

Original Research Article

Integrated Multi-Dataset Transcriptomic and Network Analysis Reveals GAPDH as a Prominent Hub Gene and Identifies Key Molecular Alterations in Malignant Pleural Mesothelioma

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**ABSTRACT**

Background: Malignant pleural mesothelioma (MPM) is a life-threatening cancer of the pleura that is usually related to asbestos exposure, has a long latent period, progresses quickly, has a poor prognosis, and few treatment options. It is, therefore, crucial to recognize molecular changes and therapeutic targets.

Methodology: Five GEO datasets (GSE51024, GSE42977, GSE112154, GSE2549, GSE29370) were analyzed to determine the genes that were differentially expressed between MPM and normal tissues. For gene ontological and pathway enrichment analysis, the Enrichr, DAVID and Metascape were used, and for pathway characterization, KEGG and Reactome were used. STRING-based protein-protein interaction (PPI) network was analyzed by using Cytoscape and cytoHubba plugin to identify the hub genes. Druggability assessment was then carried out to prioritize the drugs for further consideration.

Results: DEGs related to inflammatory response, extracellular matrix organization, apoptotic signaling and cell proliferation were identified from the integrated analysis. The pathways enriched with the enriched pathways were PI3K-Akt signaling, focal adhesion, p53 signaling, and extracellular matrix-receptor interaction. Through PPI analysis, highly connected hub genes were identified and GAPDH was a major molecular hub in the datasets analyzed.

Conclusion: The integrated transcriptomic and network-based approach provided important molecular changes and potential targets for MPM. One of the hub genes that were strongly expressed was GAPDH, which may have a biological significance. It needs further clinical and experimental validation for its diagnostic, prognostic and therapeutic significance.

Keywords: Malignant pleural mesothelioma, Transcriptomics; Bioinformatics, Differentially expressed genes; GEO, Protein-protein interaction, Hub genes, Druggable targets, Systems biology.

INTRODUCTION

Malignant pleural mesothelioma (MPM) is an aggressive type of cancer that is mainly linked to exposure to the asbestos [1]. The prognosis for MPM is poor and there are few treatment options available [2]. Understanding of pathogenesis of MPM is dependent on characterization of molecular changes [3]. Molecular characterization can be useful to develop future diagnostic and therapeutic strategies [4]. The incidence of mesothelioma is less than 1% of all cancer types. Its occurrence has been reported to be on the rise, and is expected to rise to a peak in the next decade or two [5]. Until 1950, malignant mesothelioma was thought to occur very rarely and was not accepted by some pathologists. After World War II when the use of asbestos was increased, a causal connection between asbestos exposure and mesothelioma came to be recognized [6]. Western countries saw a major reduction in the use of asbestos but asbestos use had an impact on the morbidity of mesothelioma due to the long latency period of asbestos use [7]. The time between exposure to asbestos and onset of disease varies from 15 to 60 years [8]. Mesothelioma is primarily seen in adults, and is more prevalent in men than in women [9]. The majority of cases of mesothelioma are found in men, around 70–80% [10]. The disease is more prevalent in the 5th-7th decade of life [11]. The diagnosis of these younger patients (20-40 years) was often made in childhood, and was found to be correlated with childhood exposure [12]. Some of the more frequent early symptoms of mesothelioma include chest pain and difficulty breathing [13]. In some cases, patients with malignant mesothelioma develop finger clubbing, which can affect up to 30% of them [14]. Most often the tumor develops in the parietal pleura and may extend across the surfaces of the lungs by way of the fissures [15]. In advanced disease, involvement of the pericardium can give rise to clinical signs of cardiac tamponade [16]. Old surgical incisions and injection sites for needles may also be the site of mesothelioma [17]. The rare clinical associations are: autoimmune haemolytic anaemia and hyper-erythrozoaemia [18]. The molecular advances have led to the discovery of potential non-invasive biomarkers that are relevant to mesothelioma [19]. Some candidates that have been reported are mesothelin, fibulin-3, circulating

microRNAs, or the BAP1-associated cancer susceptibility [20]. While there is some evidence from clinical trials of low effectiveness of treatment and poor prognosis for many patients with malignant mesothelioma [21]. The results of these studies suggest that mesothelioma should be treated as a unique disease condition and treated with disease specific therapeutic strategies [22]. The mesoderm forms embryo development into the mesodermal tissue, which in turn forms the mesothelium that lines the developing coelomic cavities [23]. In fact, the mesothelial derivatives also participate in the envelopment of the reproductive organs during development [24]. Serosal fluid: between the visceral and the parietal mesothelium provide protection from infection and reduce friction of the organs of the abdominal cavity with the abdominal wall. [25] The structure of mesothelial cells is well conserved throughout the pleura, pericardium and peritoneum [26]. In the adult, the mesothelium has a basement membrane, many cell-cell adhesion and polarity towards the apex and the base [27]. The barrier function is not the only essential one of the mesothelium, but also to move organs or to perform general physiological functions [28]. Hence, the present integrated transcriptomic and network-based analysis is of interest to identify differentially expressed genes, key hub genes and potentially druggable molecular targets in MPM. To this end, the present integrated transcriptomic and network-based analysis is of interest for the identification of differentially expressed genes, key hub genes and possibly druggable molecular targets of MPM.

METHODOLOGY

An integrated bioinformatics analysis of multiple data sets was used to identify molecular changes and potential therapeutic targets for MPM. Five publicly available gene expression datasets (GSE51024, GSE42977, GSE112154, GSE2549 and GSE29370) containing both MPM and normal pleural tissue samples were retrieved from the Gene Expression Omnibus (GEO). The DEGs between MPM and normal tissues were analyzed for their functional and biological significance through Gene Ontology and pathway enrichment. To explore the relationships between the identified proteins, protein-protein

interaction (PPI) network analysis was conducted and the highly connected hub genes were selected. The genes with the potential therapeutic relevance were then identified by druggability assessment.

Gathering Gene Expression Data (Tumor vs Normal)

We used statistics to determine which set of genes expressed differently between the tumour samples and the normal tissue samples.

We chose five Geo datasets for further analysis. (GSE51024, GSE42977, GSE112154, GSE2549, and GSE29370)

Druggable Target Identification

Using Druggable proteins as filters, select DEGs

From the top differentially expressed genes table, the most significant differentially expressed genes (DEGs) or filtered differentially expressed genes (FDEGs) will be selected by choosing to keep genes with the log fold change > 1 and the adjusted p value > 5 . The genes that exist will be removed for further testing. The filtering step is used to identify druggable proteins, leaving out the differentially expressed genes.

Functional Enrichment & Pathway Analysis

We examined which genes were up or down regulated in malignant mesothelioma, as well as special tools to help understand what biological processes/pathways these genes may be associated with. Tools such as Enricher, DAVID, and Metascape were used to analyze the DEGs for enrichment in Gene Ontology (GO) terms, including biological processes (BP), molecular functions (MF), and cellular components (CC). Among the results, many DEGs were strongly associated to important biological functions related to the inflammatory response, organization of the extracellular matrix, apoptotic signaling, and cell proliferation. Pathways enriched by these genes derived from Pathway Analysis of Reactome and KEGG databases were related to cancer-related pathways such as PI3K-Akt signalling pathway, focal adhesion, p53 signalling and ECM-receptor interaction.

The pathways are well recognized as being significant for cancer development, growth, spread to other parts of the body and development of resistance to treatment. The functional and pathway enrichment

analysis revealed the important hub genes and drug targets for drug screening. The results also yielded valuable information on the molecular events involved with the progression of mesothelioma.

PPI Network and Hub Gene Analysis

Each data set was joined together with a cross-species query to create a network. The Cytoscape cytoHubba plugin was used to investigate the hub genes in the network with various measures including MCC, DMNC, MNC, DEGREE, EPC, Bottleneck, Eccentricity, Closeness, Radiality, Betweenness, Stress and Clustering Coefficient. To find the gene that is most important across all the different interaction networks, the resulting protein-protein interaction network was looked at

RESULT

Integrated analysis of the selected GEO datasets identified differentially expressed genes associated with MPM. Functional enrichment analysis demonstrated the involvement of these genes in biological processes and signaling pathways relevant to tumor development and progression.

Identified Significant Upregulated and Downregulated Gene in GEO2R

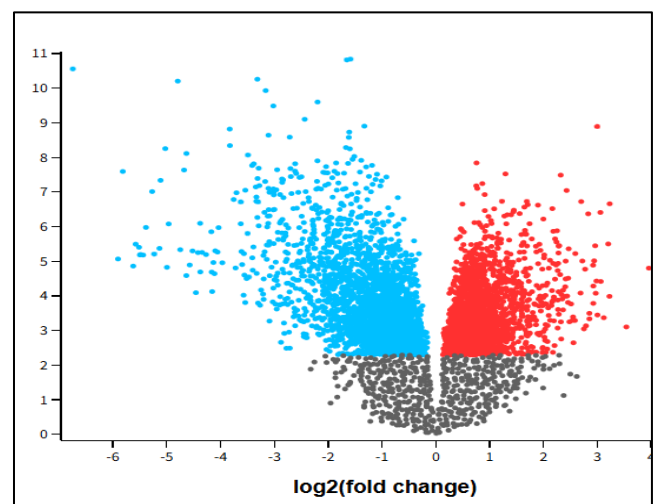


Figure 1: GSE51024: Gene expression of malignant mesothelioma Tumor [tumor vs normal, Padj<0.05]

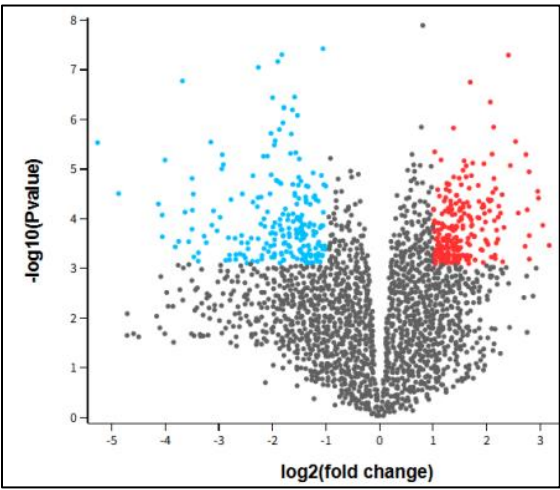


Figure 2: GSE42977: Sequential Binary Gene-Ratio Tests [tumour vs normal, Padj<0.05]

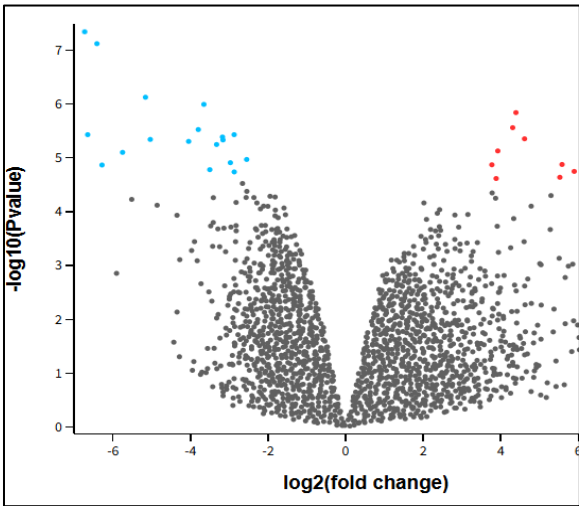


Figure 5: GSE29370: Gene expression profiling of malignant mesothelioma [tumor vs normal, Padj<0.05]

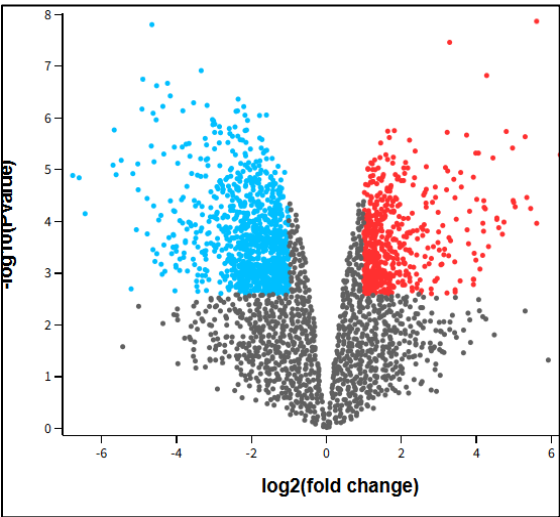


Figure 3: GSE112154: Gene expression profiling of diffuse malignant peritoneal [tumor vs normal, Padj<0.05]

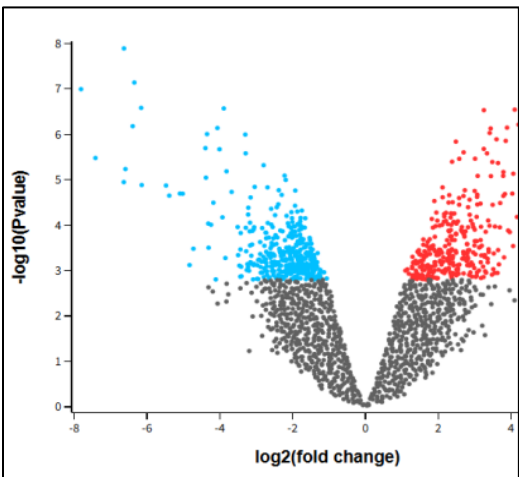


Figure 4: GSE2549: Malignant pleural mesothelioma [tumor vs normal, Padj<0.05]

Protein-Protein Interaction Analysis STRING

PPI network analysis identified highly connected hub genes, among which GAPDH emerged as a prominent molecular hub. Integration of differential expression, network, and druggability analyses enabled the prioritization of candidate molecular targets with potential relevance to MPM.

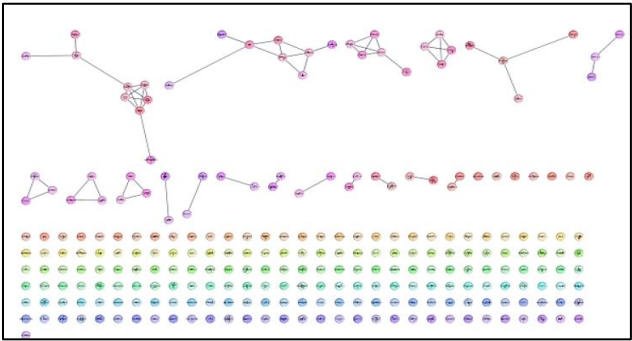


Figure 6: Protein-protein interaction (PPI) network visualization generated from analysis of the GSE51024 dataset

Identified HUB genes

By combining information about how genes are connected in a network and analyzing how proteins interact, GAPDH was found to be an important gene that is closely linked to many others in the network of genes related to malignant pleural mesothelioma. Although it's usually seen as a gene involved in basic body maintenance, its huge increase in activity and central role in the studied groups (GSE51024, GSE42977, GSE112154, GSE2549, and GSE29370) show that it plays a special role in causing MPM. The high

level of node connections shows that GAPDH acts as a key molecular link that connects several broken networks in cancerous tissue, compared to healthy pleural tissue.

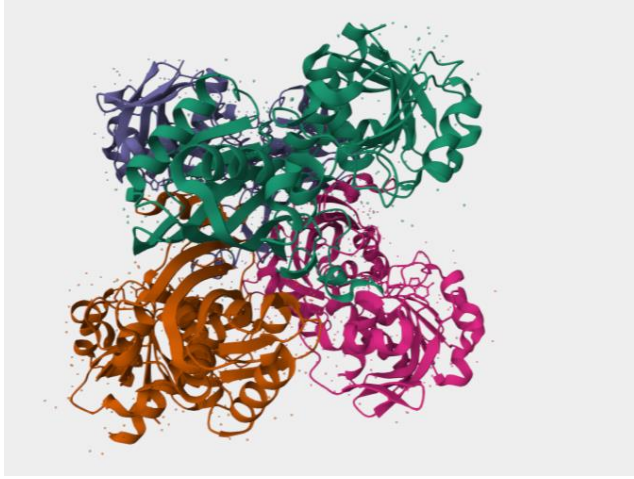


Figure 7: 3D macromolecular crystal structure of the GAPDH protein enzyme

Cytoscape Result

The recreated Protein-Protein Interaction network was loaded into Cytoscape for the examination of topological features and the visualization of important molecular nodes. Through the use of the cytoHubba plugin, the network was assessed using the Maximal Clique Centrality and node degree methods to systematically highlight key regulatory components. Among the nodes that were studied, GAPDH stood out as a significant gene with high connectivity, showcasing an extremely elevated node degree and securing the top position in the interaction framework. This central position in the Cytoscape network accentuates its importance as a vital bottleneck that propels the molecular signaling pathway associated with malignant mesothelioma.

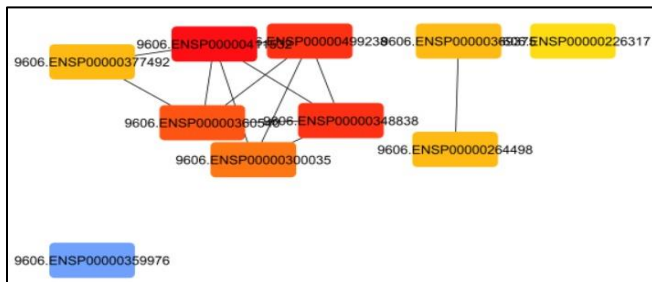


Figure 8: Filtered sub-network of top hub genes extracted using Cytoscape

Table 1: Top 10 hub genes ranking table

Rank	Name	Score
1	9606.ENSEP00000411532	14
2	9606.ENSEP00000499238	12
2	9606.ENSEP00000348838	12
4	9606.ENSEP00000360540	8
5	9606.ENSEP00000300035	6
6	9606.ENSEP00000359976	3
7	9606.ENSEP00000264498	2
7	9606.ENSEP00000369375	2
7	9606.ENSEP00000377492	2
10	9606.ENSEP00000226317	1

Through the utilization of topological algorithms in the cytoHubba extension of Cytoscape, the significant regulatory components of the protein-protein interaction network were effectively ranked. A specific subset of important hub genes was identified due to their elevated node degrees and maximal clique centrality (MCC) rankings. Within this highly ranked group, GAPDH was identified as a pivotal bottleneck node, displaying numerous connections with other leading genes. These elite nodes symbolize the fundamental molecular network that propels the severe progression of malignant mesothelioma.

DISCUSSION

Malignant pleural mesothelioma (MPM) is an aggressive form of cancer, with complex molecular changes and few therapeutic options. In the current study, five independent GEO datasets were integrated to identify differentially expressed genes involved in the process of MPM and the pathways that were enriched were inflammation, ECM organization, apoptosis, cellular proliferation, PI3K-Akt signaling, focal adhesion, p53 signaling, and ECM-receptor interaction. PPI-network analysis also revealed that GAPDH was a prominent hub gene, suggesting that metabolic processes might have an important relationship with the rest of the molecular network of MPM. These observations are made with multiple independent datasets, making them more reproducible by decreasing dependency on a single experimental cohort.

The results are similar to those obtained by Zhang et al. [29] that analyzed MPM by integrated

bioinformatics and found a number of differentially expressed genes associated with ECM–receptor interaction, focal adhesion, PI3K-Akt signaling, and PPAR signaling. They also found several highly interconnected hub genes that were involved with MPM prognosis. The pathway level findings from these studies are congruent with the present study and suggest that ECM remodeling, cell adhesion, and PI3K-Akt signaling are relevant pathways in MPM. The latter analysis, however, combined five GEO datasets, and identified GAPDH as a key hub, indicating another molecular hallmark of MPM – metabolic connectivity.

GAPDH is also shown as a central node, which is further substantiated by association of MPM with changes in cellular metabolism. Glycolysis related genes were studied by Xiao et al. [30] in MPM and they revealed that many glycolysis related gene sets are upregulated in tumor tissues. They were also able to construct a bioinformatics and machine-learning based glycolysis-related prognostic model. Our PPI network is also rife with GAPDH, which is central to the glycolytic pathway, thus giving a biological context to the observations. However, the current computational result does not prove that GAPDH is directly responsible for the progression of MPM. Therefore, its high connectivity should be seen as a potential molecular feature to be functionally validated, but not as a validated therapeutic target.

The enrichment of extracellular matrix and cell-adhesion pathways in the present study is also in agreement with the results obtained by Morani et al. [31]. They analyzed these cells for gene expression within a single experiment and found a molecular signature of both cell adhesion and extracellular matrix organization, along with genes that regulate the cell's mitosis and the inhibition of apoptosis. A number of the identified proteins were then shown to be over-expressed in MPM cell lines, validating the potential biological relevance of these proteins. The results here are similar to those obtained from our enrichment, implying that changes in the organization of ECM and changes in cell–matrix interactions represent molecular characteristics of MPM that are recurring. Therefore, the present GAPDH-based network is to be understood in a wider

molecular context, such as metabolism, adhesion, proliferation and extracellular signaling.

Another consideration for the interpretation of the present results are molecular heterogeneity. Laure et al. [32] conducted both genomic and transcriptomic analyses of the MPM samples and showed significant molecular changes that are relevant for pre-clinical studies. They pointed out the need to ensure that biological systems used for subsequent validation are appropriate because of the differences between patient-derived tumor material and the experimental models. This is especially important in the present study, because in any five GEO datasets, there can be variation in the characteristics of the samples, the composition of the tissues, disease subtype, and the experimental platform. However, validation in independent patient populations will be required to assess the extent to which this is a generalizable result across clinically diverse MPM populations, and how well it can be applied to them.

Recently, Severson et al. [33] performed multiomic, histologic, and single-cell RNA-sequencing analysis of pleural mesothelioma to characterize the tumor and identify states of malignant cells linked to prognosis. Their results show that there is significant cellular and molecular heterogeneity in MPM which is not adequately captured by bulk transcriptomic analysis. The GAPDH hub that was identified in the present study could probably be a common molecular change shared by all the transcriptional programs involved in tumor development, but an exact cellular origin cannot be deduced from the present bulk GEO datasheets. Future single cell and spatial transcriptomic studies might help to define if the signaling of GAPDH is specific to defined subpopulations of malignant cells or to the tumor microenvironment.

The major strength of the present study therefore lies in the integration of three analyses (Differential-expression, Functional enrichment, PPI-network) and druggability analysis across five independent GEO datasets. The multi-dimensional approach allowed GAPDH to be ranked based on network connectivity and not only on differential expression. The results, however, are still only computational and hypothesis

generating. Computational druggability does not imply therapeutic efficacy and network centrality does not imply causality, as mentioned in the present manuscript. These results need to be confirmed by quantitative gene-expression analysis, protein-level assessment, functional inhibition or knockdown, and independent clinical cohorts before GAPDH is a clinically meaningful biomarker or therapeutic target.

In summary, the present results suggest that MPM is associated with orchestrated changes in metabolic processes, extracellular matrices, adhesion molecules, inflammation, and proliferation. By mapping several prominent hubs across the integrated data sets, the identification of GAPDH as one of the hubs potentially provides an important molecular candidate, especially given the known importance of glycolytic alterations in MPM. However, the present results should be viewed not as proof of a causal or therapeutic function of GAPDH, but as a foundation for further studies.

CONCLUSION

Malignant pleural mesothelioma is still a highly aggressive disease with little treatment options and a short prognosis. For the current study, an integrated multi-dataset bioinformatics approach was used to annotate the transcriptional changes that occurred in MPM based on five independent GEO datasets. Analysis of differential expression and functional and pathway enrichment gave insights into the biological processes and molecular pathways associated with the disease.

The PPI-network analysis and hub-gene prioritization further allowed to identify highly connected molecular candidates including GAPDH as among the most well-connected genes in the constructed network. An extra method used to prioritize genes with potential therapeutic relevance was the druggability assessment.

The present study offers a comprehensive transcriptomic and network-based approach for the identification of molecular changes, hub genes and drug targets for the treatment of malignant pleural mesothelioma. The candidates selected can be used as a guide for further mechanistic, clinical and experimental

validation studies to establish their diagnostic, prognostic and therapeutic potential in MPM.

Ethical Approval: Institutional Review Board approval was not required.

Declaration of Patient Consent: Patient consent was not required as there are no patients in this study.

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Conflicts of Interest: The authors declare that they have no conflicts of interest.

Use of Artificial Intelligence (AI) - Assisted Technology for Manuscript Preparation: The authors confirm that no artificial intelligence (AI) - assisted technology was used to assist in the writing or editing of the manuscript, and no images were manipulated using AI tools.

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AUTHOR CONTRIBUTIONS

Siddhant Srivastav: Conceptualization, data curation, bioinformatics analysis, methodology, literature review, manuscript drafting, and final approval of the manuscript.

Shishir Goswami: Methodology, data analysis, interpretation of results, literature review, manuscript review, critical revision, and final approval of the manuscript.

Ruby Singh: Conceptualization, supervision, interpretation of findings, manuscript editing, critical revision, and final approval of the manuscript.

ABBREVIATIONS USED IN THE STUDY

GAPDH: Glyceraldehyde-3-phosphate dehydrogenase;

MPM: Malignant pleural mesothelioma;

GEO: Gene Expression Omnibus;

DEG: Differentially expressed gene;

FDEG: Filtered differentially expressed gene;

GO: Gene Ontology;

BP: Biological process;

MF: Molecular function;

CC: Cellular component;

PPI: Protein–protein interaction;

KEGG: Kyoto Encyclopedia of Genes and Genomes;

ECM: Extracellular matrix;

PI3K: Phosphoinositide 3-kinase;

AKT: Protein kinase B;

PPAR: Peroxisome proliferator-activated receptor;

MCC: Maximal clique centrality;

DMNC: Density of maximum neighborhood component;

MNC: Maximum neighborhood component;

EPC: Edge percolated component.

DECLARATION ON PUBLICATION ETHICS

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