Received: 30 December 2023 | Revised: 1 May 2024 | Accepted: 22 May 2024

DOI: 10.1002/hsr2.2167

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Enhancing the revelation of key genes and interaction networks in non-small cell lung cancer with major depressive disorder: A bioinformatics analysis

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Funding information

Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences, Grant/Award Number: 2019PT320003; National Key Laboratory of Respiratory Diseases of China, Grant/Award Number: SKLRD-OP-202208; China Scholarship Council, Grant/Award Number: 202306670011; Science and Technology Fund project of Guizhou Provincial Health Commission, Grant/Award Number: 2023-3-5; Research Fund Projects of Guizhou Provincial Immunotherapy Research Talent Base in China, Grant/Award Number: RCJD2018-11; National Natural Science Foundation of China, Grant/Award Number: 82060308; Science and Technology Plan Project of Guizhou Provincial in China, Grant/Award Numbers: GPPH-NSFC-2020-6, GPPH-NSFC-2020-7, GCC [2022]037-1

Abstract

Background and Aims: Lung cancer is ranked as the second most prevalent form of cancer worldwide. Nonsmall cell lung cancer (NSCLC) represents the predominant histological subtype. Research suggests that one-third of lung cancer patients also experiencing depression. Antidepressants play an indispensable role in the management of NSCLC. Despite significant advancements in treatment, lung cancer patients still face a high mortality rate. Major depressive disorder (MDD) and related antidepressants involved in treatment efficacy and prognosis of NSCLC. However, there has been a lack of screening and analysis regarding genes and networks associated with both NSCLC and MDD.

Methods: To investigate the correlation between MDD and NSCLC, our discovery and validation analysis included four datasets from the Gene Expression Omnibus database from NSCLC or MDD. Differential gene expression (DEGs) analysis, GO and KEGG Pathway, and protein-protein interaction network analyzes to identify hub genes, networks, and associated observations link between MDD and NSCLC.

Results: The analysis of two datasets yielded a total of 84 downregulated and 52 upregulated DEGs. Pathway enrichment analyzes indicated that co-upregulated genes were enriched in the regulation of positive regulation of cellular development, collagen-containing extracellular matrix (ECM), cytokine binding, and axon guidance. We identified 20 key genes, which were further analyzed using the MCODE plugin to identify two core subnetworks. The integration of functionally similar genes provided valuable insights into the potential involvement of these hub genes in diverse biological processes including angiogenesis humoral immune response regulation inflammatory response organization ECM network.

Conclusion: We have identified a total of 136 DEGs that participate in multiple biological signaling pathways. A total of 20 hub genes have demonstrated robust associations, potentially indicating novel diagnostic and therapeutic targets for both diseases.

KEYWORDS
bioinformatics, differentially expressed genes, enrichment analysis, major depressive disorder, nonsmall cell lung cancer, protein–protein interaction networks

1 | INTRODUCTION

Lung cancer is the second leading type of cancer known across the globe. Among then, nonsmall cell lung cancer (NSCLC) represents the predominant histological subtype among lung malignancies.[1,2] Lung cancer often caused by factors such as long-term smoking, environmental pollution, or genetic predisposition. Currently, the treatment modalities for lung cancer primarily encompass surgical intervention, radiotherapy, chemotherapy, and immunotherapy.[3] However, despite the advances in various strategies available to mitigate and address the impact of these factors on lung cancer, the majority of lung cancer patients tend to present at an advanced stage that is not amenable to curative treatment,[4] which underscore the urgency of achieving a favorable therapeutic outcome in advanced stages of the disease. The current uncertainty surrounding treatment outcomes, the debilitating progression of cancer, and the adverse effects of treatments have gradually led to a growing recognition of psychological stress as a crucial component within the continuum of cancer treatment that strongly correlates with cancer outcomes.[5,6]

Unfortunately, lung cancer tends to be one of the neglected cancers that impacted by psychological stress.[7] Among these psychological stresses, depression is a critical and familiar factor characterized by symptoms such as low mood, diminished interest, reduced self-esteem, and impaired daily functioning.[8] Compared to other cancer patients, lung cancer patients are more likely to experience depression.[9,10] Clinical research shows that NSCLC patients identified depression rate as six times compared with healthy patients.[11] Due to endocrine abnormalities, adverse effects of drugs and stressful events caused by psychological stress are considered to be involved in the onset of depression.[12–14] Therefore, there have a bidirectional influence between lung cancer and depression.[15] On one hand, the diagnosis of lung cancer itself can elicit significant psychological distress and anxiety, while the physical discomfort, nausea, fatigue, and other treatment-related side effects can further increase the risk of depression.[16] On the other hand, depression can impact immune system functioning, chronic inflammatory responses, and lifestyle factors, potentially increasing the susceptibility to developing lung cancer which often has a detrimental effect on their quality of life.[17,18] A study published in JAMA found a significant association between depression and the risk of developing lung cancer, with the severity of depression positively correlating with the risk of mortality from lung cancer.[19] The mortality risk is 17% elevated in cancer patients with comorbid depression as compared to those without depression.[20] Moreover, depression linked with poor survival in patients with postsurgical NSCLC.[11] This phenomenon may elucidate the mechanism by which depression exacerbates lung cancer in patients, leading to treatment failure and a dismal prognosis. Furthermore, the prevalence of major depressive disorder (MDD) among cancer patients is significantly higher, with rates of occurrence up to four times greater than that observed in the general population.[21] While the prevalence of MDD was most pronounced among patients with lung cancer (13.1%), followed by gynecologic cancer (10.9%), breast cancer (9.3%), colorectal cancer (7.0%), and genitourinary cancer (5.6%).[10,22]

Importantly, there have considerable progress in the field of depression management. Antidepressant treatments also play a significant role in the physiological aspects of cancer.[23,24] For example, as a triple reuptake inhibitor of serotonin, norepinephrine, and dopamine antidepressants ansofaxine hydrochloride can modulate the antitumor immunity, inhibits the growth of cancer.[25] The patients diagnosed with lung cancer who underwent both mindful breathing training and diary-based rehabilitation guidance demonstrated a significant amelioration in their depressive symptoms.[26,27] Normalizes the gut microbiota can increase anti-inflammatory biomarkers to display antidepressant like effects in depression mouse,[28] while the gut microbiota plays a crucial role in lung cancer tumor pathogenesis by regulating the host metabolism and immune response.[28,29] Additionally, antidepressants can enhance antitumor effects on lung cancer cells by increasing intracellular reactive oxygen species levels and inhibiting antioxidant formation in tumor cells or by suppressing the activity of the oncogenic protein yes-associated protein 1 (YAP1).[30] Selective serotonin reuptake inhibitors, sertraline and fluoxetine, suppressed the growth of NSCLC by inhibiting the mTOR activity.[31] Given that interventions targeting depressive symptoms and tailored treatment regimens may have potential for inhibiting tumor growth and enhancing prognosis,[32] it is imperative to identify the targets of depression in cancer patients who may benefit from treatment strategies targeting depressive symptoms as a matter of utmost public health priority. Hence, given the absence of identified pathogenic pathways linking depression to lung cancer patients and despite extensive research efforts, it is imperative to urgently identify biomarkers and signaling pathways for effective therapy and prevention management of NSCLC.

Gene Expression Omnibus (GEO) datasets play a crucial role in advancing biological and medical research, which provide valuable insights into gene expression patterns and regulatory mechanisms, aiding researchers in understanding the molecular basis of diseases, identifying potential biomarkers, and uncovering novel therapeutic targets.[33] Herein, we utilized gene expression profiles for MDD and NSCLC, conducted bioinformatic analyzes and validation tests to identify hub genes as potential biomarkers for both diseases. Through this approach, we identified key genes and related networks that link the intertwined biology pathways of MDD and NSCLC patients. Understanding associated factors in

NSCLC combined with MDD may be beneficial for exploring gene pathways involved in depression among lung cancer patients, ultimately improving treatment strategies.

2 | MATERIALS AND METHODS

2.1 | Data processing and analysis

The GSE98793 (MDD), GSE76826 (MDD), GSE33532 (NSCLC), and GSE19804 (NSCLC) datasets were downloaded from the GEO database (https://www.ncbi.nlm.nih.gov/geo/) using R software version 4.3.1 (https://www.r-project.org/). The R software was employed for all dataset processing and analysis. The GSE98793 dataset (GPL570 platform), comprises gene expression data selected from whole blood samples of 64 patients diagnosed with MDD using the MINI questionnaire and an equal number of healthy controls. The data collection period spans from January 2016 to January 2018. MDD-associated GSE76826 (GPL17077 platform) included 32 outpatients and inpatients between May 2017 and July 2021, the severity of depressive symptoms was assessed using the Structured Interview Guide for the Hamilton Depression (SIGH-D) rating scale. The remission of the syndrome was defined as a stage in which a participant did not meet the criteria for a MINI major depressive episode continuously for 2 months and achieved a SIGH-D score below 8. These samples were categorized into the MDD and healthy groups based on their respective sources, adhering to stringent criteria for group assignment. The GSE33532 dataset (GPL570 platform) identified gene expression profiling of primary tumors and matched normal lung tissue from 20 NSCLC patients, at four different sites (A, B, C, D) from 2011 to 2019. The gene expression analysis of GSE19804 (GPL570 platform) was

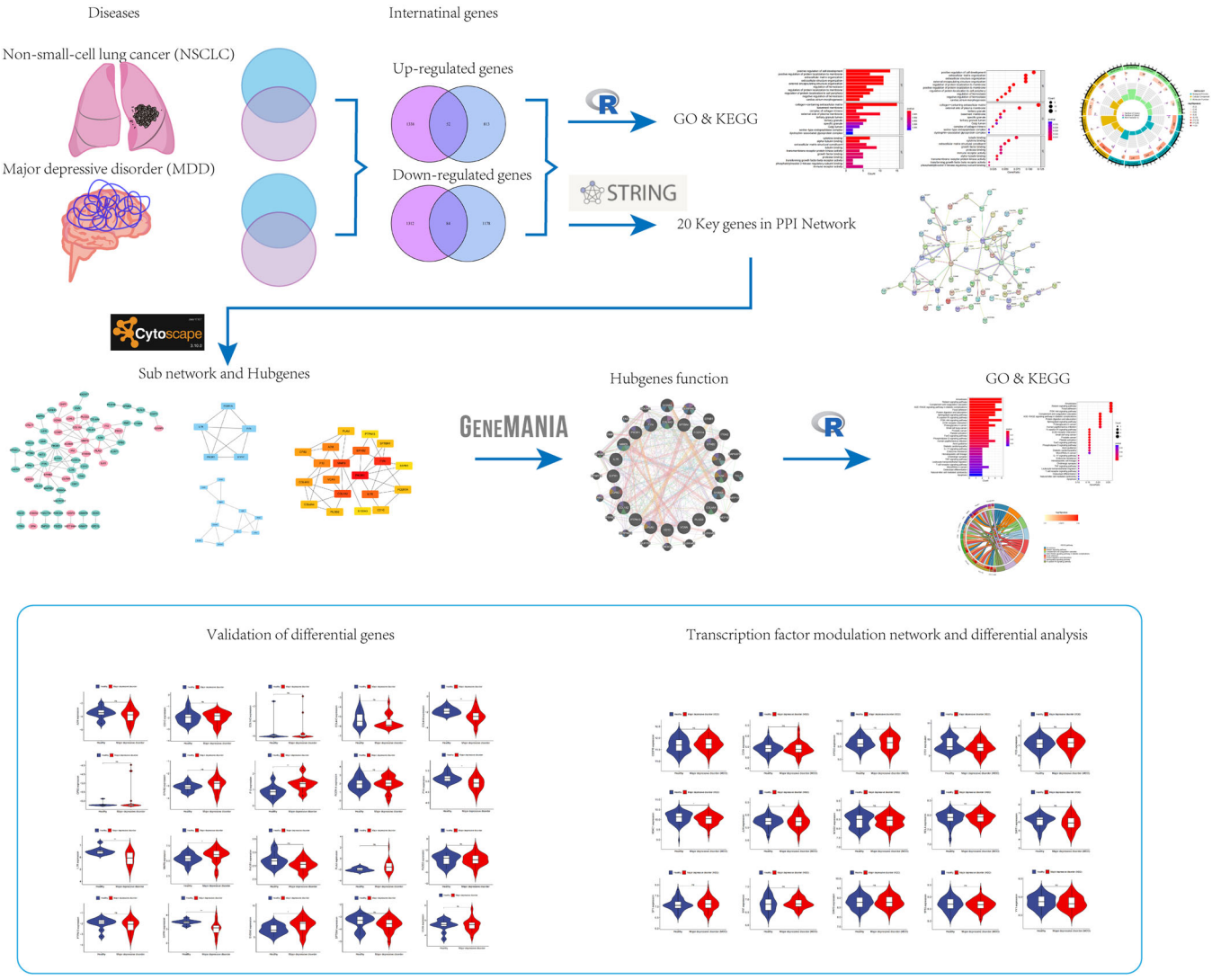

FIGURE 1 Flow diagram of the study design. The primary objective of this study is to identify the overlapping differentially expressed genes between the two datasets, followed by an analysis of enriched pathways. Subsequently, we aim to identify key genes and their associated functional genes and transcription factors. Finally, experimental validation will be conducted for these identified key genes and transcription factors.

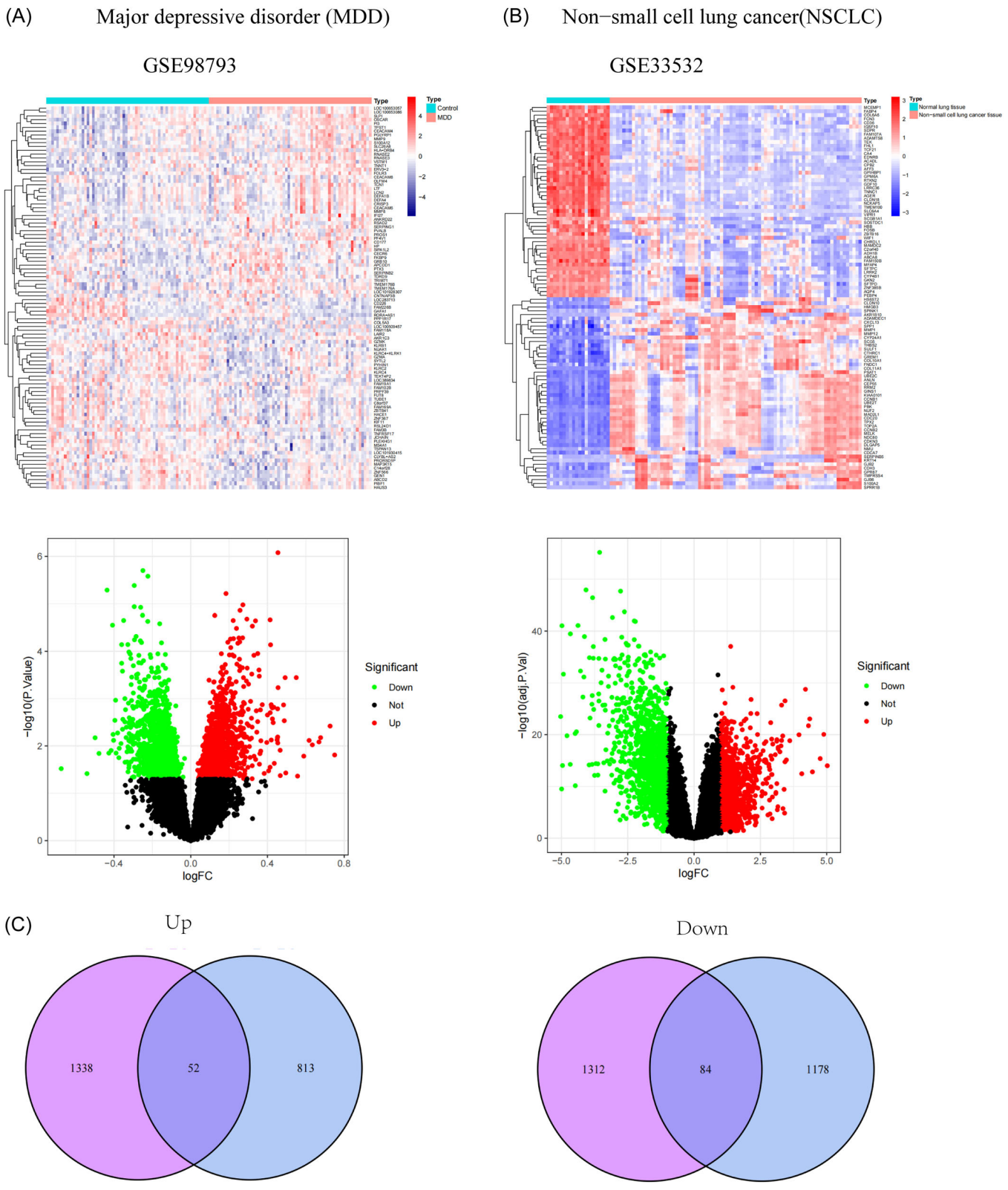

FIGURE 2 The DEGs in the gene expression profiling datasets. The packet intersection genes of MDD and NSCLC exhibited 52 upregulated genes and 84 downregulated genes. (A) Heatmap and Volcano plot of the GSE98793 dataset are presented. (B) The heatmap and Volcano plot of the GSE33532 dataset are displayed, where black nodes represent genes with no significant difference in expression, red nodes indicate upregulated genes, and blue nodes denote downregulated genes. (C) Venn diagrams demonstrate the number of upregulated and downregulated genes in both datasets. The intersection represents the common DEGs between the two datasets. The DEGs in the gene expression profiling datasets were visualized using a heatmap, volcano plot, and Venn diagram based on the criteria of |log2 fc| >1 and adjusted $p < 0.05$ to facilitate data interpretation. DEG, differential gene expression; MDD, major depressive disorder; NSCLC, nonsmall cell lung cancer.

validated using a cohort of 120 nonsmoking female lung cancer samples collected from 2010 to 2020. The samples were classified into the NSCLC group and control group based on their different sources. Figure 1 illustrates a simplified workflow of the current investigation.

2.2 | Differentially expressed genes (DEGs) analysis

To extract as much genetic information as possible about the differences that might cause the two diseases, We performed a separate analysis to identify DEGs between MDD and NSCLC, which were subsequently utilized in the subsequent analyzes. Firstly, we employed the limma package (version 3.44.0) in R (version 4.3.1) for standardizing and correcting the dataset of MDD gene expression profiling (GSE98793) and the NSCLC gene expression profiling dataset (GSE33532), while simultaneously annotating the corresponding gene names. A rigorous threshold ($|\log2FC| > 1.0$, $p < 0.05$) was applied to assess the associations of DEGs in patients diagnosed with MDD or NSCLC. The VennDiagram package in R (version 4.3.1) was used to generate the intersection of co-expression DEGs between MDD and NSCLC. Volcano plots were created using R software to visualize the DEGs obtained from the two datasets, illustrating all statistically significant DEGs (Figure 2).

2.3 | Discovery analysis in Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway

We employed R package "clusterProfiler" to conduct GO and KEGG enrichment analyzes on the DEGs on upregulated and downregulated genes based on MDD/NSCLC interactional genes with the aim of investigating potential mechanisms underlying pathway enrichment in these two diseases.[34] The GO pathway enrichment analyzes were employed to identify potential biological processes (BP), molecular functions (MF), and cellular components (CC)[35] (Figure 3).

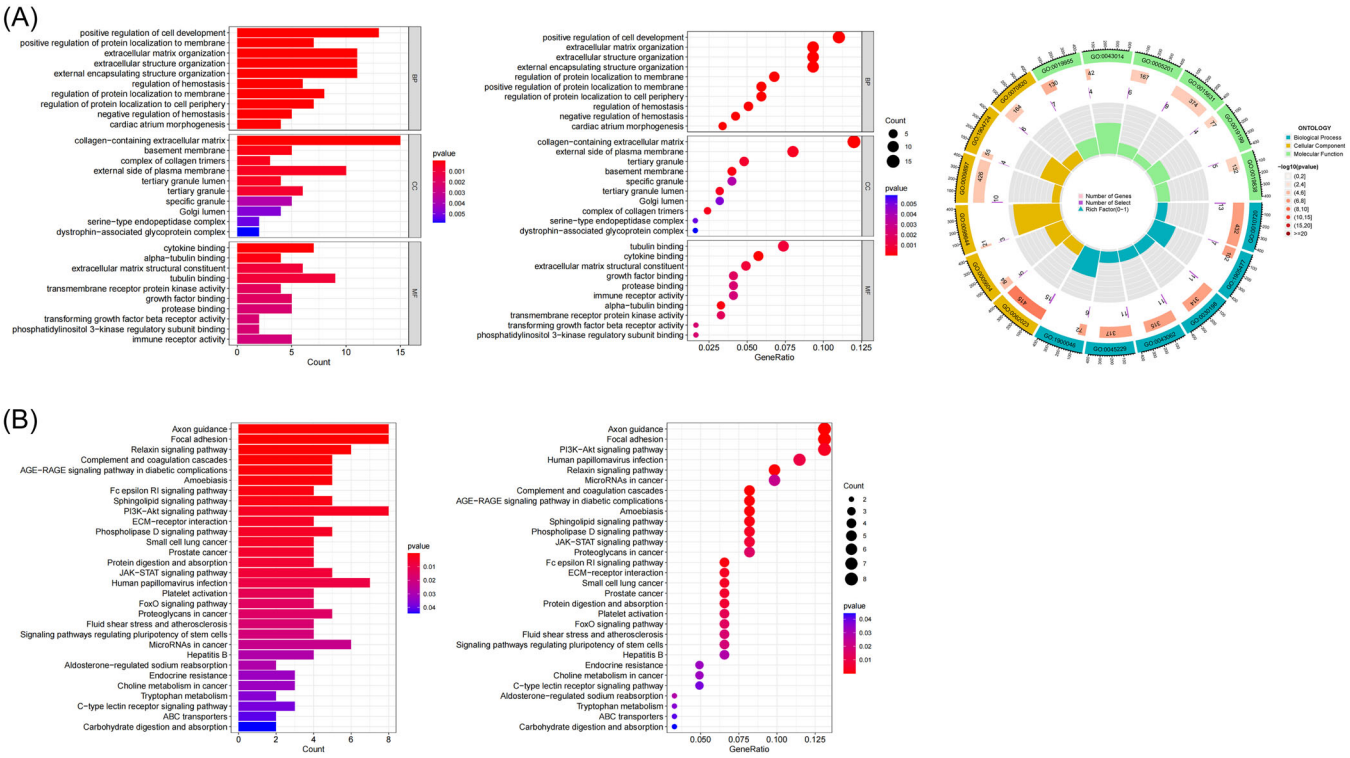

FIGURE 3 Functional annotation of genes involved in the interplay between MDD and NSCLC. The MDD and NSCLC can exert their effects through multiple shared GO terms and KEGG pathways. (A) Bubble diagrams, bar graphs, and circlize charts were used to visualize the GO enrichment analysis results for genes involved in MDD/NSCLC interactions. (B) Bubble diagrams and bar graphs were utilized to display the KEGG pathway analysis outcomes for these interactional genes. The rich factor is calculated by dividing the number of input genes annotated in a specific term by the total number of genes annotated in that term, using the given formula: Rich factor = number of input genes under this pathway term/number of all annotated genes under this pathway term. The presence of a higher rich factor signifies a heightened level of pathway enrichment. GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; MDD, major depressive disorder; NSCLC, nonsmall cell lung cancer.

2.4 | Protein–protein interaction (PPIs) networks analysis

To comprehensively investigate the biological functions of coexpressed DEGs between the two groups, we analyzed the associated DEGs using the STRING online analysis tool (version 11.5; http://string-db.org, November 1, 2023),[36] which predicts protein functional associations and PPIs. This step was aimed at predicting potential protein interactions among the encoded proteins, utilizing a medium confidence score (>0.4). The resulting DEGs were visualized using Cytoscape (version 3.7.1; https://cytoscape.org/), the degree of each protein node and subnetworks core using MCODE plugin was calculated. The "cytoHubba" plugin software in Cytoscape was utilized to compute a topological parameter, enabling the identification of the top 20 hub DEGs associated with this network. This methodology facilitated the further identification of the top 20 hub DEGs, which established related pathways characterized by a connectivity degree of ≥3. The shared protein-coding genes represent pivotal genetic factors linked to MDD in association with NSCLC.

2.4.1 | GeneMANIA analyzes

GeneMANIA (http://www.genemania.org) is a flexible web interface server that generates hypotheses about gene function, analyzes gene lists with precision and prioritizes genes for functional assays with utmost accuracy. The genes showing positive and negative correlations were inputted into GeneMANIA to unveil intricate protein-protein interactions, gene regulation mechanisms, coexpression patterns, and pathway associations.

2.5 | Analysis of hub gene-associated transcription factor (TF) network

We also used Sentence Based Text Mining (TRRUST) database (https://www.grnpedia.org/trrust/) to identify the hub gene of transcriptional regulatory TFs for the co-expressed DEGs, Then Cytoscape was applied, and the hub gene-TF network was constructed. This study shed light on their regulatory roles, leading

TABLE 1 Top 20 overlapping expressed upregulated and downregulated genes identified in MDD and NSCLC.

Upregulated Gene name	Description	Downregulated Gene name	Description
PAFAH1B3	Platelet activating factor acetylhydrolase 1b catalytic subunit 3	LRRC36	Leucine rich repeat containing 36
SRPK1	SRSF protein kinase 1	RTKN2	Rhotekin 2
EPHB2	EPH receptor B2	GPM6A	Glycoprotein M6A
IER5L	Immediate early response 5 like	SPTBN1	Spectrin beta, nonerythrocytic 1
PLOD2	Procollagen-lysine,2-oxoglutarate 5-dioxygenase 2	ANGPTL1	Angiopoietin like 1
PTGFRN	Prostaglandin F2 receptor inhibitor	CPB2	Carboxypeptidase B2
SPINT2	Serine peptidase inhibitor, Kunitz type 2	S1PR1	Sphingosine-1-phosphate receptor 1
SAPCD2	Suppressor APC domain containing 2	RGCC	Regulator of cell cycle
LAD1	Ladinin 1	ABCB1	ATP binding cassette subfamily B member 1
ABCB6	ATP binding cassette subfamily B member 6	RRN3P1	RRN3 pseudogene 1
CKAP4	Cytoskeleton associated protein 4	FAM86B2-DT	FAM86B2 divergent transcript
SOX4	SRY-box transcription factor 4	SOX7	SRY-box transcription factor 7
RASAL1	RAS protein activator like 1	PZP	PZP alpha-2-macroglobulin like
ANKRD22	Ankyrin repeat domain 22	MS4A7	Membrane spanning 4-domains A7
IQGAP3	IQ motif containing GTPase activating protein 3	COL4A3	Collagen type IV alpha 3 chain
LYPD1	LY6/PLAUR domain containing 1	A2M-AS1	A2M Antisense RNA 1
LOXL2	Lysyl oxidase like 2	UTRN	Utrophin
H2BFS	H2B.S histone 1	TGFBR3	Transforming growth factor beta receptor 3
CRABP2	Cellular retinoic acid binding protein 2	PRKCH	Protein kinase C eta
PROC	Protein C, inactivator of coagulation factors Va and VIIIa	MAPRE2	Microtubule associated protein RP/EB family member 2

Abbreviations: MDD, major depressive disorder; NSCLC, nonsmall cell lung cancer.

to discover the treatment targets of MDD and NSCLC. These results guide future experimental research and clinical transformation.

2.6 | Statistical analysis and data manipulation

The statistical analyzes and data visualization in this study were conducted using the highly acclaimed R statistical software version 4.3.1, renowned for its comprehensive range of tools and packages that facilitate robust data analysis and visualization. Cytoscape software (version 3.9.1), Perl 5.32.1 (https://www.perl.org), and R Bioconductor packages were employed for the analysis in this study. All statistical *p*-values were two-sided, with a significance level set at $p < 0.05$.

3 | RESULTS

3.1 | Identification of DEGs between MDD and NSCLC

The MDD datasets obtained from the GSE98793 dataset revealed a total of 2786 genes that exhibited differential expression in association with MDD. In comparison to the control group, 1396 genes were found to be downregulated while 1390 genes were upregulated, as evidenced by a heatmap and volcano plot (Figure 2A). We identified a total of 2127 DEGs associated with MDD in the GSE33532 dataset. Among these, 1262 genes were found to be downregulated while 865 genes were upregulated when compared to the healthy control group, as illustrated in Figure 2B. The Venn diagram shows 136 overlapping genes shared between MDD and NSCLC-related DEGs. Through conducting an overlap analysis between the two datasets, we have identified a total of 84 downregulated and 52 upregulated DEGs (false discovery rate [FDR] < 0.05) (Figure 2C and Table 1). The findings suggest that these genes play a pivotal role in the development or progression of either MDD or NSCLC.

3.2 | GO functional and KEGG pathway enrichment analysis of DEGs

To gain insight into the commonalities of biological functions and pathways affected by these DEGs, the enrichment analysis revealed 481 significant GO terms (BP: 403; CC: 25; and MF: 53) and highlighted a total of 32 KEGG pathways (FDR < 0.05), and the top five of each item is presented (Figure 3A and Table 2). Representative BP terms included positive regulation of cellular development, positive regulation of protein localization to the membrane, and extracellular matrix (ECM) organization; representative CC terms included collagen-containing ECM, basement membrane, and complex of collagen trimers; representative MF terms included cytokine binding, alpha-tubulin binding, and ECM structural constituent. The representative KEGG pathways identified in this study encompassed axon guidance, focal adhesion, relaxin signaling pathway, complement and coagulation cascades. Furthermore, the AGE-RAGE signaling pathway, which has been implicated in the development

TABLE 2 The top five GO terms in enrichment analyzes of DEGs.

Category term	ID	Description	*p*-value	Counts
BP	GO:0010720	Positive regulation of cell development	<0.0001	13
BP	GO:1905477	Positive regulation of protein localization to membrane	<0.0001	7
BP	GO:0030198	Extracellular matrix organization	<0.0001	11
BP	GO:0043062	Extracellular structure organization	<0.0001	11
BP	GO:0045229	External encapsulating structure organization	<0.0001	11
CC	GO:0062023	Collagen-containing extracellular matrix	<0.0001	15
CC	GO:0005604	Basement membrane	<0.0001	5
CC	GO:0098644	Complex of collagen trimers	<0.0001	3
CC	GO:0009897	External side of plasma membrane	<0.0001	10
CC	GO:1904724	Tertiary granule lumen	<0.0001	4
MF	GO:0019955	Cytokine binding	<0.0001	7
MF	GO:0043014	Alpha-tubulin binding	<0.0001	4
MF	GO:0005201	Extracellular matrix structural constituent	<0.0001	6
MF	GO:0015631	Tubulin binding	<0.0001	9
MF	GO:0019199	Transmembrane receptor protein kinase activity	<0.001	4

Abbreviations: BP, biological process; CC, cellular component; DEG, differential gene expression; GO, Gene Ontology; MF, molecular function.

of diabetic complications, is also worth investigating (Figure 3B). The combination of these GO terms and KEGG pathways exhibit a synergistic impact on the morbidity of both MDD and NSCLC, providing potential therapeutic strategies for these two diseases.

4 | CORRELATION NETWORK ANALYSIS OF HUB GENES/PROTEINS

The results of correlation network analysis for genes/proteins are depicted in Figure 4A,B, visualized using a graphical representation. The genes were ranked and prioritized based on their score values, resulting in the identification of the top 20 genes as prime candidates through meticulous screening. Key genes are COL4A3, SPTBN1, FCER1A, EPHB2, F12, A2M, S100A9, COL4A4, PLOD2, VCAN, CD1C, PLAU, PTPN13, COL1A2, CPB2, S1PR1, IL7R, MMP9, PIK3R1, and FYN (Figure 4C). The analysis of key network modules using the MCODE plugin reveals that the target gene interaction network comprises two distinct sub-networks. Subnetwork 1 consists of 5 nodes and 9 edges, while subnetwork 2 encompasses 10 nodes and 16 edges (Figure 4D).

To elucidate the interaction among hub genes, we employed the "cytoHubba" algorithm to discern the top 20 hub genes. The comprehensive information of all 20 genes was presented in Table 3, encompassing complete gene names, RRA method scores, directionality, and primary functionalities. The regulatory network of these hub genes was constructed by integrating functionally similar genes from the GeneMANIA database, thereby elucidating their potential involvement in diverse biological functions: angiogenesis, humoral immune response, regulation of inflammatory response, ECM organization, regulation of peptidase activity, negative regulation of response to external stimulus and blood coagulation (Figure 5).

4.1 | GO functional annotation and KEGG pathway enrichment analysis of target genes

We conduct GO functional annotation and KEGG pathway enrichment analysis for hub genes, separately. The GO analysis unveiled that the hub genes were predominantly enriched in four distinct BPs, namely blood coagulation, regulation of hemostasis,

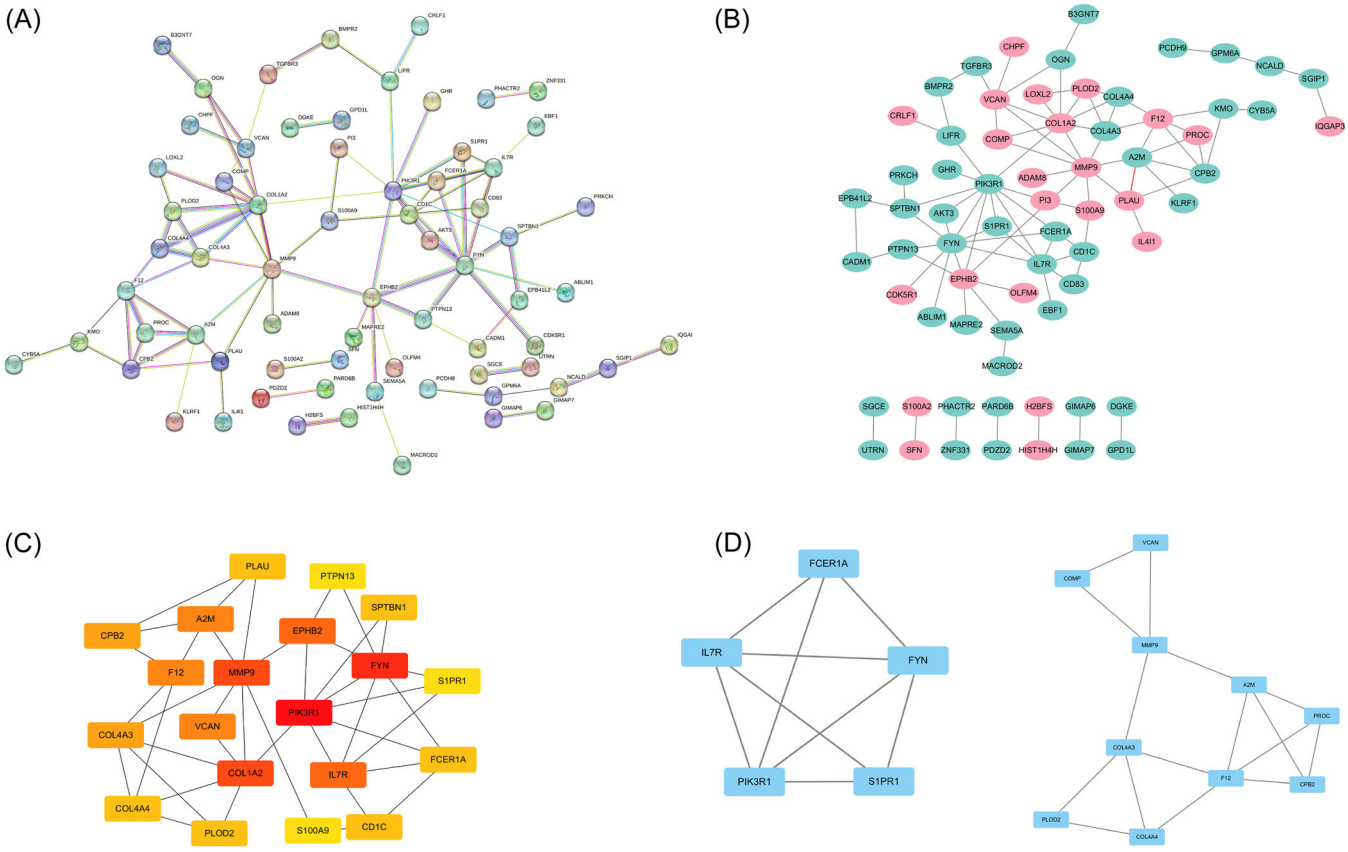

FIGURE 4 PPIs network and subnetworks of key genes. The relevant differential genes were analyzed, resulting in the extraction of 20 key genes. Subsequently, two core gene subnetworks were identified. (A) The PPIs network of the targets as studied in the STRING database. (B) All the circle indicates that the DEGs does belong to the core gene. Red represents upward DEGs, blue represents downward DEGs; Linear representation these genes have regulatory relationship. (C) PPIs network for modules which are a candidate from the PPIs network using the cytoHubba plugin. The gradient ranging from dark red to light red signifies the variation in the number of edges, transitioning from a higher count to a lower count. (D) Subnetwork modules composed of pivotal genes. DEGs, differential gene expression; PPIs, protein–protein interaction network.

TABLE 3 MDD/NSCLC interactional hub genes.

Hub gene	Description	Score	Direction	Primary function
COL4A3	Collagen type IV alpha 3 chain	0.708	Down	Angiogenesis, basement membrane
SPTBN1	Spectrin beta, nonerythrocytic 1	0.685	Down	Axonogenesis, neuron projection guidance
FCER1A	Fc fragment of IgE receptor Ia	0.663	Down	Localization to membrane, regulation of protein localization to membrane
EPHB2	EPH receptor B2	0.642	Up	Axonogenesis, blood coagulation,
F12	Coagulation factor XII	0.625	Up	Blood coagulation, fibrin clot formation
A2M	Alpha-2-macroglobulin	0.624	Down	Blood coagulation, fibrin clot formation
S100A9	S100 calcium binding protein A9	0.622	Up	Fatty acid binding, humoral immune response
COL4A4	Collagen type IV alpha 4 chain	0.618	Down	Basement membrane, collagen trimer
PLOD2	Procollagen-lysine,2-oxoglutarate 5-dioxygenase 2	0.616	Up	Intermolecular collagen cross-links
VCAN	Versican	0.600	Up	Extracellular matrix structural constituent
CD1C	CD1c molecule	0.600	Down	Peptide binding
PLAU	Plasminogen activator, urokinase	0.588	Up	Blood coagulation, cell adhesion mediated by integrin,
PTPN13	Protein tyrosine phosphatase nonreceptor type 13	0.588	Down	Glycerolipid biosynthetic process, glycerophospholipid biosynthetic process
COL1A2	Collagen type I alpha 2 chain	0.584	Up	Blood coagulation, coagulation,
CPB2	Carboxypeptidase B2	0.570	Down	Blood coagulation, coagulation,
S1PR1	Sphingosine-1-phosphate receptor 1	0.569	Down	Lamellipodium organization
IL7R	Interleukin 7 receptor	0.570	Down	Cellular response to chemical stress, extracellular matrix organization
MMP9	Matrix metallopeptidase 9	0.540	Up	Cellular response to chemical stress, extracellular matrix organization
PIK3R1	Phosphoinositide-3-kinase regulatory subunit 1	0.505	Down	Axonogenesis, blood coagulation
FYN	FYN proto-oncogene, Src family tyrosine kinase	0.504	Down	Axonogenesis, blood coagulation

Abbreviations: MDD, major depressive disorder; NSCLC, nonsmall cell lung cancer.

coagulation regulation, and regulation of protein localization to membrane. The cellular composition primarily consisted of an ECM rich in collagen, as well as the lumen of the endoplasmic reticulum, as shown in Figure 6A–C. MF primary focused on ECM structural constituent. The KEGG enrichment analysis unveiled a remarkable enrichment of the hub genes in pathways associated with amoebiasis, relaxin signaling, focal adhesion, and PI3K-Akt signaling (Figure 6D–F).

4.2 | Prediction of hub gene-related TFs

We predict that a total of 15 families of TFs interact with hub genes. Among all the hub genes, matrix metallopeptidase 9 (MMP9) is predicted to have the highest number of interactions with TFs, including HDAC1, CIITA, SRF, JUN, FOS, RELA, NFKB1, EP300, ETS1, SIRT1 and STAT3 (Figure 7). The subsequent gene, COL1A2, exhibits interactions with RELA, NFKB1, CIITA, SIRT1, EP300, HDAC1, and YY1. PLAU demonstrates interactions with NFKB1, RELA, SRF, FOS, ETS1, JUN, and SP1. These findings suggest that these hub genes may be regulated by these TFs and engage in biological functions associated with MDD and NSCLC.

4.3 | Validation of hub genes

Other MDD and NSCLC datasets were retrieved from the GEO data library. Finally, GSE76826 dataset (MDD) was selected to analyze the differential expression levels of these hub genes between MDD and healthy controls (Figure 8). Although we did not see evidence of significant differences in some genes, we identified differences in COL4A4, F12, FYN, IL7R, MMP9, S1PR1, and S100A9 genes. Compared with the control group, MDD patients had significantly increased in F12, MMP9, S100A9 and decreased in COL4A4, FYN,

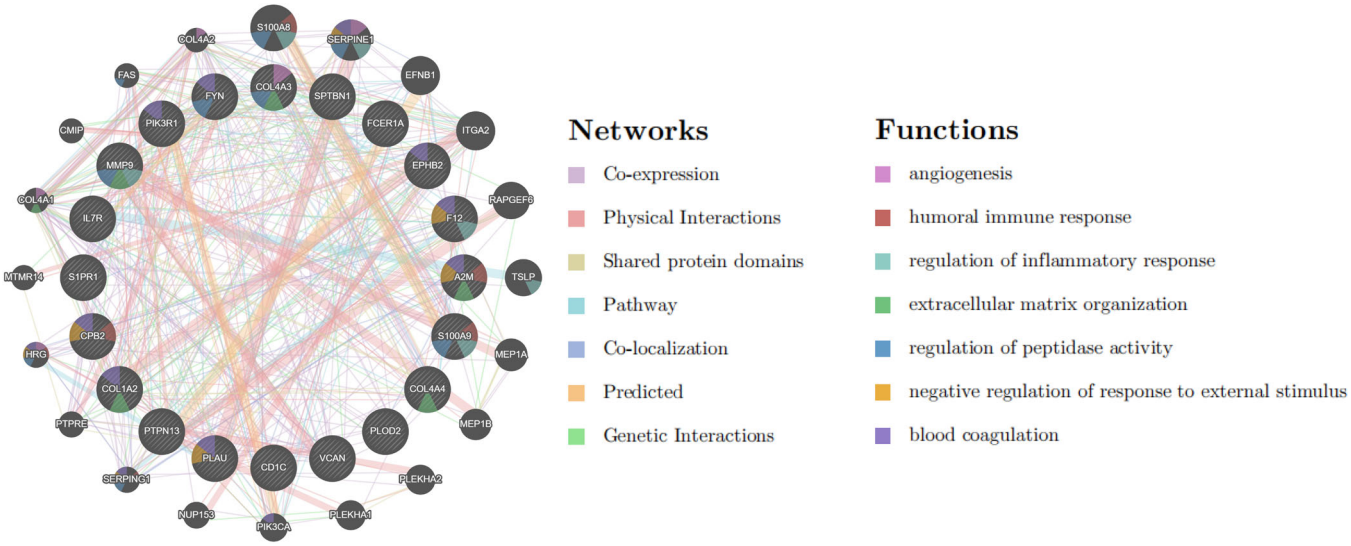

FIGURE 5 PPIs network of the 20 hub-genes target networks. The networks and their functions are explained, emphasizing their potential contributions to various biological processes. The PPIs network of the 20 hub-genes target network was constructed utilizing the GeneMANIA database, with edges color-coded to represent a plethora of bioinformatics methods such as co-expression, website prediction, shared protein domains and co-localization. Furthermore, nodes in the network were color-coded based on functional enrichment analysis of the query gene list. PPI, protein–protein interaction network.

IL-7R, S1PR1. In the GSE19804 (lung cancer) dataset, we validated lung cancer and Control patients. Compared with the control group, lung cancer patients had significantly decreased in COLA2, EPHB2, F12, MMP9, PLAU, PLCO2, VCAN and increased in A2M, COL4A3, CPB2, FCER1A, IL7R, PIK3R1, S1PR1, S100A9, SPTBN1. We were unable to demonstrate a difference among different genes, the implication is that certain genes might not be suitable as predictive target genes.

4.4 | Validation of TFs

Compared with the healthy group, MDD patients had significantly decreased in HDAC1. Lung cancer patients exhibited significant downregulation of CEBPB, NFKB1, STAT3, RELA, CIITA, FOS, CEBPB, ETS1, JUN, and SP1 expression levels compared to the control group. Conversely, HDAC1 and TP53 were significantly upregulated. Although we saw some evidence of change in EP300, SIRT1, SRF, and YY1 genes, differences between groups did not meet conventional levels of statistical significance (Figure 9).

5 | DISCUSSION

5.1 | The interaction between NSCLC and MDD is influenced by multiple factors

Presently, depression and lung cancer are significant health concerns that impact millions of individuals with unpredictable and severe consequences for their physical and mental well-being.[37] Despite appearing unrelated, these two topics exhibit intricate interactions and influences on multiple levels.[9,10] Patients with lung cancer often experience feelings of sadness, despair, helplessness, and immense stress associated with the illness, which can lead to depression.[38] NSCLC tumor indirectly impact the nervous system due to its proximity to neural structures.[39] These resulting depression may cause patients to neglect or refuse treatment, thereby impacting their ability to combat the disease.[40] Conversely, the World Health Organization has ranked MDD as the third leading cause of disease burden, with projections indicating that it will emerge as the foremost cause by 2030.[41] MDD refers to a prevalent and debilitating condition characterized by profound physiological, biological, and psychosocial alterations that have detrimental consequences such as persistent feelings of profound sadness, extreme fatigue, self-blame and even suicidal thoughts or attempts that can pose significant harm.[42,43] The prevalence of depression in cancer patients has been reported to be 3–5 times higher than the rate observed in the general population, ranging from 15% to 29%. Furthermore, lung cancer demonstrated a promotive effect of psychological distress on tumor hallmarks via stress-related crucial neurotransmitters and hormones.[14] The co-occurrence of MDD and lung cancer in patients gives rise to a detrimental cycle that adversely affects treatment adherence and compromises the effectiveness of multiple therapeutic interventions. Thus, identification of key co-target site and improves the therapy management of MDD and NSCLC patients are crucial for the rehabilitation of lung cancer patients. However, none of these studies have provided insights into the underlying pathways and key genes linking MDD and lung cancer.

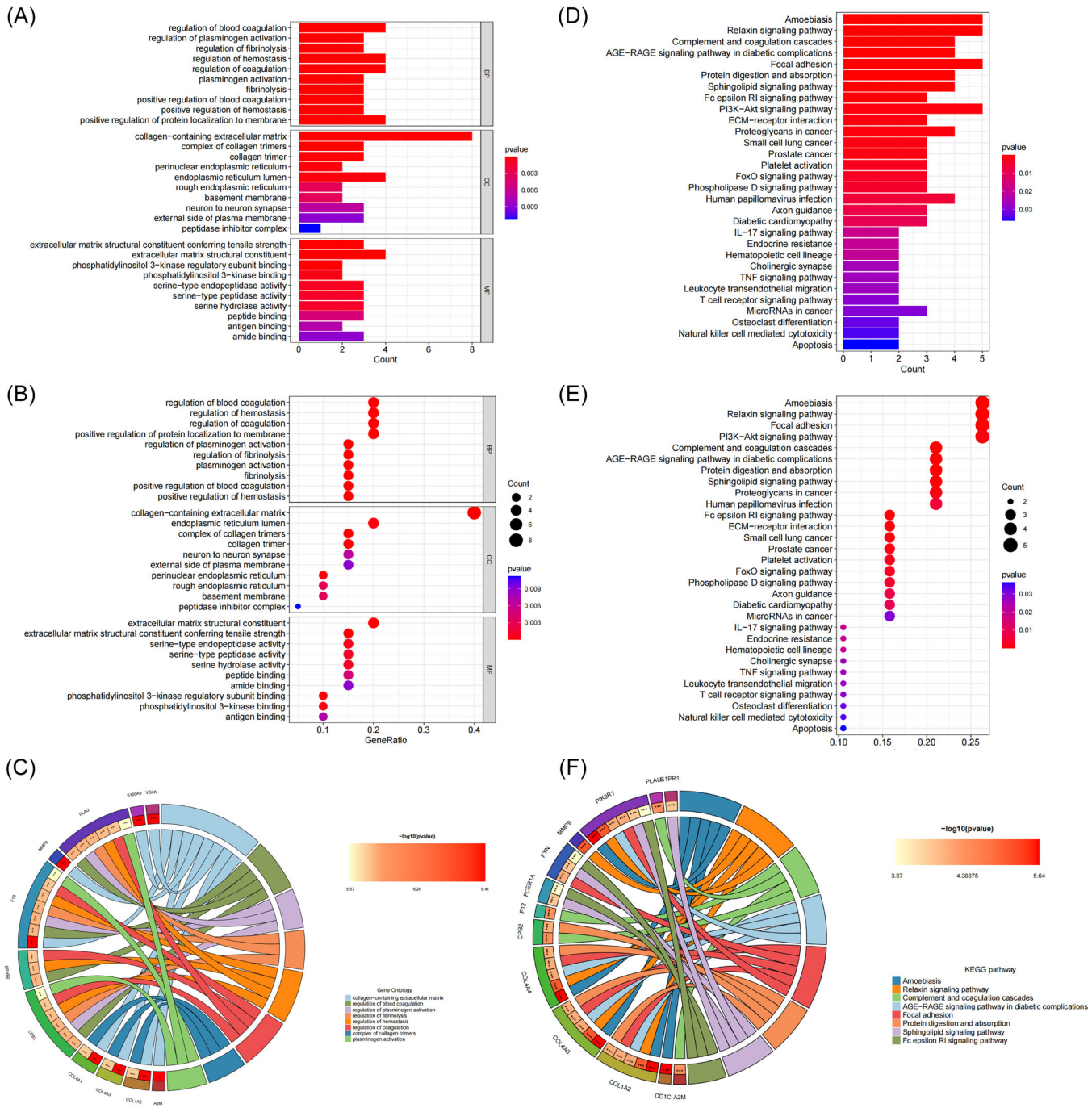

FIGURE 6 Results of GO term and KEGG pathways enrichment. The GO term revealed a predominant enrichment of hub genes in four distinct biological processes. The KEGG enrichment analysis demonstrated a remarkable enrichment of the hub genes in four specific pathways. (A) Bar chart depicting GO enrichment analysis results for hub genes. (B) Bubble plot illustrating GO signaling pathway enrichment analysis results for hub genes. (C) Circlize diagram displaying GO enrichment analysis results for hub genes. (D) Bar chart and KEGG pathway map showing KEGG enrichment analysis results for hub genes. (E) Bubble plot presenting KEGG enrichment analysis results for hub genes. (F) Circlize diagram demonstrating KEGG signaling pathway enrichment analysis results for hub genes. GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

5.2 | The shared genes and pathway targets are present between MDD and NSCLC

In our study, this article aims to investigate the gene correlation between MDD and NSCLC, while analyzing the related signaling networks implications for MDD as well as NSCLC. Consequently, bioinformatic mining was conducted, the GSEs of microarray data obtained from MDD and NSCLC, which were evaluated using a series of bioinformatic methods. We found that there have overlapping DEGs between MDD and NSCLC. The presence of common shared

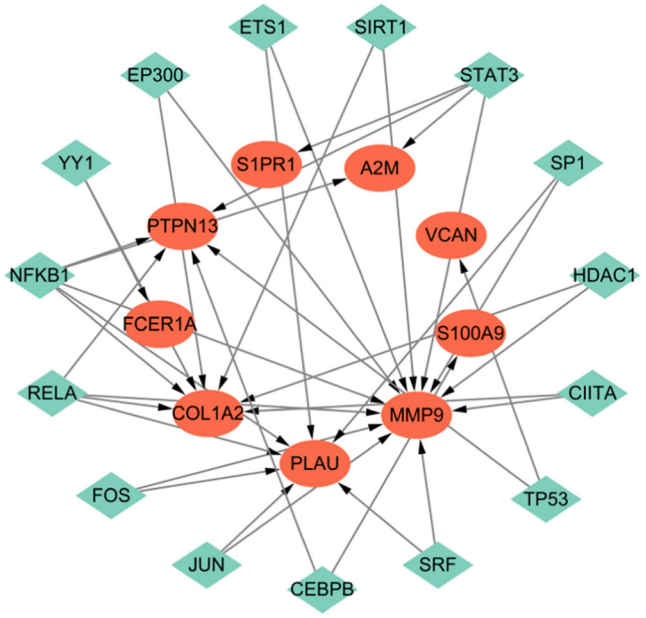

FIGURE 7 Network of hub genes and transcription factors (TFs). The 9 core genes were associated with a total of 15 TFs, with MMP9 exhibiting the highest number of associations. In the network analysis diagram of hub genes and TFs, and orange color represents gene and green color represents transcription factor. MMP9, matrix metallopeptidase 9.

DEGs between MDD and NSCLC suggests their potential involvement in both disorders, making them critical targets for developing effective strategies.

5.3 | The signaling crossed pathways establish a significant association between MDD and NSCLC

Functional annotation implied that these DEGs were primarily associated with cell development, collagen-containing ECM, cytokine binding and axon guidance. The canonical pathways of MDD patients usually include ensheathment of neurons, PTEN signaling, and axonal guidance signaling in brain.[44] While a dynamic, bidirectional interaction between the nervous system and cancer can modulated the neural stem/precursor cell population, cellular membrane potential and depolarization to impact neurons and axonal, driving the growth of cancers.[45] On the other hand, the involvement of NSCLC related to ECM organization, CCs containing collagen within the ECM, and MFs as constituents of ECM structure.[46] And matrix metalloproteinase 8 (MMP8) and FRAS1-related ECM protein 3 are related with MDD.[47] Some cytokines, such as interferon (IFN)-α, tumor necrosis factor-α, and interleukin (IL)-6 is closely associated with MDD.[48,49] It has been discovered that the synergistic effect of elevated levels of IL-1β and IFN-γ induces maximal PD-L1 expression in NSCLC cancer cells. The IL-1β-MAPK axis presents a promising therapeutic target for attenuating PD-L1-mediated suppression of antitumor immunity.[50] Besides, the axon guidance signaling pathway displayed the most prominent level of enrichment, consistently observed across all stress models and individuals diagnosed with MDD,[44] linked to changes in axon guidance molecules and their receptors, which could contribute to abnormalities in neural connectivity and communication.[51] Whereas, the interaction of the axon guidance factor Sema4D assumes a pivotal role in the formation of vasculogenic mimicry in NSCLC by activating the RhoA/ROCK pathway and regulating tumor cell plasticity and migration.[52] The collective findings indicate that both MDD and NSCLC contribute to disease progression and development via shared pathways.

5.4 | Hub genes related function in both NSCLC and MDD

Subsequently, we identified 20 core genes from the pool of DEGs, namely PIK3R1, FYN, MMP9, COL1A2, EPHB2, IL7R, VCAN, A2M, F12, COL4A3, CPB2, FCER1A, COL4A4, PLOD2, SPTBN1, CD1C, PLAU, COMP, and S1PR1. Notably, they are primarily involved in ECM signaling pathway, immune response as well as regulation of inflammation and vascular system integrity and functionality. For example, the modulation of MMP9 expression was predominantly achieved through the inhibition of signaling pathways involving transforming growth factor-β and SMAD family members 2/3 (Smad2/3).[53] The PLOD2 enzymes play a pivotal role in the posttranslational modification and folding of collagen, culminating in the formation of an inflexible ECM that triggers the expression of genes associated with EMT and cancer stem cells, leading to metastatic dissemination of cancer.[54] The IL-7R receptor licenses a population of memory $CD8^+$ T cells that exhibit superior efficacy in antitumor responses.[55] FCEIRIA involved in allergic airway inflammation.[56] The levels of B-lymphocyte subsets and the IgG1-to-IgG2a ratio exhibited a significant increase in PLAU negative mice subsequent to membranous nephropathy induction.[57] COLA3 displayed distinct characteristics in terms of the infiltration of immune cells and polarization of tumor-associated macrophages.[58] Additionally, COL4A3 as a specific susceptibility gene for the development of polypoidal choroidal vasculopathy.[58] Among these genes, PIK3R1 was foremost expressed between MDD and NSCLC, followed by FYN, MMP9 and COL1A2. Hub genes PIK3R1 in the ACC were identified in MDD of mice.[59] Similar study demonstrated that miR-486-5p directly targets the PIK3R1 gene, and a negative correlation exists between the expression levels of miR-486-5p and PIK3R1 in tumor tissues.[60] The interaction between Fyn and Src with a Gαq-coupled mGlu5 receptor was observed in striatal neurons of mice with depression.[61] The upregulation of FYN impedes the EMT process in lung cancer cells by suppressing the PI3K/AKT signaling pathway.[62] Furthermore, the diagnostic accuracy for bipolar disorder was significantly enhanced by incorporating PIK3R1 and FYN into the Support Vector Machine model.[63] Emerging evidence suggests that there is a decrease in the overall balance between excitatory and inhibitory activity in the cortex of individuals with MDD. The presence of MMP9 in plasma, lung tissue, and tumor extracts can

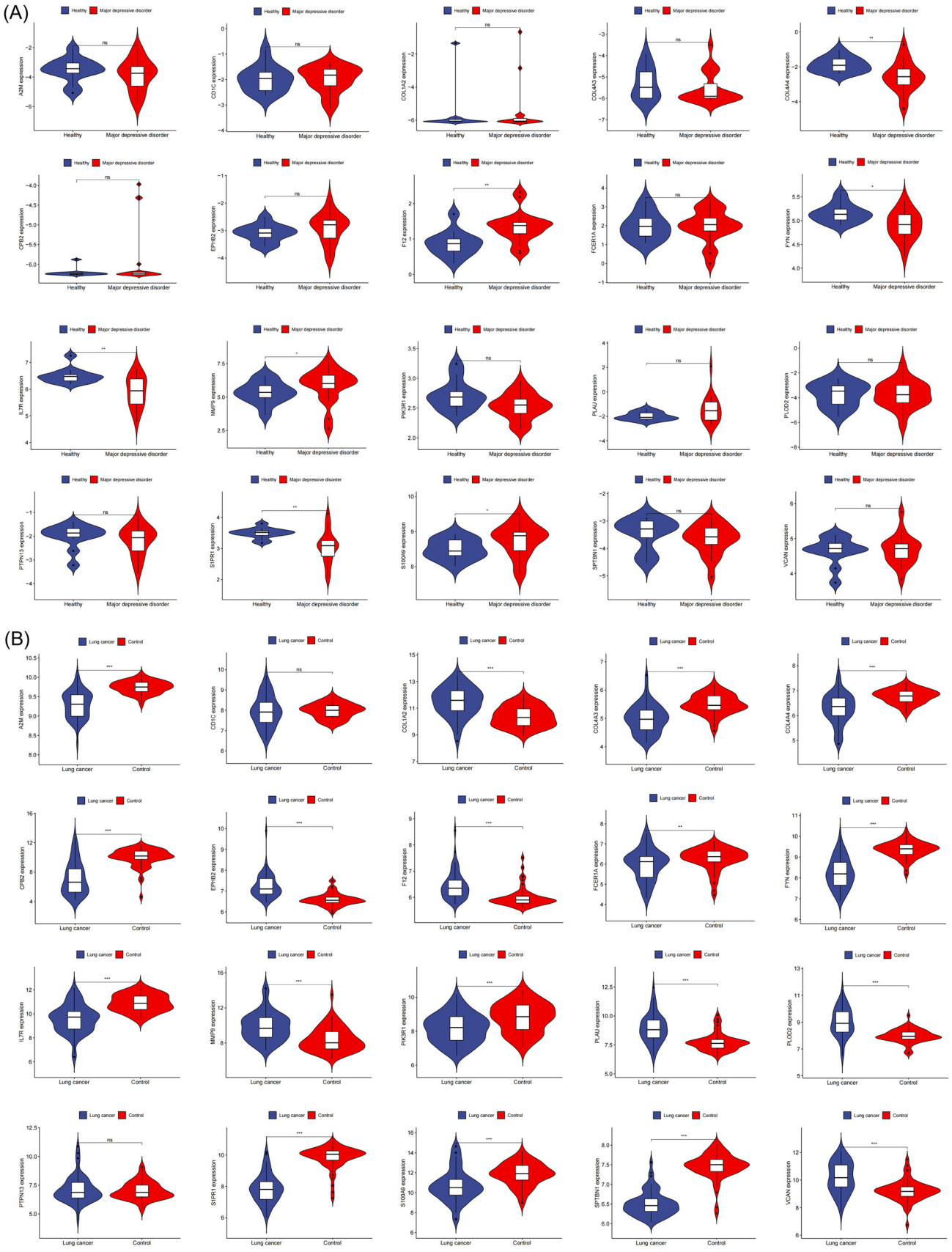

FIGURE 8 Verified of hub genes from differential analysis. The expression of A2M, COLA2, COL4A3, CPB2, EPHB2, F12, FCER1A, IL7R, MMP9, PIK3R1, PLAU, PLCO2, S1PR1, S100A9, SPTBN1, and VCAN in GSE19804 dataset of NSCLC (A) and in GSE76826 dataset of MDD (B), $p < .001$ was denoted as "***", $p < 0.01$ as "**", $p < 0.05$ as "*", and $p > 0.05$ as "ns."

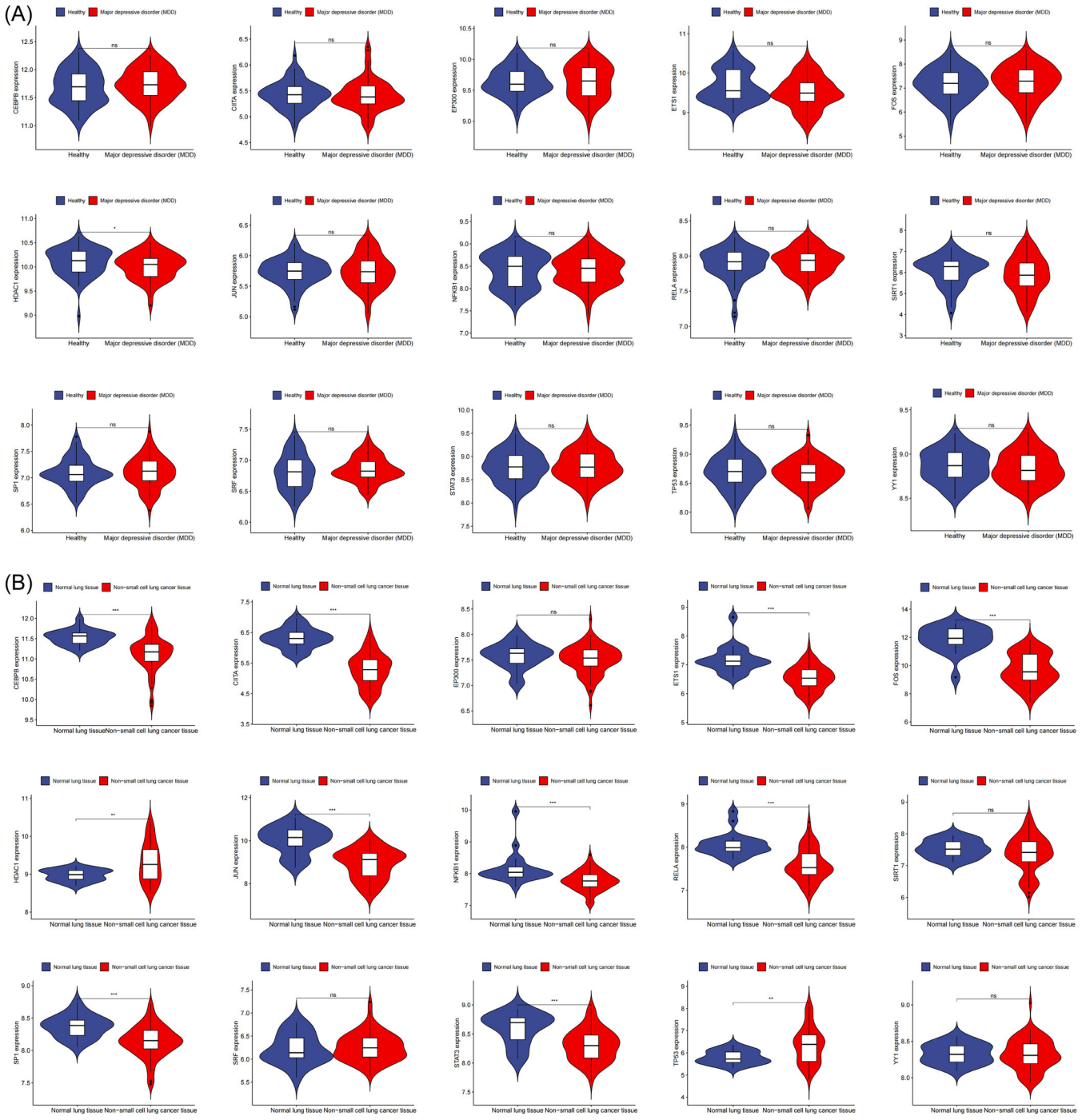

FIGURE 9 The violin map of TFs of severe specific genes. The validation of alterations in MDD (A) and NSCLC (B) across the following TFs: CEBPB, NFKB1, STAT3, RELA, CIITA, FOS, HDAC1, CEBPB, EP300, ETS1, JUN, SIRT1, SP1, SRF, TP53, and YY1 in GSE19804 dataset of NSCLC (A) and in GSE76826 dataset of MDD (B), $p < 0.001$ was denoted as "***", $p < 0.01$ as "**", $p < 0.05$ as "*", and $p > 0.05$ as "ns." MDD, major depressive disorder; NSCLC, nonsmall cell lung cancer; TF, transcription factor.

facilitate the early detection and diagnosis of lung cancer[64] and it has been shown to augment the migratory, invasive, and EMT properties of NSCLC cells.[65] As a result of neuronal activity, MMP9 has been found to contribute to the antidepressant effectiveness of venlafaxine, a serotonin/norepinephrine reuptake inhibitor, in male mice.[66] COL1A2 plays a significant role in the underlying mechanisms of comorbidity between heart failure and depression.[67] The overall survival times of lung cancer patients with high expression of COL1A2 were found to be significantly inferior compared to those with low expression.[68] These shared genes provide novel targets for further mechanistic investigations into the pathogenesis and treatment of both MDD and NSCLC.

5.5 | The identification and comprehension of crossed biological process in proteins

Further PPIs network results showed that these 20 genes could enriched in pathways targeted to tumor and depression, such as inflammatory and immune response pathways, angiogenesis and ECM. The MDD-trait was also found to be associated with genes implicated in inflammatory processes, immune system activation, and impaired bioenergetics.[69] Therapeutic strategies harnessing the immune system and inflammatory burden index[70] to eliminate tumor cells have been successfully used for lung cancer.[71] Besides, angiogenesis is a fundamental biological process that involves the sprouting and growth of new blood vessels from pre-existing ones, playing a pivotal role in both the development and progression of lung cancer. Significantly, the levels of Angiopoietin-1, Angiopoietin-2, and Angiopoietin-4 underscore their profound impact on the intricate processes involved in the development, progression, and metastasis of lung cancer.[72] Whereas, there have increased angiotensinogen levels in MDD patients.[73] Moreover, subtype-specific ECM signatures linked to tumor initiation and predictive of premalignant progression activate distinct matrix remodeling programs in both tumor and stromal cells, thereby reinforcing resistance and promoting progression through intracellular signaling pathways.[74] ECM regulates cell communication, modulates neuronal function, and plays a role in stress-induced changes.[75] Therefore, comprehending these pathways is imperative for comprehending the functionality in both NSCLC and MDD.

5.6 | The vital function of MMP9 in NSCLC and MDD

MMP9 is an enzyme protein belonging to the MMP family that plays a crucial role in collagen degradation, basement membrane degradation, inflammation regulation, cell migration and invasion. Despite limited research on hub gene-related pathways such as regulation of coagulation and the relaxin signaling pathway in NSCLC and MDD, there is a wealth of studies on interacting TFs. MMP9 serves as the site of action for multiple TFs in our study, plays a pivotal role in collagen degradation,[76] basement membrane degradation, inflammation regulation. The MMP9 has been extensively studied and its close association with proliferation, migration, and invasion has been well-documented, primarily implicated in the metastasis of NSCLC.[77–79] In microvasculitis, the entry of monocytes and T cells into the blood vessel wall is elegantly regulated by MMP9. T cells rely on MMP9-producing monocytes to gracefully traverse the basement membrane containing collagen-IV.[80] The activation of the fibrinolytic system contributes to the development of colitis by inducing the activation of MMP9 or other proteolytic enzymes, thereby promoting tissue degradation and inflammation.[81] The collective findings indicate that MMP9 exhibits diverse functional roles in both MDD and NSCLC.

In conclusion, bioinformatics analysis has identified key genes and networks associated with MDD and NSCLC, providing valuable insights into the biology of these diseases and their connections to inflammation and the immune system. These findings offer essential clues for identifying novel therapeutic targets and personalized treatment strategies for patients with MDD or NSCLC. Additionally, comprehensive support and treatment are crucial in managing these patients. By combining specialized targeted therapy with strengthened mental health services, we can effectively assist them in overcoming lung cancer and depression, improving their quality of life, and enhancing rehabilitation success rates.

AUTHOR CONTRIBUTIONS

Huan Gui: Conceptualization; data curation; formal analysis; investigation; methodology; resources; software; validation; writing—original draft; writing—review & editing. **Xulong Chen**: Data curation; investigation; validation; writing—original draft; writing—review & editing. **Yingjie Nie**: Conceptualization; data curation; investigation; supervision; validation; writing—original draft; writing—review & editing. **Xiangyan Zhang**: Conceptualization; data curation; investigation; supervision; validation; writing—original draft; writing—review & editing.

ACKNOWLEDGMENTS

We would like to express our sincere gratitude to all the individuals and institutions who contributed to this study. We are especially thankful to the participants for their valuable contribution and cooperation. We acknowledge the students, researchers, and laboratory personnel involved in data collection and analysis for their dedicated efforts. Sources of funding—Study design: Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (2019PT320003), and the National Natural Science Foundation of China (82060308). Collection and analysis: National Key Laboratory of Respiratory Diseases of China (SKLRD-OP-202208), Science and Technology Plan Project of Guizhou Provincial in China (GPPH-NSFC-2020-6; GPPH-NSFC-2020-7; GCC [2022]037-1). Interpretation of data and writing of the report: Research Fund Projects of Guizhou Provincial Immunotherapy Research Talent Base in China (RCJD2018-11). The report for publication: China Scholarship Council (202306670011), Science and Technology Fund project of Guizhou Provincial Health Commission (2023-3-5).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All authors have read and approved the final version of the manuscript had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis. The data that support the findings of this study are openly available in GEO database at https://www.ncbi.nlm.nih.gov/geo/.

TRANSPARENCY STATEMENT

The lead author Yingjie Nie affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that

no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7-30.
3. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. *Mayo Clin Proc*. 2008;83(5):584-594.
4. Molina JR, Adjei AA, Jett JR. Advances in chemotherapy of non-small cell lung cancer. *Chest*. 2006;130(4):1211-1219.
5. Niedzwiedz CL, Knifton L, Robb KA, Katikireddi SV, Smith DJ. Depression and anxiety among people living with and beyond cancer: a growing clinical and research priority. *BMC Cancer*. 2019;19(1):943.
6. Rodriguez-Gonzalez A, Velasco-Durantez V, Martin-Abreu C, et al. Fatigue, emotional distress, and illness uncertainty in patients with metastatic cancer: results from the prospective NEOETIC_SEOM study. *Curr Oncol*. 2022;29(12):9722-9732.
7. Sullivan DR, Mongoue-Tchokote S, Mori M, Goy E, Ganzini L. Randomized, double-blind, placebo-controlled study of methylphenidate for the treatment of depression in SSRI-treated cancer patients receiving palliative care. *Psycho-Oncology*. 2017;26(11):1763-1769.
8. Maj M, Stein DJ, Parker G, et al. The clinical characterization of the adult patient with depression aimed at personalization of management. *World Psychiatry*. 2020;19(3):269-293.
9. Massie MJ. Prevalence of depression in patients with cancer. *J Natl Cancer Inst Monogr*. 2004;2004(32):57-71.
10. Shahedah KK, How SH, Jamalludin AR, Mohd Faiz MT, Kuan YC, Ong CK. Depressive symptoms in newly diagnosed lung carcinoma: prevalence and associated risk factors. *Tuberc Respir Dis*. 2019;82(3):217-226.
11. Deng L, Chen B. Two-scale assessment of anxiety and depression in postoperative non-small cell lung cancer patients: their prevalence, risk factors, and prognostic potency. *Irish J Med Sci (1971 -)*. 2023;192(6):2613-2619.
12. Krishnan V, Nestler EJ. The molecular neurobiology of depression. *Nature*. 2008;455(7215):894-902.
13. Yang L, Zhao Y, Wang Y, et al. The effects of psychological stress on depression. *Curr Neuropharmacol*. 2015;13(4):494-504.
14. Gui H, Chen X, Li L, et al. Psychological distress influences lung cancer: advances and perspectives on the immune system and immunotherapy. *Int Immunopharmacol*. 2023;121:110251.
15. Wang YH, Li JQ, Shi JF, et al. Depression and anxiety in relation to cancer incidence and mortality: a systematic review and meta-analysis of cohort studies. *Mol Psychiatry*. 2020;25(7):1487-1499.
16. Hopwood P, Stephens RJ. Depression in patients with lung cancer: prevalence and risk factors derived from quality-of-life data. *J Clin Oncol*. 2000;18(4):893.
17. Iyer S, Taylor-Stokes G, Roughley A. Symptom burden and quality of life in advanced non-small cell lung cancer patients in France and Germany. *Lung Cancer*. 2013;81(2):288-293.
18. Arrieta Ó, Angulo LP, Núñez-Valencia C, et al. Association of depression and anxiety on quality of life, treatment adherence, and prognosis in patients with advanced non-small cell lung cancer. *Ann Surg Oncol*. 2013;20(6):1941-1948.
19. Berchuck JE, Meyer CS, Zhang N, et al. Association of mental health treatment with outcomes for US veterans diagnosed with non-small cell lung cancer. *JAMA Oncology*. 2020;6(7):1055-1062.
20. Pinquart M, Duberstein PR. Depression and cancer mortality: a meta-analysis. *Psychol Med*. 2010;40(11):1797-1810.
21. Bortolato B, Hyphantis TN, Valpione S, et al. Depression in cancer: the many biobehavioral pathways driving tumor progression. *Cancer Treat Rev*. 2017;52:58-70.
22. Walker J, Cassidy J, Sharpe M, SMaRT Oncology-3 Trialists. The third symptom management research trial in oncology (SMaRT oncology-3): a randomised trial to determine the efficacy of adding a complex intervention for major depressive disorder (depression care for people with lung cancer) to usual care, compared to usual care alone in patients with lung cancer. *Trials*. 2009;10:92.
23. Fasipe OJ. The emergence of new antidepressants for clinical use: agomelatine paradox versus other novel agents. *IBRO Reports*. 2019;6:95-110.
24. Lee E, Park Y, Li D, Rodriguez-Fuguet A, Wang X, Zhang WC. Antidepressant use and lung cancer risk and survival: a meta-analysis of observational studies. *Cancer Res Commun*. 2023;3(6):1013-1025.
25. Jing Q, Wan Q, Nie Y, et al. Ansofaxine hydrochloride inhibits tumor growth and enhances Anti-TNFR2 in murine colon cancer model. *Front Pharmacol*. 2023;14:1286061.
26. Chaurasiya N, Leon F, Muhammad I, Tekwani B. Natural products inhibitors of monoamine oxidases-potential new drug leads for neuroprotection, neurological disorders, and neuroblastoma. *Molecules*. 2022;27(13):4297.
27. van der Velden AM, Scholl J, Elmholdt EM, et al. Mindfulness training changes brain dynamics during depressive rumination: a randomized controlled trial. *Biol Psychiatry*. 2023;93(3):233-242.
28. Liu P, Liu Z, Wang J, et al. Immunoregulatory role of the gut microbiota in inflammatory depression. *Nat Commun*. 2024;15(1):3003.
29. Feng C, Li N, Gao G, He Q, Kwok LY, Zhang H. Dynamic changes of the gut microbiota and its functional metagenomic potential during the development of non-small cell lung cancer. *Int J Mol Sci*. 2024;25(7):3768.
30. Wang Y, Wang X, Wang X, et al. Imipramine impedes glioma progression by inhibiting YAP as a Hippo pathway independent manner and synergizes with temozolomide. *J Cell Mol Med*. 2021;25(19):9350-9363.
31. Zhang H, Xu H, Tang Q, Bi F. The selective serotonin reuptake inhibitors enhance the cytotoxicity of sorafenib in hepatocellular carcinoma cells. *Anti-Cancer Drugs*. 2021;32(8):793-801.
32. Kemp AH, Quintana DS, Gray MA, Felmingham KL, Brown K, Gatt JM. Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. *Biol Psychiatry*. 2010;67(11):1067-1074.
33. Barrett T, Wilhite SE, Ledoux P, et al. NCBI GEO: archive for functional genomics data sets--update. *Nucleic Acids Res*. 2013;41(Database issue):991-995.
34. Hein DM, Deng W, Bleile M, et al. Racial and ethnic differences in genomic profiling of early onset colorectal cancer. *J Natl Cancer Inst*. 2022;114(5):775-778.
35. Dennis Jr., G. *DAVID: Database for Annotation, Visualization, and Integrated Discovery*. *Genome Biol*. 2003;4(5):P3.
36. Szklarczyk D, Morris JH, Cook H, et al. The STRING database in 2017: quality-controlled protein-protein association networks, made broadly accessible. *Nucleic Acids Res*. 2017;45(D1):D362-D368.
37. <Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet, 2024.

38. Smith HR. Depression in cancer patients: pathogenesis, implications and treatment (Review). *Oncol Lett*. 2015;9(4):1509-1514.
39. Takeda M, Okamoto I, Nakagawa K. Clinical impact of continued crizotinib administration after isolated central nervous system progression in patients with lung cancer positive for ALK rearrangement. *J Thorac Oncol*. 2013;8(5):654-657.
40. Prakash J, Yadav Y, Srivastava K, Madhusudan T. Psychosocial correlates of medication adherence in patients with depressive illness. *Ind Psychiatry J*. 2019;28(1):135-140.
41. Chand SP, Arif H, Kutlenios RM. Depression (Nursing), *in* StatPearls. StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.; 2023.
42. Bains N, Abdijadid S, Miller JL. Major Depressive Disorder (Nursing), *in* StatPearls. StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC; 2024.
43. Remes O, Mendes JF, Templeton P. Biological, psychological, and social determinants of depression: a review of recent literature. *Brain Sci*. 2021;11(12):1633.
44. Gui S, Liu Y, Pu J, et al. Comparative analysis of hippocampal transcriptional features between major depressive disorder patients and animal models. *J Affect Disord*. 2021;293:19-28.
45. Keough MB, Monje M. Neural signaling in cancer. *Annu Rev Neurosci*. 2022;45:199-221.
46. Huang Y, Guo DM, Bu S, et al. Systematic analysis of the prognostic significance and roles of the integrin alpha family in non-small cell lung cancers. *Adv Ther*. 2023;40(5):2186-2204.
47. Nikolova YS, Iruku SP, Lin CW, et al. FRAS1-related extracellular matrix 3 (FREM3) single-nucleotide polymorphism effects on gene expression, amygdala reactivity and perceptual processing speed: an accelerated aging pathway of depression risk. *Front Psychol*. 2015;6:1377.
48. Davies KA, Cooper E, Voon V, Tibble J, Cercignani M, Harrison NA. Interferon and anti-TNF therapies differentially modulate amygdala reactivity which predicts associated bidirectional changes in depressive symptoms. *Mol Psychiatry*. 2021;26(9):5150-5160.
49. Ali T, Rahman SU, Hao Q, et al. Melatonin prevents neuroinflammation and relieves depression by attenuating autophagy impairment through FOXO3a regulation. *J Pineal Res*. 2020;69(2):e12667.
50. Hirayama A, Tanaka K, Tsutsumi H, et al. Regulation of PD-L1 expression in non-small cell lung cancer by interleukin-1β. *Front Immunol*. 2023;14:1192861.
51. Mahmud A, Avramescu RG, Niu Z, Flores C. Awakening the dormant: role of axonal guidance cues in stress-induced reorganization of the adult prefrontal cortex leading to depression-like behavior. *Front Neural Circuits*. 2023;17:1113023.
52. Xia Y, Cai XY, Fan JQ, et al. The role of sema4D in vasculogenic mimicry formation in non-small cell lung cancer and the underlying mechanisms. *Int J Cancer*. 2019;144(9):2227-2238.
53. Zou T, Liu Z, Cao P, et al. Fisetin treatment alleviates kidney injury in mice with diabetes-exacerbated atherosclerosis through inhibiting CD36/fibrosis pathway. *Acta Pharmacol Sin*. 2023;44:2065-2074.
54. Amaar YG, Reeves ME. The role of RASSF1C in the tumor microenvironment. *Curr Issues Mol Biol*. 2023;45(2):1113-1126.
55. Micevic G, Daniels A, Flem-Karlsen K, et al. IL-7R licenses a population of epigenetically poised memory CD8(+) T cells with superior antitumor efficacy that are critical for melanoma memory. *Proc Natl Acad Sci USA*. 2023;120(30):e2304319120.
56. Crosson T, Wang JC, Doyle B, et al. FcεR1-expressing nociceptors trigger allergic airway inflammation. *J Allergy Clin Immunol*. 2021;147(6):2330-2342.
57. Jao TM, Wu CZ, Cheng CW, et al. Urokinase plasminogen activator deficiency aggravates cationic bovine serum albumin-induced membranous nephropathy through T helper cell type 2-Prone immune response in mice. *Lab Invest*. 2023;103(7):100146.
58. Dong L, Fu L, Zhu T, et al. A five-collagen-based risk model in lung adenocarcinoma: prognostic significance and immune landscape. *Front Oncol*. 2023;13:1180723.
59. Wei Y, Qi K, Yu Y, et al. Analysis of differentially expressed genes in the dentate gyrus and anterior cingulate cortex in a mouse model of depression. *BioMed Res Int*. 2021;2021:1-17.
60. Tian F, Wang J, Ouyang T, et al. MiR-486-5p serves as a good biomarker in nonsmall cell lung cancer and suppresses cell growth with the involvement of a target PIK3R1. *Front Genet*. 2019;10:688.
61. Mao LM, Wang JQ. Linkage of non-receptor tyrosine kinase fyn to mGlu5 receptors in striatal neurons in a depression model. *Neuroscience*. 2020;433:11-20.
62. Xue F, Jia Y, Zhao J. Overexpression of FYN suppresses the epithelial-to-mesenchymal transition through down-regulating PI3K/AKT pathway in lung adenocarcinoma. *Surg Oncol*. 2020;33:108-117.
63. Wu X, Zhu L, Zhao Z, et al. Application of machine learning in diagnostic value of mRNAs for bipolar disorder. *Nord J Psychiatry*. 2022;76(2):81-88.
64. Kowalczyk A, Nisiewicz MK, Bamburowicz-Klimkowska M, et al. Effective voltammetric tool for simultaneous detection of MMP-1, MMP-2, and MMP-9; important non-small cell lung cancer biomarkers. *Biosens Bioelectron*. 2023;229:115212.
65. Xu Y, Yang Q, Fang Z, Tan X, Zhang M, Chen W. TRIM66 promotes malignant progression of non-small-cell lung cancer cells via targeting MMP9. *Comput Math Methods Med*. 2022;2022:1-8.
66. Alaiyed S, McCann M, Mahajan G, et al. Venlafaxine stimulates an MMP-9-dependent increase in excitatory/inhibitory balance in a stress model of depression. *J Neurosci*. 2020;40(22):4418-4431.
67. Huang K, Zhang X, Duan J, et al. STAT4 and COL1A2 are potential diagnostic biomarkers and therapeutic targets for heart failure comorbided with depression. *Brain Res Bull*. 2022;184:68-75.
68. Su C, Liu WX, Wu LS, Dong TJ, Liu JF. Screening of hub gene targets for lung cancer via microarray data. *Comb Chem High Throughput Screening*. 2021;24(2):269-285.
69. Shukla R, Newton DF, Sumitomo A, et al. Molecular characterization of depression trait and state. *Mol Psychiatry*. 2022;27(2):1083-1094.
70. Xie H, Ruan G, Wei L, et al. The inflammatory burden index is a superior systemic inflammation biomarker for the prognosis of non-small cell lung cancer. *J Cachexia Sarcopenia Muscle*. 2023;14(2):869-878.
71. Mountzios G, Remon J, Hendriks LEL, et al. Immune-checkpoint inhibition for resectable non-small-cell lung cancer - opportunities and challenges. *Nat Rev Clin Oncol*. 2023;20:664-677.
72. Tsakogiannis D, Nikolakopoulou A, Zagouri F, et al. Update overview of the role of angiopoietins in lung cancer. *Medicina*. 2021;57(11):1191.
73. Çakici N, Bot M, Lamers F, et al. Increased serum levels of leptin and insulin in both schizophrenia and major depressive disorder: a cross-disorder proteomics analysis. *Eur Neuropsychopharmacol*. 2019;29(7):835-846.
74. Parker AL, Bowman E, Zingone A, et al. Extracellular matrix profiles determine risk and prognosis of the squamous cell carcinoma subtype of non-small cell lung carcinoma. *Genome Med*. 2022;14(1):126.
75. Spijker S, Koskinen MK, Riga D. Incubation of depression: ECM assembly and parvalbumin interneurons after stress. *Neurosci Biobehav Rev*. 2020;118:65-79.
76. Wadowska K, Błasiak P, Rzechonek A, Śliwińska-Mossoń M. Analysis of MMP-2-735C/T (rs2285053) and MMP-9-1562C/T (rs3918242) polymorphisms in the risk assessment of developing lung cancer. *Int J Mol Sci*. 2023;24(13):10576.
77. Ge W, Gong Y, Li Y, et al. IL-17 induces non-small cell lung cancer metastasis via GCN5-dependent SOX4 acetylation enhancing MMP9 gene transcription and expression. *Mol Carcinog*. 2023;62:1399-1416.

78. Wang X, Huang M, Xie W, Ding Q, Wang T. Eupafolin regulates non-small-cell lung cancer cell proliferation,migration, and invasion by suppressing MMP9 and RhoA via FAK/PI3K/AKT signaling pathway. *J Biosci*. 2023;48:1.
79. Jouida A, O'Callaghan M, Mc Carthy C, Fabre A, Nadarajan P, Keane MP. Exosomes from EGFR-mutated adenocarcinoma induce a hybrid EMT and MMP9-dependant tumor invasion. *Cancers*. 2022;14(15):3776.
80. Watanabe R, Maeda T, Zhang H, et al. MMP (matrix metalloprotease)-9-Producing monocytes enable T cells to invade the vessel wall and cause vasculitis. *Circ Res*. 2018;123(6):700-715.
81. Munakata S, Tashiro Y, Nishida C, et al. Inhibition of plasmin protects against colitis in mice by suppressing matrix metalloproteinase 9-mediated cytokine release from myeloid cells. *Gastroenterology*. 2015;148(3):565-578.

How to cite this article: Gui H, Chen X, Nie Y, Zhang X. Enhancing the revelation of key genes and interaction networks in non-small cell lung cancer with major depressive disorder: a bioinformatics analysis. *Health Sci Rep*. 2024;e2167. doi:10.1002/hsr2.2167