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Original Research

Identify of Potential Genetic Biomarkers for Hepatitis C Virus Related Hepatocellular Carcinoma

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Abstract

Objectives: Hepatocellular carcinoma (HCC) is a considerable global health concern. This study attempts to analyze gene expression data between liver tissues with HCV-related HCC and healthy liver tissues to identify potential biomarkers that contribute to HCC development.

Methods: We analyzed RNA sequencing data from liver tissues with HCV-related HCC and healthy liver tissues in this study. We retrieved the dataset from NCBI using the code GSE140845. We performed gene expression analysis using the Limma software package in the R programming language, defining genes as differentially expressed if they had a log2 fold change (log2FC) > 1 and a p > 0.05. We conducted data visualization using scatter plots, UMAP, volcano plots, and mean difference (MD) plots.

Results: A total of 20,868 genes were analyzed between the HCV-HCC and healthy liver tissue groups, and 3,303 genes were found to be significantly differentially expressed. Genes such as AKR1B10, MUC13, SLC22A11, and SPINK1 showed upregulation in the HCV-HCC group, whereas CNDP1, IGFALS, PVALB, and CLEC4M showed downregulation. These genes have the potential to serve as biomarkers and play critical roles in understanding the mechanisms of HCC development.

Conclusion: This study highlights the differential regulation of genes associated with HCV-HCC, emphasizing their potential roles in the pathogenesis of HCC. Notably, the identified biomarkers hold promise as therapeutic targets. These findings may contribute to personalized medicine approaches and enable the development of novel strategies for the prevention and treatment of HCC.

Keywords: HCC, HCV, HCV-related HCC, Gene expression analysis, Biomarkers

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Globally, hepatocellular carcinoma (HCC), the primary form of liver cancer, is the fourth leading cause of cancer-related death, responsible for over 800,000 deaths in 2017 alone. As such, it poses a serious threat to global health.[1, 2] The prevalence of liver cancer varies greatly, with East Asia having the highest rates, which can be more than five times higher than in places like South Asia and Eastern Europe.[1] This geographical disparity is mostly due to the high incidence of viral hepatitis infections, including hepatitis B virus (HBV) and hepatitis C virus (HCV) cause a worldwide fatality rate of 76%.[3] Vaccination progress in immunization and treatment methodologies, the prevalence of liver cancer continues to be significant, especially in low- and middle-income nations with restricted healthcare access.[3, 4]

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HCV, a hepatotropic RNA virus, is a bloodborne infection that only impacts the liver. The majority of patients infected with HCV do not spontaneously eradicate the infection, resulting in a chronic condition. Chronic hepatitis C virus (HCV) infection can progress to severe liver diseases, including fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). While approximately 71 million people are currently infected with HCV, only 20–30% develop cirrhosis, and 1–4% of cirrhotic patients progress to HCC annually.[5, 6] HCV infection constitutes a burgeoning worldwide health concern. HCV is prevalent in many countries and is progressively exerting significant pressure on society and healthcare systems. Chronic sequelae, such as cirrhosis and HCC, are increasingly common.[7] The natural history of chronic HCV infection is characterized by slow progression, with severe liver disease developing in only a minority of cases within the first 10–15 years post-infection. Therefore, patient age at infection and the duration of chronic infection are key factors influencing morbidity and mortality.[8]

The processes via which HCV leads to HCC are complex, encompassing both direct viral impacts and host genetic influences. The inflammatory environment caused by chronic HCV infection fosters conditions conducive to genetic mutations and genomic instability, which are indicative of cancer progression.[9, 10] Through the induction of oxidative stress and the generation of reactive oxygen species (ROS), HCV can cause DNA damage and subsequent mutations, thereby promoting carcinogenesis.[9, 10] Genomic and epigenomic modifications significantly contribute to HCV-related HCC. Multiple studies have identified specific genetic variations that may influence an individual's susceptibility to HCC in the context of HCV infection. Genetic polymorphisms in CTLA-4 and IL-4 are linked to an increased incidence of HCC in individuals infected with hepatitis C virus.[11, 12]

In summary, the association between HCV and HCC is defined by chronic inflammation, genetic predisposition, and direct viral carcinogenic processes. Comprehending these relationships is essential for formulating tailored prevention and therapy strategies for HCV-related HCC. This study will use gene expression data from HCV-related HCC and normal liver tissues to perform differential expression analyses and evaluate the relationship between HCV and HCC. The goal is to identify genes that exhibit differential regulation in the HCC group. Advanced bioinformatics analysis will support the identification of these genes as biomarkers for HCC, suggesting their role in the disease's development.

Methods

Data Set

To understand the genetic background of HCV-related HCC, this study analyzed microRNA data (RNA sequence data) from normal liver tissue and liver tissue with HCV-related HCC. The data used in this study were obtained from the National Center for Biotechnology Information (NCBI) under accession number GSE140845.

RNA-Sequence Analysis (RNA-Seq)

RNA sequencing (RNA-seq), a well-established and powerful technology, has revolutionized transcriptomics by enabling quantitative and comprehensive analysis of complete transcriptomes. Unlike hybridization-based methods, RNA-seq directly sequences RNA, allowing for the discovery of novel transcripts and precise quantification of known transcripts. This sequencing-based approach offers several advantages, including a broad dynamic range for expression level measurement, reduced background noise leading to highly accurate and reliable data, and precise determination of exon-intron boundaries, single nucleotide polymorphisms (SNPs), and other transcript variants. Due to these advantages, RNA-seq is well-suited for a wide range of discovery-based research projects.[13]

Transcriptomics

The transcriptome represents the complete set of RNA transcripts—including mRNA, tRNA, rRNA, and non-coding RNAs—produced by a cell, tissue, or organism at a specific time. Unlike the relatively stable genome, the transcriptome is highly dynamic and responsive to environmental factors such as pH, nutrient availability, temperature, and intercellular signaling. Fluctuations in gene transcription in response to various cellular processes drive these changes, altering the mRNA composition of the transcriptome. Consequently, the transcriptome provides a snapshot of actively expressed genes within a given context, highlighting the crucial interplay between environment and biological systems.[13, 14]

Transcriptomics is the study of the entire complement of mRNA transcripts generated from a cell's genome, yielding information on their expression profiles. Microarray analysis and next-generation sequencing are widely employed in transcriptomic studies to investigate precise alterations in the transcriptome under specific conditions.[14]

Transcriptomic studies have become increasingly important in elucidating the role of gene expression changes (both up- and downregulation) in complex diseases such as cancer. These studies also provide insights into the interconnectedness of these changes and the underlying biochemical pathways and molecular mechanisms governing cell life cycles and disease progression.[14, 15]

Gene Expression Analysis

Alterations in the physiological state of an organism or cell are invariably reflected in changes in gene expression. Con-

sequently, the assessment of gene expression is of considerable importance in all areas of biological research. DNA microarray technology, which utilizes the hybridization of mRNA molecules to a dense array of immobilized target sequences complementary to specific genes, is one such method employed for gene expression analysis. Investigating the influence of chemical agents on gene expression regulation can provide valuable insights into both functional and toxicological properties. Furthermore, analysis of clinical samples from healthy and diseased individuals can lead to the discovery of novel biomarkers.[16]

Bioinformatics Analysis Phase

Gene expression data from liver tissues with HCV-related HCC and normal liver tissues were analyzed using the limma package in R.[17] Limma, a software suite designed for differential expression analysis using linear models, is applicable to various gene expression technologies, including microarrays, RNA-seq, and qPCR. By employing Empirical Bayes methods, limma provides robust results, particularly with small sample sizes. The analysis generated log2 fold change (log2FC) values, ranking genes by their expression differences. Genes with log2FC > 1 were considered upregulated, while those with log2FC < -1 were considered downregulated.

Data distribution was visualized using box plots. Sample relationships were explored using Uniform Manifold Approximation and Projection (UMAP). Differential gene expression (both up- and downregulated) was visualized using volcano plots, which display the relationship between statistical significance (y-axis) and log2FC (x-axis). In these plots, red indicates upregulated genes, blue indicates downregulated genes, and black indicates genes with no significant change in expression. Mean Difference (MD) plots were also used to visualize differential expression, plotting log2FC against average log2 expression levels. The MD plots used the same color scheme as the volcano plots.

Results

The study includes data from 5 liver tissues with HCV-related HCC and 5 healthy liver tissues. The gender of the 10 individuals was male. The microRNA data were obtained from liver tissues.

Figure 1 shows the scatter plots of the 10 samples used in the study. In the graph, the HCV-HCC symbol is used to represent HCV-related patients and the non-HCC symbol is used to represent healthy liver tissues. The graph was used to show the distribution of values in the samples. A color-coded plot (Fig. 2) was used to assess data normalization

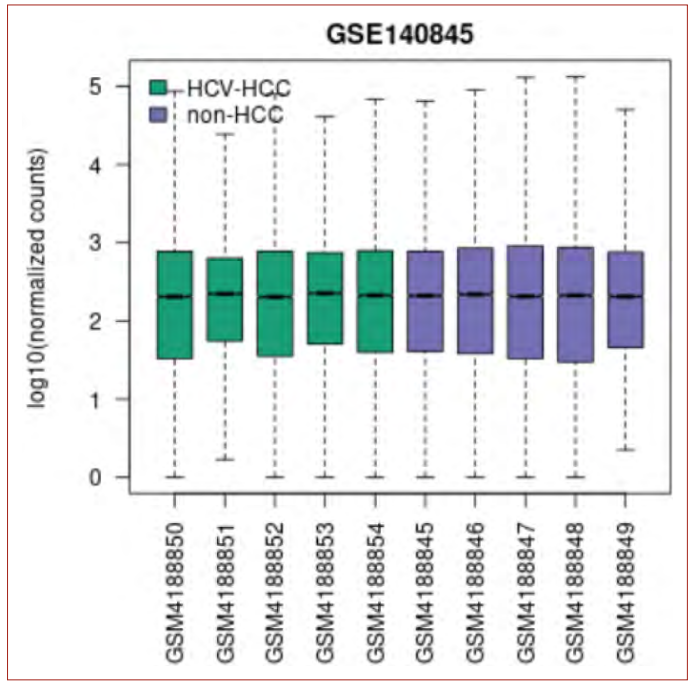

Figure 1. Distribution plot of the samples.

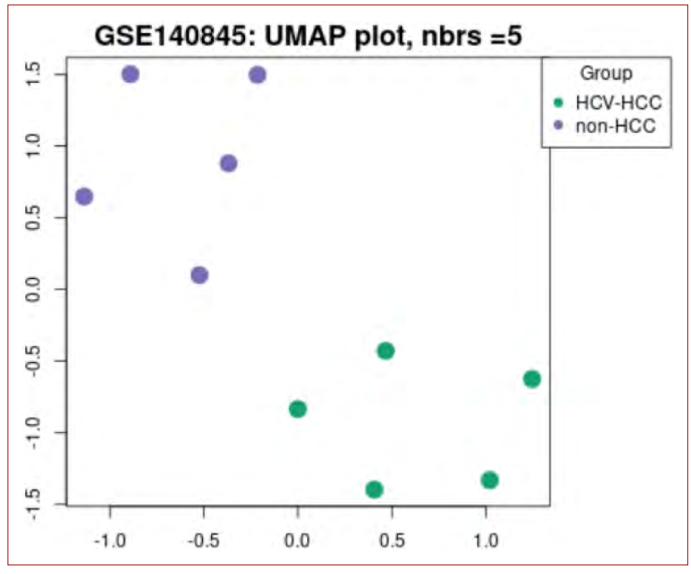

Figure 2. UMAP plot of the samples.

before differential expression analysis. The UMAP plot (Fig. 2) demonstrates clear sample clustering based on similar characteristics.

The distribution and clustering pattern of the different groups provide important clues about the biological or molecular similarities of the samples. Green dots represent HCV-HCC tissue samples, while purple dots represent non-HCC tissue samples. This distinction provides a remarkable separation in the classification and grouping of samples and is an effective tool for visualizing different biological states in the dataset.

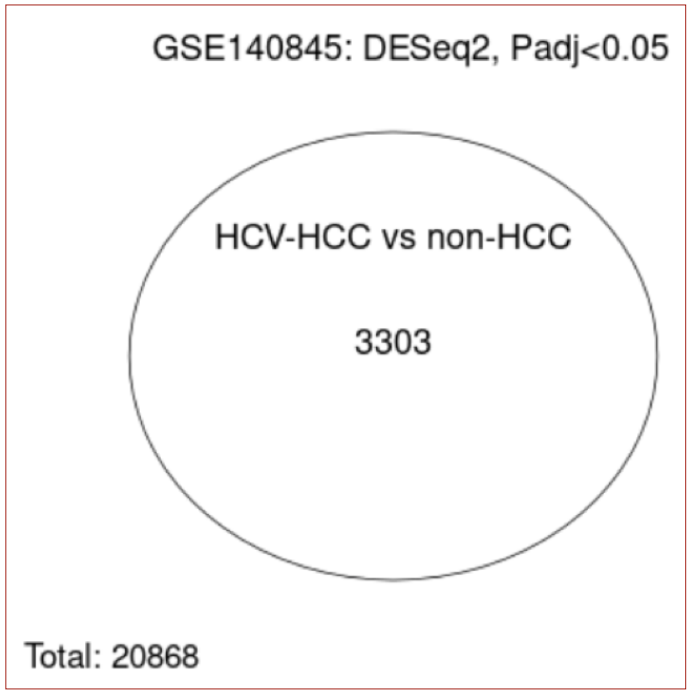

Figure 3. Graph comparing genes between HCV-HCC and non-HCC groups.

Figure 3 represents the comparison of genes between HCV-HCC and non-HCC groups. According to the graph, the total number of genes analyzed is 20868. This represents the number of all genes included in the study. In addition, 3303 genes were statistically significantly differentially expressed between these two groups. The graph was obtained under the condition of |log2FC| > 1.0 (absolute log2 fold change value greater than 1.0) and $p < 0.05$.

Table 1 presents the top 10 upregulated genes identified in the comparison between the two groups. When determining gene expression up-regulation, certain threshold values were taken into account in order to consider statistical significance and biological importance. In this context, the criteria of |log2FC| > 1.0 (absolute log2 fold change value greater than 1.0) and p-value less than 0.05 were used to evaluate the regulation status of genes. These thresholds provide a reliable and standardized approach to determine whether genes show significant differences. The results obtained may contribute to the identification of potential biomarkers by shedding light on the biological significance of genetic differences between groups.

Table 1. Genes up-regulated in HCV-HCC tissues relative to non-HCC

GeneID	padj	pvalue	lfcSE	stat	log2FoldChange	baseMean	Symbol
57016	1,33E-26	3,86E-30	0,725	11,40698	8,26721	5981,23	AKR1B10
56667	2,18E-39	2,11E-43	0,549	13,81374	7,58536	1199,66	MUC13
55867	1,41E-06	2,23E-05	1,509	4,454916	6,72114	480,73	SLC22A11
6424	5,12E-04	2,23E-05	1,425	4,240711	6,042391	325,54	SFRP4
28942	3,29E-12	7,16E-15	1,495	3,987738	5,961361	317,51	IGKV1-8
2719	3,29E-12	7,16E-15	0,766	7,781625	5,96135	1755,83	GPC3
6690	1,41E-06	1,82E-08	1,057	5,628574	5,94965	479,27	SPINK1
60676	2,76E-06	3,93E-08	1,048	5,589756	5,855787	2470,66	PAPPA2
6707	2,76E-06	3,93E-08	1,061	5,494151	5,829656	42,54	SPRR3
441282	2,19E-16	2,01E-19	0,629	9,012934	5,670096	162,67	AKR1B15

Table 2. Genes down-regulated in HCV-HCC tissues relative to non-HCC

GeneID	padj	pvalue	lfcSE	stat	log2FoldChange	baseMean	Symbol
84735	2,47E-28	5,98E-32	0,569	-11,7641	-6,68851	1182,83	CNDP1
730249	4,65E-04	1,97E-05	1,474	-4,2687	-6,29032	378,38	ACOD1
3483	1,29E-40	6,22E-45	0,433	-14,0652	-6,09531	2606,88	IGFALS
5816	8,59E-14	1,24E-16	0,707	-8,27873	-5,85585	26,03	PVALB
10332	3,28E-12	6,97E-15	0,731	-7,78511	-5,68733	931,33	CLEC4M
51266	1,55E-08	1,03E-10	0,88	-6,46222	-5,68658	384,76	CLEC1B
1544	1,32E-11	3,51E-14	0,747	-7,57803	-5,66012	10238,93	CYP1A2
22865	5,71E-09	3,37E-11	0,851	-6,62959	-5,64195	140,16	SLITRK3
339390	9,44E-09	5,93E-11	0,86	-6,54549	-5,63175	940,09	CLEC4G
3781	2,27E-20	1,10E-23	0,561	-10,0325	-5,62507	361,09	KCNN2

Analysis of the dataset identified 10 significantly downregulated genes in the comparison between the two groups (Table 2), using the same log2 fold change threshold (<-1) as for upregulated genes. Differential gene expression between the groups was visualized using volcano plots (Fig. 4) and Mean Difference (MD) plots (Fig. 5). Volcano plots display the relationship between statistical significance and log2 fold change, while MD plots show log2 fold change against mean log2 expression levels. In both plots, red indicates upregulation and blue indicates downregulation, facilitating the identification of genes with significant expression changes. These differentially expressed genes represent potential biomarkers and may play critical roles in disease processes, providing valuable insights for understanding disease mechanisms and identifying therapeutic targets.

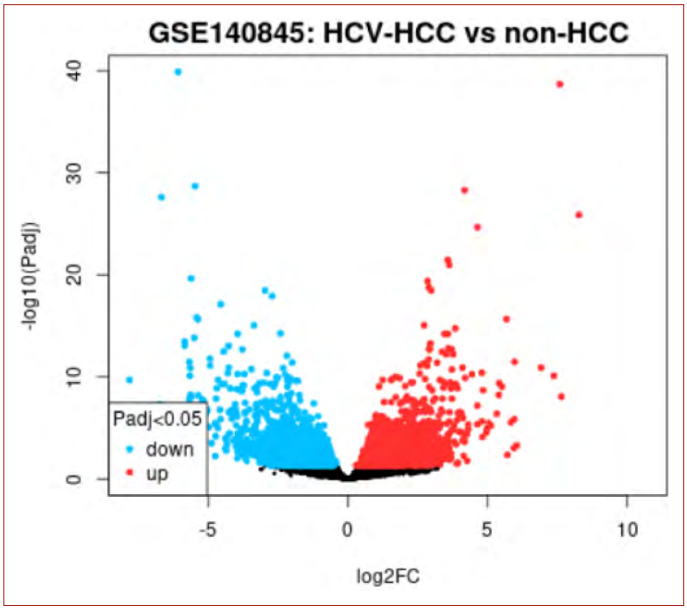

Figure 4. Volcano plot of transcripts in HCV-HCC and non-HCC tissues. (Red dots represent transcripts that increased and black dots represent transcripts whose expression level remained unchanged).

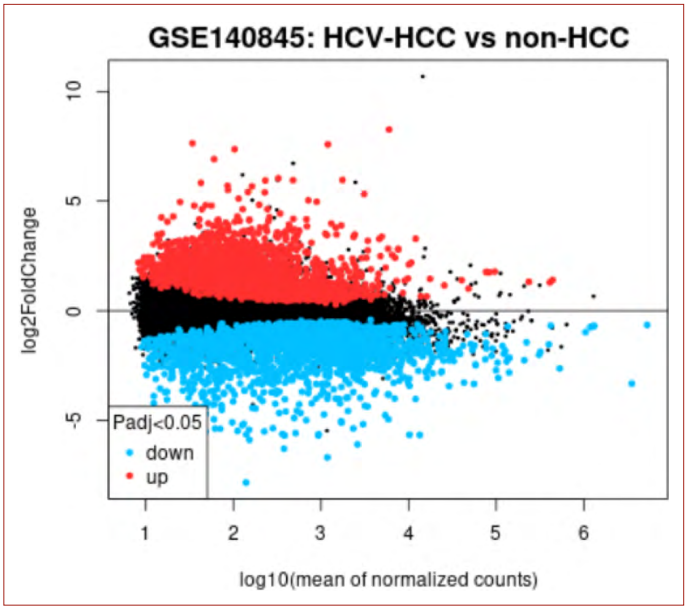

Figure 5. MD plot of transcripts in HCV-HCC and non-HCC tissues (Red dots represent transcripts that increased, and black dots represent transcripts whose expression level remained unchanged).

Discussion

Hepatocellular carcinoma (HCC), a highly aggressive cancer with distinct epidemiological features, remains a major global public health concern due to its substantial economic and health burden.[18-21] Key risk factors include hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholism, metabolic dysfunction-associated steatohepatitis (MASH), and exposure to dietary toxins such as aflatoxins and aristolochic acid, particularly in developed countries. In these cases, HCC often develops following prolonged chronic hepatitis, frequently in the context of HBV- or HCV-related cirrhosis, with an annual incidence of 2–5% in this population.[22] The poor overall survival associated with HCC necessitates improved therapeutic strategies targeting these risk factors to reduce the global disease burden. Consequently, there is growing interest in genomic and molecular research to identify early diagnostic and prognostic markers, elucidate liver carcinogenesis pathways, and develop new therapeutic targets to improve clinical management. Enhanced HCC surveillance is therefore expected to significantly reduce global incidence in the coming decades.[19, 23]

Chronic HCV infection significantly elevates the chance of HCC, with research demonstrating that those with HCV possess a relative risk of 17 for acquiring liver cancer in comparison to the general population.[24, 25] The processes by which HCV facilitates HCC development are complex. HCV infection induces persistent inflammation, potentially resulting in liver fibrosis and cirrhosis, both of which are precursors of HCC.[26] Furthermore, HCV has been demonstrated to elicit diverse molecular alterations in hepatocytes, including the overexpression of certain microRNAs that facilitate viral replication and modify metabolic pathways linked to the etiology of liver disease.[27, 28] In summary, HCV significantly contributes to the global incidence of HCC, with its involvement in liver carcinogenesis underscored by many biological processes and epidemiological data.

This study analyzed gene expression data from HCV-related HCC and normal liver tissues to identify potential biomarkers and understand the genetic basis of HCV-related HCC. As a result of the analyses, many genes were found to be differentially regulated in the HCV-HCC group compared to non-HCC.

Bioinformatic analysis revealed numerous differentially expressed genes, with AKR1B10 showing a 306.55-fold upregulation in the HCV-HCC group compared to the non-HCC group. Similarly, MUC13,SLC22A11, SFRP4, IGKV1-8, GPC3, SPINK1, PAPPA2, SPRR3, AKR1B15 genes had 191.34, 105.41, 65.72, 62.24, 62.24, 61.39, 57.68, 56.49, 50.91 fold up-regulated gene expression, respectively.

The CNDP1 gene was down-regulated 102.53-fold in the HCV-HCC group compared to the non-HCC group. Similarly, ACOD1, IGFALS , PVALB, CLEC4M, CLEC4M, CLEC1B, CYP1A2, SLITRK3, CLEC4G, KCNN2 genes showed 78.24, 68.11, 57.68, 51.26, 51.26, 50.56, 49.86, 49.52, 49.18 fold down-regulation respectively.

Subsequent research on the identified genes holds significant promise, as they may serve as critical biomarkers in the successful treatment of HCC. These biomarkers could revolutionize pharmacological therapies by enabling the design and application of highly targeted treatments. The precise use of genetic biomarkers improves patient care and streamlines healthcare systems, enhancing efficiency. Continued advances in genetic research are expected to expand personalized medicine, transforming modern healthcare.

In conclusion, HCC represents a significant global health burden, and genetic research is indispensable for elucidating its complex pathophysiology. Given that treatment strategies are contingent on the underlying disease etiology, dedicated genetic investigations are essential for the development of targeted preventive and therapeutic strategies. Genetic screening programs for high-risk populations offer opportunities for early detection and timely intervention. Continued progress in genetic research holds great promise for the development of innovative approaches to prevent and manage HCC recurrence, thereby improving patient outcomes.

Disclosures

Ethics Committee Approval: This study utilized a publicly available dataset from the NCBI Gene Expression Omnibus (GEO). As the data were de-identified and publicly available, ethics committee approval was not deemed necessary.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – Z.K., S.A.; Design – Z.K., S.A.; Supervision – S.A.; Materials – Z.K., S.A.; Data collection &/or processing – Z.K., S.A; Analysis and/or interpretation – Z.K., S.A; Literature search – Z.K., S.A; Writing – Z.K., S.A; Critical review – S.A.

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