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Research Article

# Mps1 Knockdown in Glioblastoma Induces DNA Damage and up Regulation of Histone Methyltransferase SETD2

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## Abstract

**Objectives:** The diagnosis and treatment of glioblastoma are challenging due to the fast-growing nature of the tumour. Identifying new hallmarks of the disease is important for improving patient care. This study investigates the association between the overexpression of cell cycle checkpoint kinase Mps1 and patient outcomes in glioblastoma.

**Methods:** We analyzed available online transcriptomic and proteomic data following Mps1 knockdown in U251 glioblastoma cells. Gene ontology enrichment analysis was performed to identify key pathways activated after Mps1 knockdown.

**Results:** The analysis revealed that cell cycle transition and the intrinsic apoptosis pathway in response to DNA damage were the top pathways activated following Mps1 knockdown. Three genes and proteins emerged as common targets: BCL2L1 (encoding the protein Bcl-xL) was downregulated, while CDKN1A (encoding p21) and SETD2 (encoding the histone methyltransferase SETD2) were upregulated.

**Conclusion:** This study is the first to report the association of Mps1 inhibition with SETD2 overexpression, providing a new perspective for glioblastoma therapeutics.

**Keywords:** Mps1, glioblastoma, gene ontology, transcriptomic, proteomic, SETD2

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Glioblastoma is a rare type of cancer that starts in the brain, but it's the most common primary brain tumor in adults. It's a very fast-growing tumor that tends to spread to nearby normal brain tissue.[1] Glioblastoma starts in the brain's astrocytes, the cells that provide structural support for neurons.[2]

Nearly all patients with glioblastoma receive radiotherapy, either alone or in combination with other treatment modalities, including DNA double-strand break agents such as the alkylating agent temozolomide (TMZ) or cell cycle kinase inhibitors, with a growing panel of available small molecules.[3]

One of the key players in the cell cycle checkpoint is the kinase Mps1, short for Monopolar Spindle 1. Indeed, Mps1 is an essential dual-specificity protein kinase that phosphorylates serines/threonines and tyrosines.[4]

The most important function of Mps1 is to ensure the proper biorientation of sister chromatids on the mitotic spindle at kinetochores. Mps1 is also implicated in the error correction mechanism that resolves erroneous kinetochore–microtubule attachments.[5] In addition to its role during the cell cycle, Mps1 is involved in the genotoxic stress response, including DNA damage, arresting cells in G2/M or G1, or inducing cell death depending on the status of p53.[4] Several tumors show Mps1 overexpression, including malignant fibrous histiocytoma,[6] breast cancer,[7] neuroblastoma,[8] and glioblastoma.[9]

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The histone methyltransferases (HMTs) play major roles in oncogene and tumor evolution.[10] Moreover, HMTs constitute attractive targets for disease intervention because their enzymatic activity could be therapeutically manipulated.[3,11] One of the major HMT players is SETD2, a histone-modifying protein responsible for H3K36 trimethylation (H3K36me3). SETD2 acts as a determinant of chromatin integrity by regulating nucleosome dynamics during transcription.[12] SETD2 somatic mutations have been previously described in glioblastomas.[13–15]

Here, we report that Mps1 overexpression is a poor prognostic marker for glioblastoma patients and that Mps1 silencing provokes the intrinsic apoptotic pathway in response to DNA damage with an overactivation of the histone-modifying protein SETD2.

## Methods

### Kaplan-Meier Curve Analysis

To analyze a Kaplan-Meier survival curve, in function of Mps1 expression, we used the R2-Genomics analysis and visualization platform (https://r2platform.com), developed within the Department of Oncogenomics at the Academic Medical Center (AMC) in Amsterdam, the Netherlands.

### Gene Ontology Analysis

Network analysis and Gene Ontology analysis associated with Mps1 silencing in U251 cells were obtained with the Cytoscape software and related plugins (GeneMANIA and ClueGO).[16–18]

## Results

### Overexpression of Mps1 as a Prognostic Marker in Glioblastoma Patients

We used the R2-Genomics analysis and visualization platform to investigate whether Mps1 expression could be correlated with poor overall outcomes in glioblastoma tumors. We screened several glioblastoma gene expression datasets for Mps1 expression, designated as GSE43378,[19] GSE19578,[20] and GSE43107 (Fig. 1A–C),[21] and from the Cancer Genome Atlas Program TCGA (Fig. 1D), respectively. Kaplan-Meier curves showed that high Mps1 expression was associated with poor overall survival, supporting Mps1 expression as a poor prognostic marker for glioblastoma tumors.

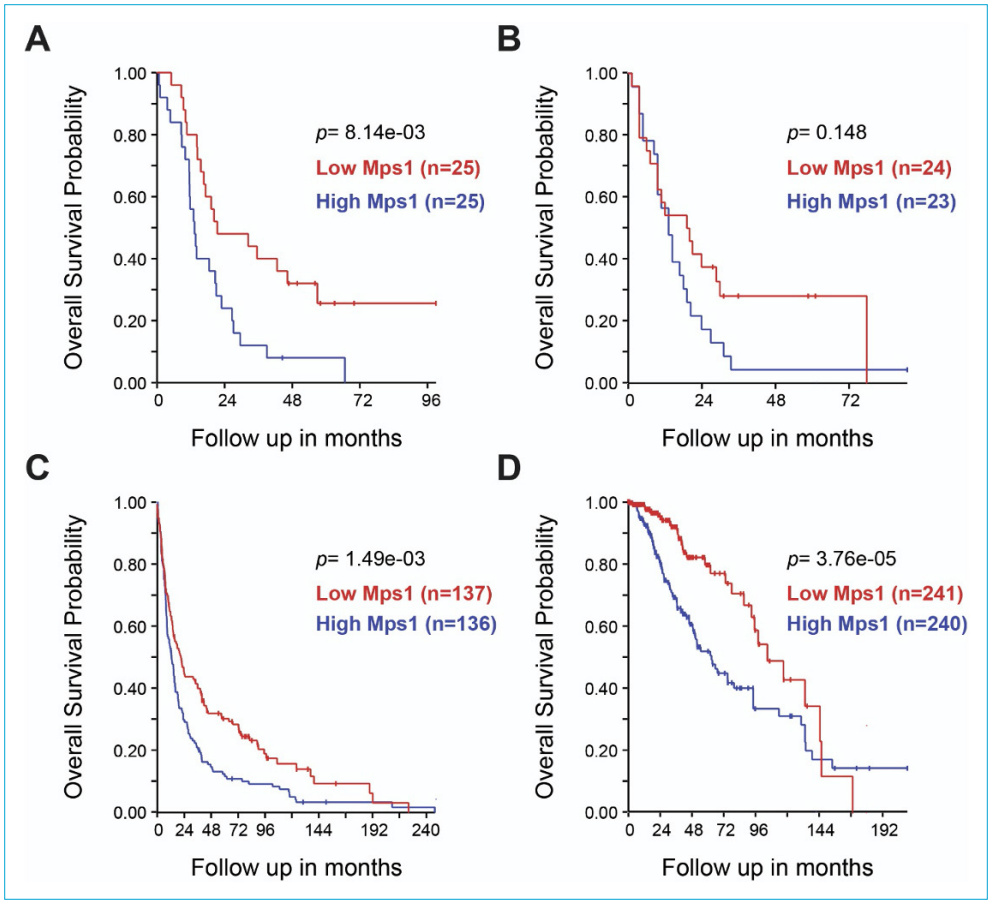


**Figure 1.** Mps1 expression predicts clinical outcome in glioblastoma patients. **(a-d)** Kaplan–Meier curves reporting patient's overall survival probability with respect to Mp1 expression.

## Mps1 Knockdown in Glioma Cells Targets the Intrinsic Apoptotic Pathway in Response to DNA Damage

In order to investigate the effect of Mps1 knockdown in glioma cells, we took advantage of two published studies using the same glioma cell model, the U251 cells, and specific small interfering RNA against Mps1. The first study investigated the gene expression changes after Mps1 down-regulation using microarray analysis.[22] The raw data of this study is deposited in Gene Expression Omnibus under the reference GSE57091. The second study explored the modulation of phosphorylated and non-phosphorylated proteins when Mps1 is silenced using the reverse phase protein arrays (RPPAs) technique.[23] Raw data are available under the reference GSE67502. Based on these published data, we performed a Gene Ontology (GO) enrichment analysis for both transcriptomic and proteomic data to identify common biological processes involved after 24 hours of siMps1 transfection and Mps1 knockdown. Different signaling pathways were found to be engaged, as shown by the molecular network (Fig. 2A), and the regulation of the cell cycle G1/S phase transition, the cellular response to inorganic substances, and the intrinsic apoptotic-signaling pathway in response to DNA damage exhibited the highest enrichment scores, respectively (Fig. 2B).

## Mps1 Knockdown Upregulates the Histone Methyltransferase SETD2

To further explore the Gene Ontology enrichment analysis, we overlapped the transcriptomic and proteomic data. The cell cycle checkpoint pathway and the intrinsic apoptotic-signaling pathway in response to DNA damage shared two targets, BCL2L1 (encoding the protein Bcl-xL) and CDKN1A (encoding p21) (Fig. 3A, B). BCL2L1 and CDKN1A are both well-characterized in cell cycle and apoptotic signaling pathways. Unexpectedly, a third gene emerged, not among the previously mentioned pathways. The SETD2 gene (encoding SETD2) appears as a common target gene and protein when Mps1 is silenced in glioblastoma cells (Fig. 3C). SETD2 is a histone-modifying protein responsible for H3K36 trimethylation (H3K36me3).[24] The three common targets are shared among 294 genes from the transcriptomic data and 79 proteins from proteomic data (Fig. 4A). When Mps1 is silenced, BCL2L1 is downregulated, whereas CDKN1A and SETD2 are upregulated (Fig. 4B).

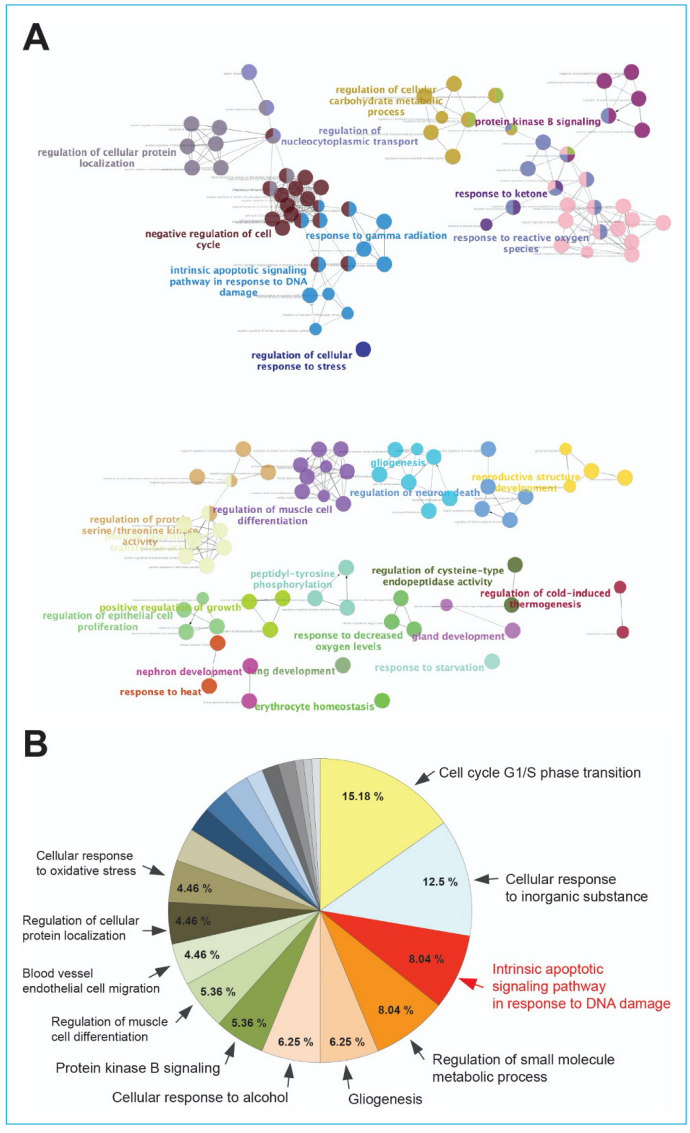


**Figure 2.** Gene ontology analysis for both transcriptomic and proteomic data following Mps1 knockdown.

**(a)** Gene ontology (GO) network view of target genes following Mps1 silencing. GO was performed using the Cytoscape with GeneMANIA and ClueGO'associated-plugins and the network-based enrichment was done following the "representative pathways" parameters. **(b)** List of the main pathways engaged after Mps1 knockdown after GO analysis.

## Discussion

Diagnosing and treating patients with glioblastoma remains challenging because glioblastoma is a very fast-growing tumor, and current treatment options are limited and dependent on the stage of the tumor.[25] An attractive approach to therapy, particularly when targeting cell cycle players, is the use of anti-mitotic drugs/agents, alone or in combination with radiotherapy.[26–29]

In our study, we found that Mps1 overexpression was associated with poor overall patient outcomes, as shown by Kaplan-Meier curves. Thus, the mitotic kinase Mps1 can be proposed as a novel prognostic marker for glioblastoma.

We took advantage of two published papers targeting

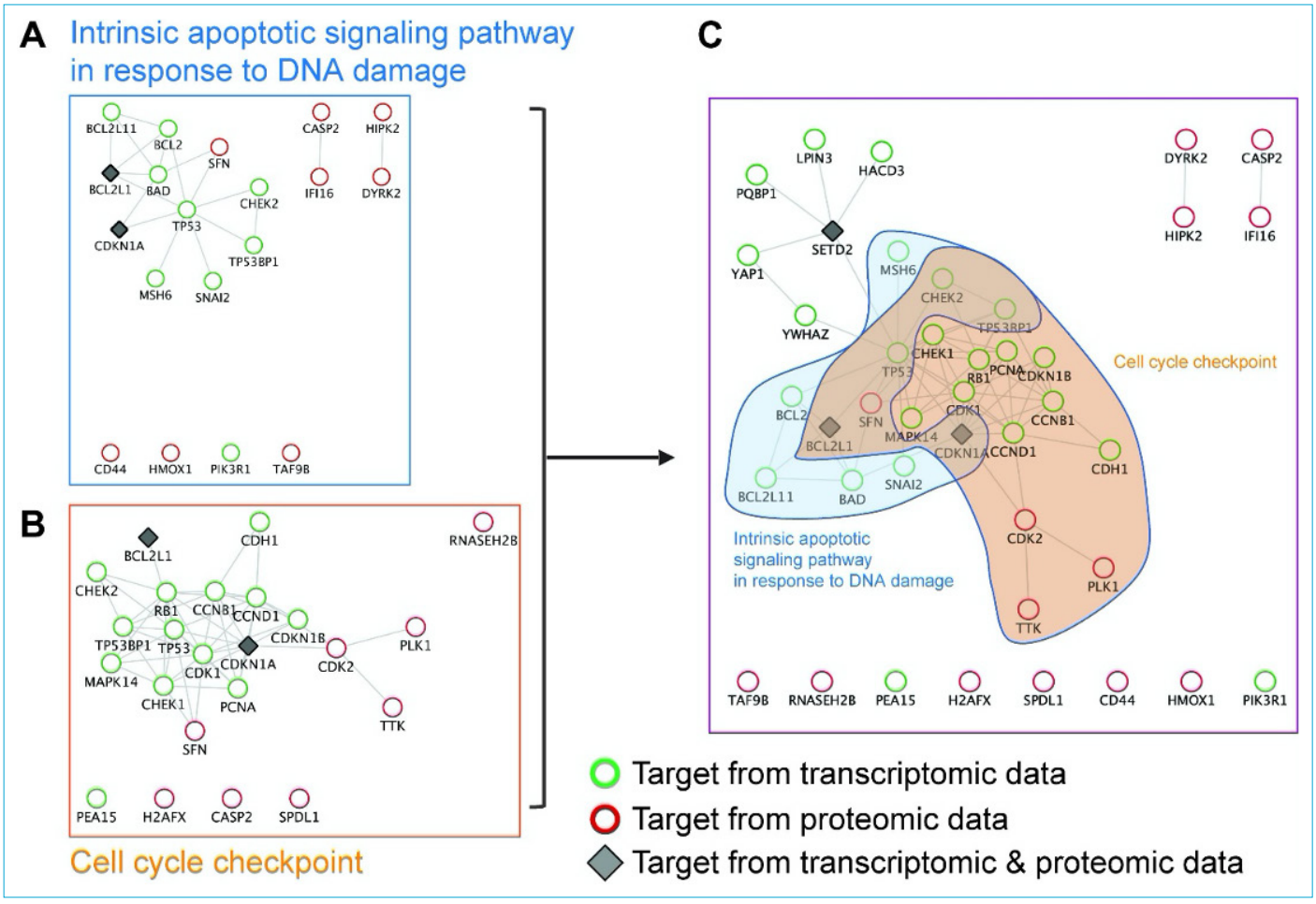


**Figure 3.** Gene ontology (GO) network view and overlap of transcriptomic and proteomic data.

**(a-c)** Network view of shared targets, genes and proteins, after Mps1 silencing. **(a)** represent the intrinsic apoptotic pathway in response to DNA damage and **(b)** the cell cycle checkpoint pathway. The green-labeled targets are extracted from transcriptomic data while red-labeled targets are extracted from proteomic data. Grey-labeled targets are common proteins found in both transcriptomic and proteomic data. **(c)** represent the overlap between the 2 pathways. The intrinsic apoptotic pathway in response to DNA damage related nodes were highlighted in bleu zones while the cell cycle checkpoint related nodes were highlighted in orange zones.

Mps1 and silencing the kinase in U251 glioblastoma cells, investigating the gene expression and protein phosphorylation changes. Then, using a bioinformatics approach and gene ontology enrichment analysis, we found that several biological pathways were involved after Mps1 knockdown. The top three processes with the highest enrichment scores were regulation of cell cycle transition, cellular response to inorganic substances, and the intrinsic apoptosis pathway in response to DNA damage. The overlap between the transcriptomic and proteomic data reduced the number of involved pathways to the cell cycle transition and the intrinsic apoptosis pathway in response to DNA damage.

Our study confirms the previous work of Maachani et al., where the authors demonstrated that Mps1 inhibition increased the radiosensitivity of glioblastoma cells through decreased repair of DNA double-strand breaks and induction of postradiation mitotic catastrophe. In addition, the molecular profiling of Mps1-silenced glioblastoma cells revealed altered expression of transcripts associated with DNA damage, repair, and replication.[30]

Mps1 inhibition has also been shown to increase DNA damage in several models. In murine tumor cells, Mps1 inhibition sensitized the cells to etoposide, an inducer of DNA double-strand breaks, by inhibiting the ligase activity of the enzyme topoisomerase II.[31] It has also been shown in kidney cancer cells 293T, breast cancer cells MCF-7, cervical cancer cells HeLa, and colon cancer cells HCT116 and H1299 that depletion of Mps1 impairs histone H2B ubiquitination, and *de facto* DNA repair and cell survival.[32] Similarly, Mps1 inhibition was found to induce DNA damage in acute myeloid leukemia.[33] Interestingly, in the first cleavage of early mouse embryos, Mps1 inhibition was shown to

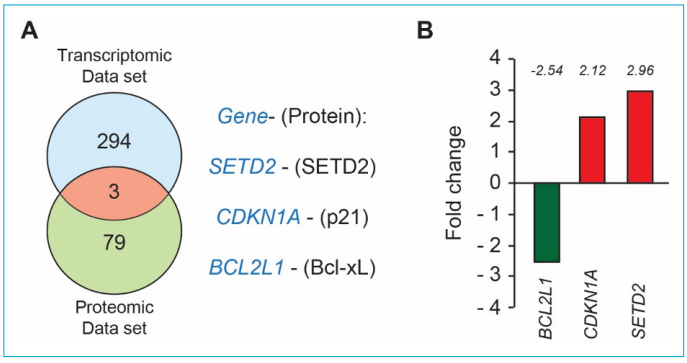


**Figure 4.** Common transcriptomic and proteomic targets following Mps1 knockdown.

**(a)** Venn diagram displays the targets (genes and proteins) that were deregulated at 24h after Mps1 silencing. Only 3 targets were shared when transcriptomic and proteomic data was overlapped. **(b)** Fold change regulation of the 3 common proteins. BCL2L1 is downregulated, whereas CDKN1A and SETD2 are upregulated.

increase DNA damage, resulting in oxidative stress-activated apoptosis and autophagy.[34]

The intersection between the transcriptomic and proteomic data analysis revealed a common set of target proteins: Bcl-xL, p21, and SETD2.

Bcl-xL belongs to the Bcl-2 family of anti-apoptotic proteins and is localized in the mitochondria.[35] Bcl-xL is one of the key regulators of apoptosis.[36] It can also regulate other important cellular functions, including autophagy, neuronal growth and survival, and plays a protective role in neuronal injury; Bcl-xL can also promote $Ca^{2+}$ transport to mitochondria, increase ATP production, and improve metabolic efficiency.[37,38] Our results correlate with the nature of the protein, as we found that Bcl-xL was downregulated after Mps1 knockdown and subsequent DNA damage and cell death.

The second target, p21 (also known as p21WAF1/Cip1), promotes cell cycle arrest in response to various stimuli, including DNA damage. Some of the anti-proliferative activities of p21 are based on its wide range of protein-protein interactions and its ability to regulate the transcription of genes, and, *de facto*, pathways activated by p21 are interconnected.[39] Cell cycle arrest induced by p21 promotes DNA repair by allowing sufficient time for damaged DNA to be repaired before cell division. In addition, permanent cell cycle arrest due to DNA damage is highly dependent on the induction of p21 and p53, leading to the retention of cyclin B1 and blockage of the cycle.[40] Again, our results are consistent with the literature, as we found that p21 was over-activated after Mps1 knockdown and consequent DNA damage.

The direct link between p21 and Bcl-xL has not been widely reported in the scientific literature; however, hyperoxia-induced oxidative stress, which activates DNA damage, involves a direct interaction between p21 and Bcl-xL.[41,42]

Another gene that appears to be upregulated in our analysis is the SETD2 gene. SETD2 stands for SET domain-containing protein 2. It's a human gene that encodes an enzyme called histone-lysine N-methyltransferase SETD2 and is involved in epigenetic regulation, specifically the modification of histone proteins. In fact, SETD2 is the only human gene encoding the histone methyltransferase responsible for the trimethylation of lysine 36 of histone H3.[43,44]

Since its identification and characterization as a transcription elongation factor, SETD2 has been reported in the literature to be involved in many other important cellular processes, including alternative RNA splicing, cell cycle progression, genomic stability, apoptotic response, and DNA damage repair.[43,44] Indeed, SETD2 is involved in the early steps of DNA damage repair signaling induced by DNA double-strand breaks, mainly via homologous recombination.[45] SETD2 promotes repair through methylation of histone H3K36,[24] and SETD2 has also been reported to stimulate DNA mismatch repair.[46]

Several recent studies have shown that genomic instability in cancer is associated with aberrant histone modifications, highlighting the importance of the histone code in maintaining genome stability.[45,47–49] Inhibiting or silencing Mps1 is one of the most widely used approaches to induce chromosomal aberrations *in vitro*, resulting in aneuploidy and mitotic catastrophe.[8,50–54]

The association of Mps1 knockdown with SETD2 overexpression that emerged from our analysis is interesting and could open new windows to understanding their coordination in cancer development and, more interestingly, in therapeutics. Indeed, the possible synergy between inhibitors of cell cycle checkpoints and inhibition or deletions of histone modifiers such as SETD2.

## Conclusion

Our study constitutes starting data for future investigations that could confirm the beneficial association between antimitotic inhibitors, particularly Mps1 inhibitors, and the inhibition of methyltransferase, particularly SETD2, in cancer chemotherapy resistance, especially in cancers that accumulate resistance to antimitotic or spindle poisons.

### Disclosures

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**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – M.J., C.K; Design – M.J.; Supervision – M.J.; Data collection &/or processing – M.J., C.K; Analysis and/or interpretation – M.J., C.K; Literature search – M.J.; Writing – M.J.; Critical review – M.J.

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