Conflict of Interest

The authors declare no conflict of interest.

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