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Bioinformatics analysis of microarray gene expression data in homo sapiens non-small cell lung cancer (LUAD)

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ABSTRACT: -
Pollution is humans' worst enemy. All kinds of pollution, including air pollution, are very harmful to the lungs. Our lungs pass air through the body, and all types of air can activate harmful genes in our body. This research tells us that smoking is injurious to health, and this is very true after seeing the results. Bioinformatics plays a major role in identifying or predicting cancer with the prospect of saving as many lives as could. AL-ML learning has a strong base to tell and gives 95% accuracy to find the proper cancer prediction. LUAD cancer has subtypes to identify the gene expression. In the particular research, non-small cell lung cancers were highlighted. Which area is most affected by the extracellular matrix where the tumor developed? In this result main aggressive genes are VTN and SPP1, who most threatening or triggered by smoking.

Biomarker tools help in this research on lung cancer to predict the future of cells. LUAD is a very aggressive, malignant type of tumor. In bioinformatics, tools analyze all kinds of results and then add all future values to them.

KEYWORDS– Biomaker, Luad, Bioinformatics Tools, Genes Networking Analysis

1. INTRODUCTION: -

Most LUADs a malignant tumors. This tumor very aggressively attacks the lung, and this type of cancer generally does not have early symptoms. After showing many reports, this cancer is 2nd most diagnosed cancer in the world. Reasons are caused by environmental factors, pollution, and smoking that humans cannot be separable in this world. Here are some fields in which it takes place that save many lives. Bioinformatics is the branch where all trigger points in cancer are studied. Bioinformatics has the best tools in which LUAD was predicted, and its biomarker genes were identified.

The GEO dataset is the first and only way to find perfect gene IDs, so in our research paper, we used GES27716 as the sample IDs. In his bioinformatics tool, see lots of the best future omics things that we have never seen before. This is an efficient and easier way to find the correct results. In this research, the bioinformatics AI ML learning part is used to predict LUAD in a deep manner, gene expression, and RNA seq to find the largest result output. Next step, LUAD genes interaction is the most important and creative part in this research part with all new findings and plots also. After finding the GEO database, identify the DEGs tools to create an experimental condition and cut off all the values to identify perfect values to make a plot. LUAD non-small cell lung cancer [NSCLC] is 55% in all cases. This disease has a low chance to

treatable, so its survival rate is very low. There are some research is ongoing research to find biomarkers and targets for these diseases' specific genes. The main biomarkers are VTN, SPP1, PLG, and CDK1.

2. METHODS AND MATERIALS: -

1. MICROARRAY DATA-

In this method, the Gene Expression Omnibus (NCBI) takes some samples that need identification and makes machine learning examples to find the value or result. In the NCBI geodata set, lung cancer adenocarcinoma, and after seeing it, all kinds of datasets are available on the GEO accessions. GES27716 ID is the Expression data from the Columbia Lung Adenocarcinoma Human Tumor Cells. This dataset contains 40 samples, 17 of which are normal tissue samples and 23 from adenocarcinoma cancer-affected males and females.

2. Identification of DEGs-

GEO2R is an online web tool (https://www.ncbi.nlm.nih.gov/geo/geo2r/?acc=GSE27716) provided by the GEO for comparing GEO series to identify DEGs across experimental conditions. The cutoff criteria were set to P-value <0.05 and logFC (fold change)>1. We excluded probe sets without exact gene symbols, and genes with two or more probe sets were averaged.

3. PPI network construction and analysis-

The Search Tool for the Retrieval of Interacting Genes (STRING; http://string-db.org; version 10.0) was used to construct the PPI network from the DEGs. The sources for interactions are text mining, databases, experiments, neighborhood, co-expression, gene co-occurrence, and fusion. We set the minimum required interaction score to 0.4. Cytoscape version 3.4.0 software was used to visualize the molecular interaction networks of the DEGs. The APP plug-in, Molecular Complex Detection (MCODE), was used to arrange the network topology to cluster densely connected genes. After the PPI networks were constructed, their key modules were searched by using the MCODE application. The parameters for inclusions are MCODE score >5, degree cutoff=2, node score cutoff=0.2, node density cutoff=0.1, k-score=2, and Max depth=100. Then, DAVID was used to perform the GO and KEGG analyses for these most significant modules.

4. KEGG and GO enrichment analyses of DEGs-

The functional annotation tools version 6.7 of the Database for Annotation, Integrated Discovery, and Visualization (DAVID; http://david.ncifcrf.gov) were used to extract biological information about our ideas. KEGG is a public database used for understanding the functions and abilities of biological systems, such as cells, organisms, and the ecosystem, from molecular-level information, especially large-scale molecular datasets acquired by genome sequencing. GO was also used to annotate genes and further analyze their biological functions. The DAVID online database was used to analyze the
function and biological process of the screened iDEGs. P<0.05 was considered to indicate statistical significance.

5. Hub gene screen and analysis-

The criterion for being a hub gene selection was a degree of≥10. Further analysis was performed using the cBioPortal online platform (http://www.cbioportal.org) to build the network of the DEGs and co-expressing genes. The mutation rates of the hub genes were also measured with the cBioPortal platform.

Cytoscape's Biological Networks Gene Oncology tool (BiNGO) (version 3.0.3) was used for the biological process analysis and visualization. Kaplan-Meier curves for overall survival and disease-free survival with these hub genes were obtained from cBioPortal and TCGA. The top 10 genes are mostly invasive. The most aggressive genes in the top 10 list are PLAU, PLG, SPP1, and VTN, which have Kaplan-Meier curves for overall survival and disease-free survival with these hub genes obtained from the GDC PLATFORM. The expression profiles of genes VTN(vitronectin) and SPP1(secreted phosphoprotein 1 osteopontin) in 10 types of malignant tumors were analyzed and displayed using the Oncomine database.

3. RESULT-

[1] IDENTIFICATION OF DEGs IN LUNG ADENOCARCINOMA - A total of 40 samples were found to be expressed in non-cancerous and lung adenocarcinoma tissues (GSE27716) after standardizing the microarray data. A total of 21 DEGs were found (VOLCANO diagram), consisting of 9 downregulated and 11 upregulated genes.

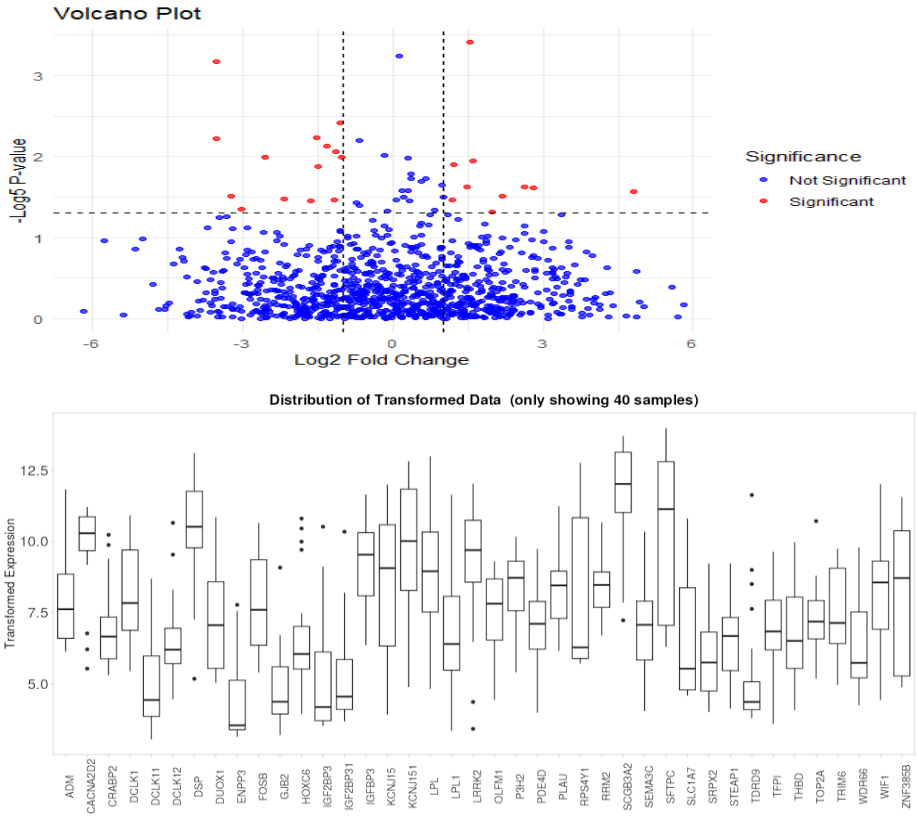
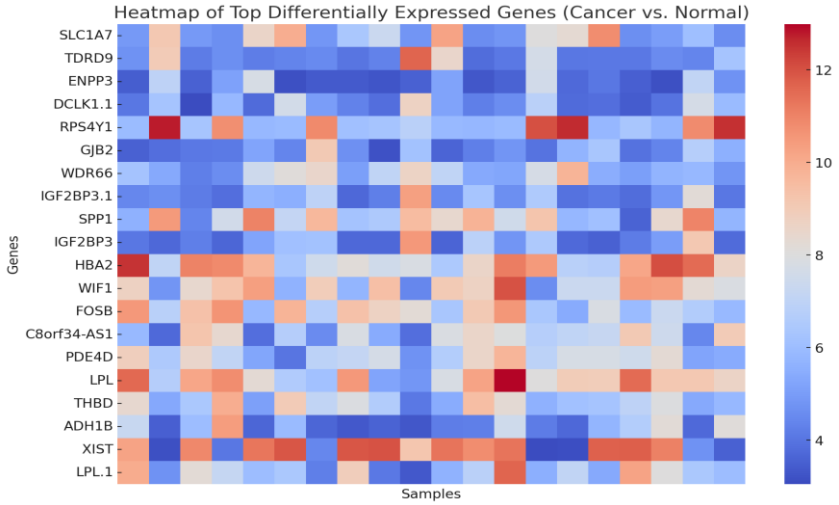


FIG 1 (a) and (b)– VOLCANO PLOT BY R SCRIPT AND BOX PLOT

Figure A is are first DEGs plot by the R script making volcano plot blue colour represents downgraded and the red colour represents upgraded.

Figure B shows the box plot for all samples.



Red = Higher gene expression (Upregulated in Cancer)

Blue = Lower gene expression (Downregulated in Cancer)

FIG 1.1(c)– HEAT MAP ALL UPREGULATED AND DOWNREGULATED

In this heatmap plot, 11 samples are invasive, and 9 samples are noninvasive. In the R script, first load all the sample data in R script. Then load the heatmap code then this part or visual this heatmap.

[2] PPI INTERACTIONS —

Cytoscapes were used to build the iDEGS ppi network to identify the significance of genes. Analysis of the genes used on the DAVID platform found the exact location where genes are involved in the complete process.

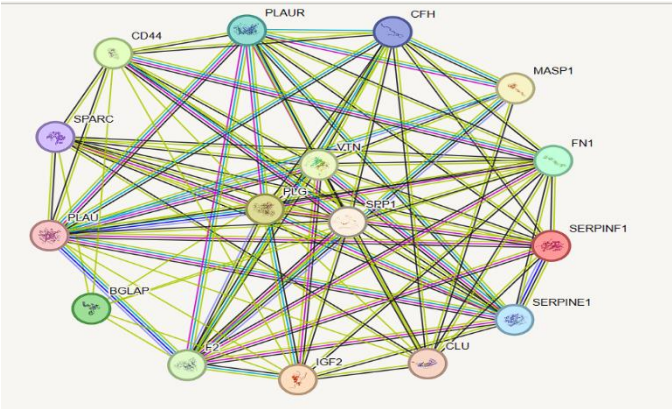


FIG 2 -CYTOSCAPE pathway enrichment analysis of DEGs in the most significant module.

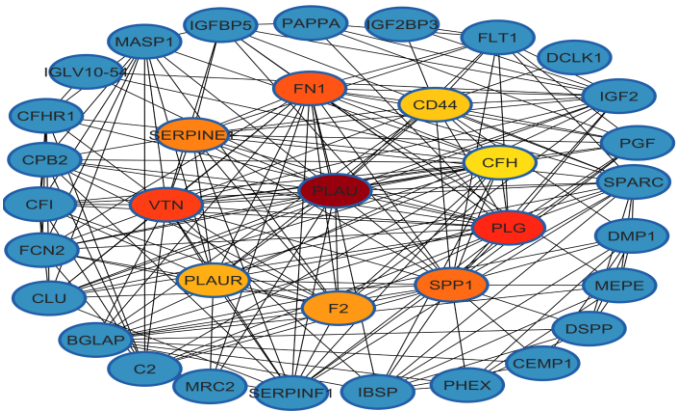


Fig 2-Cytoscape is a network of the hub genes protein-protein interaction. Where constructed a network of the 230 iDEGs genes overlapping each other was constructed, and then, after interaction top 16 nodes and 89 edges were identified, and their PPI enrichment p value is <1.0e(-)16, and avg node degree is 11.1 is the value after using strings.

Figure 2.1- Cytoscape networking after connecting with the string part, then Cytoscape constructed 35 nodes and 207 edges on the server. There are some pathway ID descriptions and FRD.
The extracellular region and spaces are about 16 on count and FRD on 1.83E-13.

PATHWAY ID	PATHWAY DESCRIPTION	Count	FDR
GO:0005576	extracellular region	16	1.83E-13
GO:0005615	extracellular space	14	1.35E-10
GO:0031093	platelet alpha granule lumen	6	1.75E-08
GO:0062023	collagen-containing extracellular matrix	8	6.27E-08
GO:0072562	blood microparticle	6	1.02E-06
GO:0070062	extracellular exosome	11	3.58E-06
GO:0098637	protein complex involved in cell-matrix adhesion	3	1.36E-04
GO:1905370	serine-type endopeptidase complex	3	1.82E-04
GO:0005604	basement membrane	4	2.79E-04
GO:0005788	endoplasmic reticulum lumen	5	3.29E-04
GO:0009986	cell surface	6	3.83E-04
GO:0005796	Golgi lumen	3	0.01200844076
GO:1904090	peptidase inhibitor complex	2	0.0120312985
GO:0009897	external side of plasma membrane	4	0.0120312985
GO:0097180	serine protease inhibitor complex	2	0.0130472464
GO:0042995	cell projection	3	0.03585973716
GO:0005925	focal adhesion	3	0.120983699
GO:0035579	specific granule membrane	2	0.1922219583
GO:0005886	plasma membrane	8	0.2231292196
hsa04610	Complement and coagulation cascades	7	2.25E-09
hsa05205	Proteoglycans in cancer	5	5.33E-04
hsa04512	ECM-receptor interaction	4	8.92E-04
hsa04510	Focal adhesion	3	0.1436167044
hsa05165	Human papillomavirus infection	3	0.2805117639
hsa04151	PI3K-Akt signaling pathway	3	0.2805117639
hsa04933	AGE-RAGE signaling pathway in diabetic complica	2	0.4205620732
hsa05150	Staphylococcus aureus infection	2	0.4205620732

FIG 2.2 –KEGG, Kyoto Encyclopedia of Genes and Genomes; GO, Gene Ontology; DEGs, differentially expressed genes; FDR, false discovery rate.
Above this table here KEGG, where gene expression is related in this table
[3] GO AND KEGG PATHWAY–The DAVID online database was used to analyze the biological classification further, as well as functions and pathways enriched in DEGs. GO analysis showed that the

biological processes (BP) of the DEGs were mainly involved in the regulation of cell proliferation, the transforming growth factor signaling pathway, cell adhesion, biological processes involved, and responses to hormone stimulus. Examination of their cell component showed that the DEGs were mainly located in the KEGG pathway. Analysis showed that the DEGs were overrepresented primarily in cell adhesion, fibrinolysis, acute phase responses, negative regulation of fibrinolysis, blood coagulation, and cell-matrix adhesion.

Trem	Description	Count	%	PValue
GO:0051918	negative regulation of fibrinolysis	5	50	1.52E-11
GO:0042730	fibrinolysis	4	40	6.65E-08
GO:0007596	blood coagulation	4	40	1.12E-05
GO:0030195	negative regulation of blood coagulation	3	30	1.73E-05
GO:0030155	regulation of cell adhesion	3	30	3.12E-04
GO:0007160	cell-matrix adhesion	3	30	0.001075823095
GO:0010755	regulation of plasminogen activation	2	20	0.001390032752
GO:0038195	urokinase plasminogen activator signaling pathway	2	20	0.001390032752
GO:0007155	cell adhesion	4	40	0.001611086472
GO:0051917	regulation of fibrinolysis	2	20	0.001852995185
GO:0006508	proteolysis	4	40	0.002005382686
GO:0051702	biological process involved in interaction with symbiont	2	20	0.002778347736
GO:0010757	negative regulation of plasminogen activation	2	20	0.00370293766
GO:0010469	regulation of signaling receptor activity	2	20	0.005549831827
GO:0048771	tissue remodeling	2	20	0.00647213717
GO:0030194	positive regulation of blood coagulation	2	20	0.00785416955
GO:0048260	positive regulation of receptor-mediated endocytosis	2	20	0.01061310882
GO:0010951	negative regulation of endopeptidase activity	2	20	0.01565345741
GO:0035987	endodermal cell differentiation	2	20	0.01565345741
GO:0006953	acute-phase response	2	20	0.01839310695
GO:2000117	negative regulation of cysteine-type endopeptidase activity	2	20	0.01839310695
GO:0009611	response to wounding	2	20	0.03108872969
GO:0050731	positive regulation of peptidyl-tyrosine phosphorylation	2	20	0.03827765132
GO:0006935	chemotaxis	2	20	0.05780333853
GO:0008360	regulation of cell shape	2	20	0.06306699357
GO:0051897	positive regulation of phosphatidylinositol 3-kinase/protein kinase B signal transduction	2	20	0.08728672744
GO:0001934	positive regulation of protein phosphorylation	2	20	0.0902747178

FIG 3- KEGG and GO pathway enrichment analysis of DEGs in the lung adenocarcinoma samples.

[4] Hub gene selection and analysis–Sixteen genes were identified with a degree ≥10 and were defined as hub genes. The degree of each gene was calculated by the CytoScape software and represented the number of other genes with which it was connected. The hub gene symbol, full name, function, and degree are listed in. cBioPortal was then used to construct a network of the 16 hub genes and their co-expressed genes. Here, it is most genes are VITRONECTIN, SECRETED PHOSPHOPROTEIN, PLASMINOGEN, and UROKINESIS. Also, taking the GDC platform to perform all top 16 genes to get this heat map gene expression pattern to visualize best apart, that VTN, SPP1, PLG, AND PLAU are the most targeted genes.

	Hub Gene	Full Name	Function	Degree
1	VTN	Vitronectin	Involved in cell adhesion, spreading, and complement regulation.	23
2	SPP1	Secreted Phosphoprotein 1 (Osteopontin)	Plays a role in bone remodeling and immune response modulation.	23
3	PLG	Plasminogen	Precursor of plasmin, essential for fibrinolysis and clot breakdown.	22
4	PLAU	Plasminogen Activator, Urokinase	Converts plasminogen to plasmin, aiding tissue remodeling.	21
5	FN1	Fibronectin 1	Involved in cell adhesion, growth, migration, and wound healing.	21
6	CFH	Complement Factor H	Regulates the complement system to prevent tissue damage.	18
7	CD44	CD44 Molecule	A cell surface protein involved in cell adhesion and migration.	16
8	F2	Coagulation Factor II (Thrombin)	Key enzyme in blood coagulation, converting fibrinogen to fibrin.	16
9	SPARC	Secreted Protein Acidic and Cysteine Rich (Osteonectin)	Modulates cell-matrix interactions and tissue remodeling.	16
10	IGF2	Insulin-Like Growth Factor 2	Plays a crucial role in fetal growth and development.	15
11	SERPINE1	Serpin Family E Member 1 (PAI-1)	Regulates fibrinolysis by inhibiting tPA and uPA.	15
12	PLAUR	Plasminogen Activator, Urokinase Receptor	Binds uPA, localizing proteolysis to the cell surface.	14
13	SERPINF1	Serpin Family F Member 1 (PEDF)	Exhibits neurotrophic and anti-angiogenic properties.	13
14	BGLAP	Bone Gamma-Carboxyglutamate Protein (Osteocalcin)	Regulates bone mineralization and calcium homeostasis.	13
15	MASP1	Mannan-Binding Lectin Serine Protease 1	Activates the lectin pathway of the complement system.	12
16	CLU	Clusterin	Involved in lipid transport, apoptosis, and complement regulation.	12

FIG 4 – TOP 16 MOST INVASIVE GENES

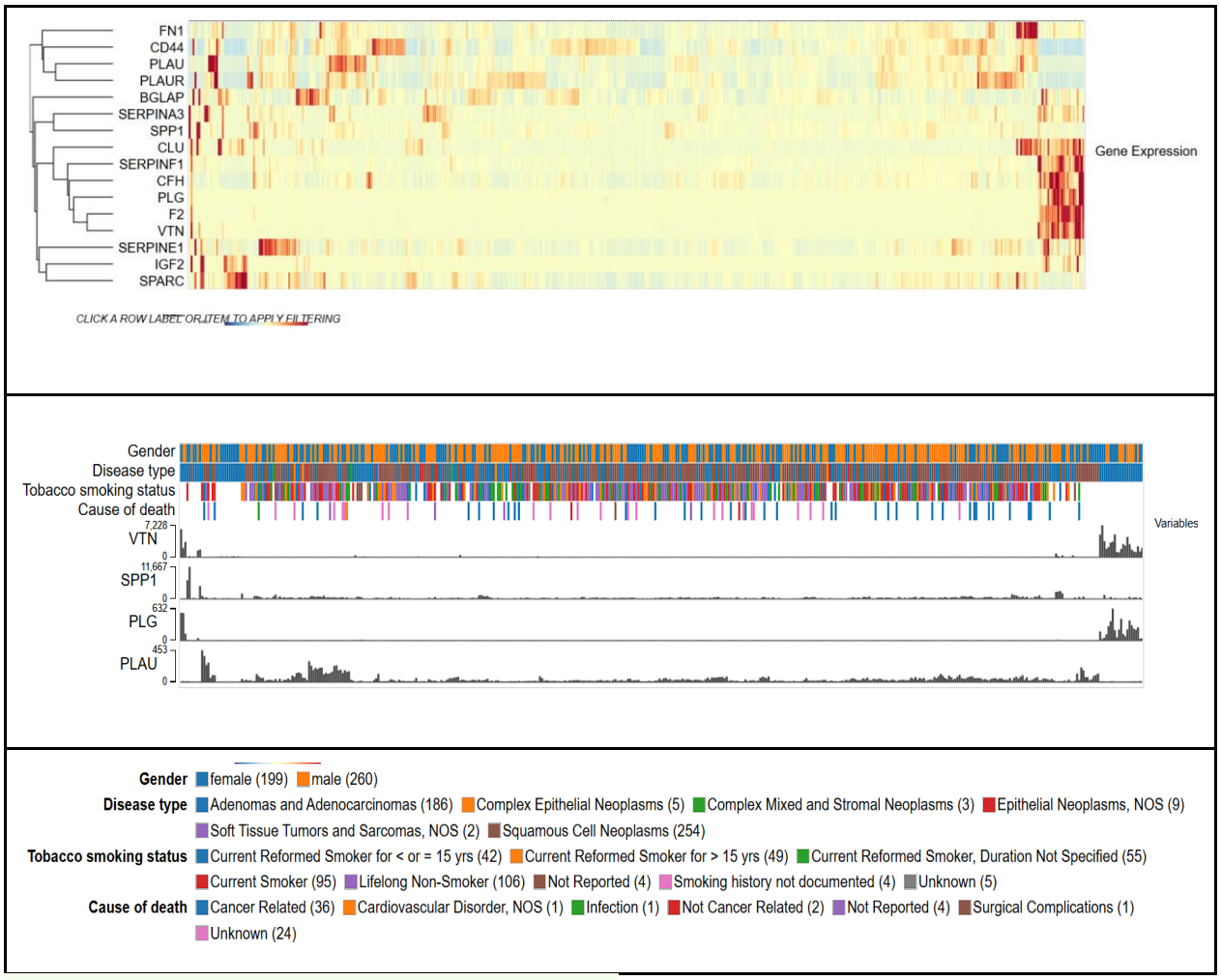


Figure 4.2 –Gene expression by GDC platform

In hub gene expression analysis top 16 genes in the table show that the top 4 are highly invasive genes, and at least 13 are connected.

The network there functions, degree 23 are upregulated parts.

Fig. 4 .2 The GDC platform was using all top 16 genes identified as clustering genes expression, where we saw that disease types, causing death, gender, tobacco status, and the top 4 variables performance.

[5] Kaplan-Meier curves SURVIVAL ANALYSIS-

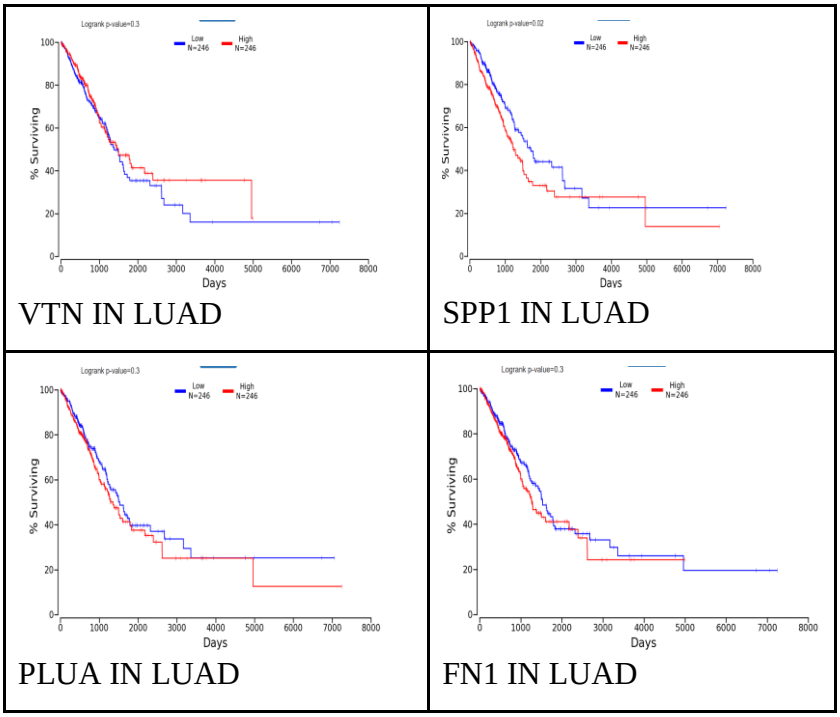


Fig 5– Kaplan-Meier plot

In this plot, the most aggressive genes are in the form of K-M PLOT. Here are in x-axis days and the y-axis survival rate. In red indicates the high value, and the blue indicates the low value, and the p-value is <0.05, which is considered statistically significant. Here 4 topmost aggressive genes in the form of a K-M plot by TCGA.

Kaplan-Meier curves tip 4 invasive genes plot shows in this form, also where seen that VTN, SPP1, PLUA, and F1 are compared with LUAD disease, where p value <0.05. This plot form is in Oncoinc (http://www.oncolnc.org/), where things are getting accurate.

4. DISCUSSION–

In the case of cancer, globally revealed that lung cancer and its subtypes which discussed in the research paper. These subtypes are mostly diagnosed with malignant tumors. This subtype is called lung adenocarcinoma, non-small cell lung cancer. These cancers are increasing very rapidly, a result of an unhealthy lifestyle. In the paper. Biomarkers for early and accurate diagnosis and prognostics can save millions of lives to assume cancer by prediction. This research combines bioinformatics analysis and basic diagnosis to identify gene mutations and specific mutation problems and resolve them as soon as possible.In this research, first, one mRNA microarray dataset was downloaded from the GEO datasets, and all selected samples were analyzed for DEGs between invasive and non-invasive sample IDs. Samples

were taken: 11 invasive and 9 non-invasive to identify actual problems. After identifying DEGs, 11 were upgraded, and 9 were downgraded in the volcano plot, which was made in an R script. The next heatmap, also in an R script, makes things more visible. After this step next step in PPI networking is constructing an analysis that puts all sample IDs and analyses to the top 16 highly invasive genes that are causing LUAD. After this put all analysis genes are put into the DAVID Platform to identify the most highly expressed genes. And make function annotation, then put all genes to analysis to make a table for gene expression, FDR, etc. After this, I got all 16 gene lists and put them into the GO and KEGG Pathway table, also in the DAVID platform. In this part, DAVID analyzes the genes' descriptions and P-values. Here next step is to identify further analysis hub genes selection and analysis here taking part here. Then calculate all genes were calculated in the Cytoscape network, which connected to the STRING network to get the most highly invasive genes. To get invasive genes, cBioPortal and TCGA analysis was done to make all top 16 genes, where the top 4 genes were identified as VTN (VITRONECTIN), SPP1 (OSTEOPONTIN), PLG (PLASMINOGEN), and PLAU (UROKINESIS) are the most highly degree genes. The VTN gene is a multifunctional glycoprotein with various physiological functions that exists in plasma and the extracellular matrix. This gene spreads and migration through binding to the integrin receptors.SPP1 gene mediates immune cell adhesion, migration activation. The PLG gene is plasminogen; this is an enzyme that breakdown down another protein called fibrin. An analysis of these results shows that VTN, SPP1, and PLG are most invasive in promoting cancer cells in the lungs, resulting in highly concentrated metastasis and leading to poor prognosis.

5. CONCLUSION–

In conclusion, our research aimed to identify DEGs associated with the development of lung adenocarcinoma. The top 16 hub genes are biomarkers of the diagnosis of lung adenocarcinoma. In this study, AI ML bioinformatics is most needed to change the expression and biological function in lung adenocarcinoma. And after all the results came, we saw that mostly genes VTN, SPP1, AND PLG are very aggressively active in the LUAD. In such recent cases, these genes are suppressed by other genes like VTN, supported by BPIFB1. This gene has a cholesterol factor that suppresses this effect.
Gene expression is calculated by various bioinformatics tools, where cancer future omics detected easily, which means bioinformatics AI and ML are very useful for future prediction of microarray gene expression.

DATA AVAILABILITY–

1. GEO DATASET
2.DEGs
3. PPI NETWORK
4 . STRINGS
5. cBioportal
6. TCGA
7 . CYTOSCAPE

REFERENCE–

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