Volume 9, Issue 7, July – 2024 International Journal of Innovative Science and Research Technology
ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUL1726

Identification and Analysis of Diagnostic and Prognostic Biomarker Genes in Sepsis using Differential Gene Expression and Protein Interaction Networks

Roopender Mehala
Assistant Scientist,
People's Laboratory of Bioinformatics and System Biology, Quick Is Cool.
Patna, India

Abstract:- Sepsis, a complex medical condition characterized by physiological and biochemical abnormalities, arises from an imbalanced host response to infection. Despite its global impact, sepsis remains underreported in economically challenged nations, highlighting the need for improved diagnostic and prognostic indicators. The emergence of gene chip technology has provided insights into differential gene expression in sepsis, paving the way for identifying pivotal genes involved in disease progression.

In this study, we employed bioinformatics analysis to investigate hub genes associated with sepsis, construct a protein interaction network, and identify potential therapeutic targets. Utilizing the microarray dataset GSE95233, we conducted KEGG pathway analysis and Gene Ontology enrichment analysis through ShinyGO 0.80. Furthermore, we constructed a protein-protein interaction network using String and identified hub genes using CYTOSCAPE software. Our findings revealed a repertoire of crucial genes, including CD4, CD8A, CCL5, IL7R, MMP9, GZMB, PRF1, TBX21, S100A12, and IL2RB, displaying significant expression patterns in sepsis and septic shock patients. These genes hold great potential as diagnostic biomarkers for sepsis, offering non-invasive diagnostic approaches and serving as viable targets for future sepsis therapeutics. Moreover, our study sheds light on the diverse range of bacterial and viral infections that could contribute to the development of sepsis in affected individuals, enhancing our understanding of this intricate condition. The utilization of bioinformatics and gene expression profiling represents a promising avenue for advancing sepsis management and improving patient outcomes.

I. INTRODUCTION

Sepsis is a critical medical condition marked by profound physiological and biochemical irregularities. The Third International Consensus (Sepsis-3) presently characterizes sepsis as" organ dysfunction resulting from an imbalanced host reaction to infection," highlighting, for the initial time, the pivotal contribution of both innate and adaptive immune responses to the onset of this clinical syndrome. The prevalence and fatality rates of sepsis are alarmingly elevated, with 30 million global infections annually, leading to 8 million fatalities each year. Nevertheless, the tally of morbidity and mortality has been underreported in nations with limited development and economic challenges. Consequently, sepsis has inflicted severe physical harm and economic strain on the populace.

The challenge in effectively treating sepsis stems from its unclear pathogenesis and the scarcity of reliable indicators for clinical diagnosis and prognosis. Despite extensive research aimed at reducing patient mortality and enhancing the quality of life for those with sepsis, progress has been limited. The advent and utilization of gene chip technology have uncovered thousands of differential genes, sparking a pivotal focus on identifying those that significantly contribute to the disease. Conducting bioinformatics analysis based on gene expression profiles holds promise for screening key hub genes and regulatory pathways, playing a crucial role in early sepsis diagnosis and the establishment of proactive warning mechanisms. This technology has the potential to revolutionize our understanding and approach to managing sepsis, offering new avenues for improved patient outcomes.

In life sciences research, bioinformatics utilizes computer technology to store, retrieve, analyse, and visualize biological information. This approach has found extensive application in identifying central genes associated with diseases at the molecular level. The primary objective of this study was to investigate hub genes associated with sepsis, build a protein interaction network, and identify key molecular targets with potential therapeutic significance.

We downloaded the microarray dataset GSE95233 to identify differentially expressed genes (DEGs) associated with sepsis. Subsequently, we utilized the online tool ShinyGO 0.80 for KEGG pathway analysis and GO database for Gene ontology and functional enrichment analysis. Further, String was employed to construct a protein-protein interaction network, and hub genes were screened using CYTOSCAPE software.

II. MATERIALS & METHODS

- *Microarray Data Source:*

The dataset GSE95233 was meticulously chosen and obtained from the Gene Expression Omnibus (GEO) (https://www.ncbi.nlm.nih.gov/geo/) for my investigation. Initially, I employed "sepsis" as the keyword for retrieval, focusing on Homo sapiens as the specified species. To ensure robust data, I selected datasets with a minimum of 25 patients. Subsequently, patients diagnosed with sepsis were categorized as the "patient" group, while healthy individuals comprised the "control" group. The expression

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUL1726

profiling arrays were conducted using the GPL570 (HG-U133_Plus_2) Affymetrix Human Genome U133 Plus 2.0 Array.

➢ *Data Processing & Identification of Differentially Expressed Genes:*

The conversion of raw data was accomplished using GEO2R. GEO2R (http://www.ncbi.nlm.nih.gov/geo/geo2r), is a tool that transforms raw data into a recognizable format. The analysis focused on identifying Differentially Expressed Genes (DEGs), utilizing screening criteria of adjusted P value < 0.05 and |log fold change (LogFC)| > 2.0|. The top ten and bottom ten DEGs, sorted based on LogFC values, were specifically chosen for gene ontology (GO) and pathway enrichment analysis. This approach ensures a thorough exploration of both the most upregulated and downregulated genes in the dataset.

➢ *GO Annotation Pathway Enrichment Analysis:*

To screen out most important genes (HUB genes) the DEGs were annotated using GO database to do functional enrichment analysis. ShinyGO 0.80 online tool was used for KEGG pathway analysis to find possible pathways in which these genes involved in. The pathway enrichment analysis was performed to find out infections associated with sepsis. The excel sheet DEGs were posted on the database and the gene ontology results were retrieved. The GO were basically in three ontologies, biological processes, cellular components, and molecular functions. The visualization of the data was performed using R studio.

➢ *PPI Network Construction:*

The STRING *(version 12.0)* database was used to construct protein-protein interaction network of DEGs. The minimum combines score for construction was taken 0.4. The interaction sheet was retrieved with their respective scores.

➢ *HUB Genes Screening:*

To visualize most important genes in the protein- protein interaction network, cytoHubba plugin in Cytoscape software *(version 3.9.1)* was used. The rank of top 10 genes with their score was exported.

III. RESULTS

➢ *Identification of DEGs*

Total 28534 genes were differentially expressed between patients and control healthy volunteers. To take only significant DEGs, Log FC >|2.0| was applied and only 197 genes were collected. Out of 197 genes 68 were upregulated and 129 were downregulated. The volcano plot is showing the distribution of DEGs where red dots are showing upregulated genes and blue dots are showing downregulated genes (figure 1).

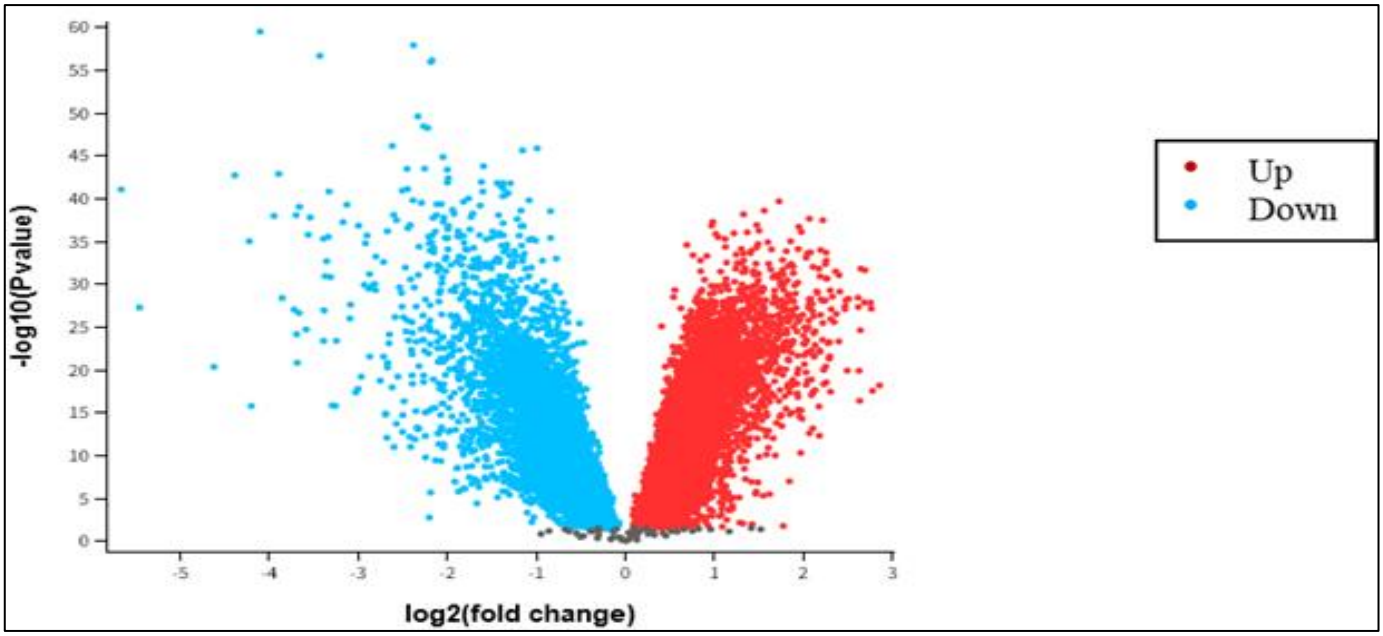

Fig 1 Volcano Plot to Check the Distribution of Differentially Expressed Genes was Plotted using GEO2R Online Tool.

Table 1 Consist of Top 10 Upregulated and Downregulated Genes with their Respective Log FC Values.

Rank	Upregulated genes	Log FC values	Downregulated genes	Log FC values
1.	GNLY	2.930062	CD177	-5.67581
2.	TBX21	2.823584	MMP8	-5.44558
3.	GPR56	2.766505	ARG1	-4.40385
4.	TRAC	2.765789	OLFM4	-4.19933
5.	S1PR5	2.719466	MCEMP1	-4.04835
6.	FGFBP2	2.706677	ANXA3	-3.90924
7.	YME1L1	2.70123	GPR84	-3.85305
8.	SAMD3	2.67052	MS4A4A	-3.7221
9.	CD8A	2.560268	ANKRD22	-3.67342
10.	CD247	2.551751	PCOLCE2	-3.65653

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUL1726

➢ *GO Annotation of DEGs:*

The GO annotation of Differentially expressed genes revealed that DEGs were involved in biological processes like neutrophil degradation, neutrophil activation, T cell activation, lymphocyte differentiation, defence response to bacterium etc figure (2). Cellular components like tertiary granule, cytoplasmic granule, vesicle lumen, specific granule membrane, and secretary granule membrane were involved figure (2). GO analysis of DEGs indicated that molecular functions like cytokine binding, immune receptor activity, RAGE receptor activity, NAD+ nucleosidase activity were involved figure (2).

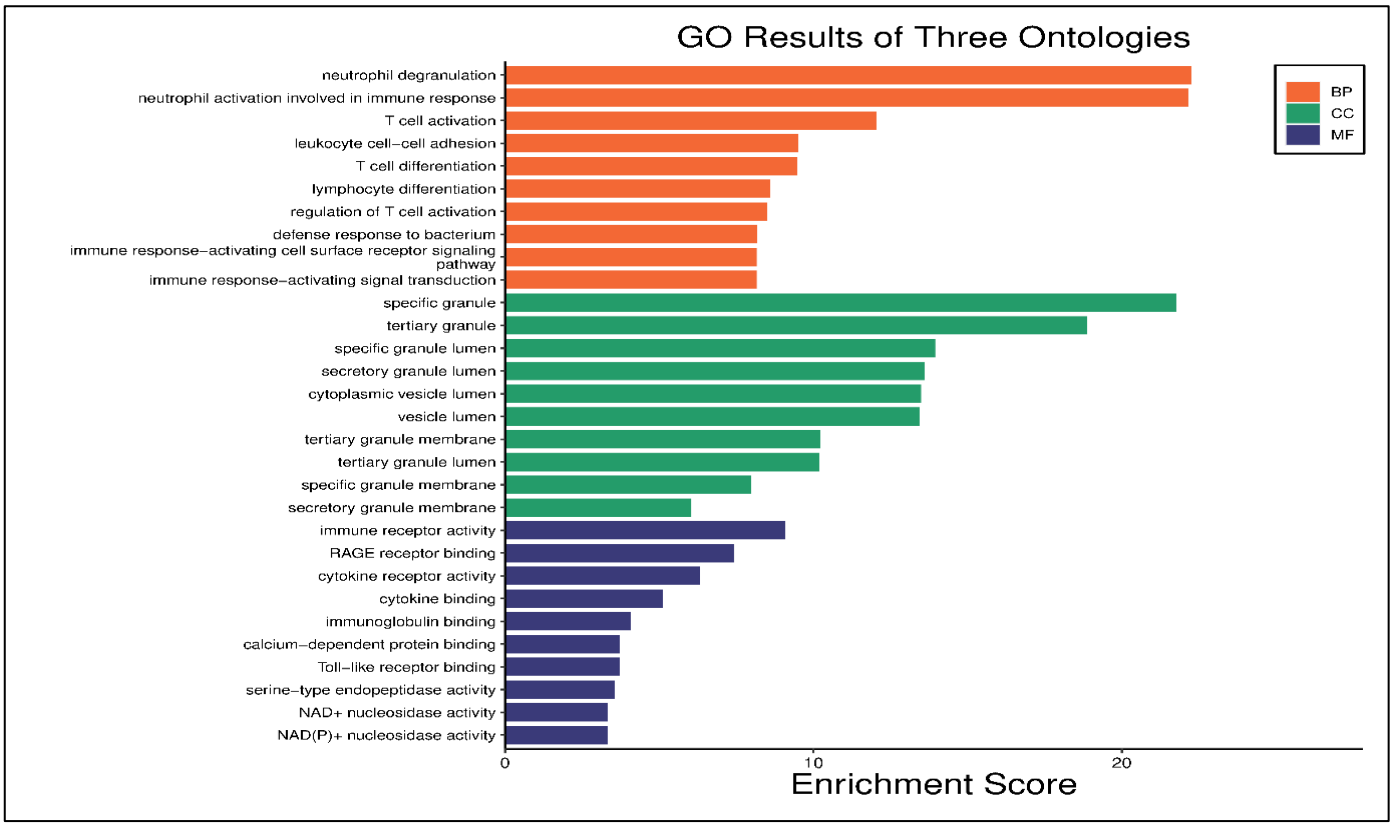

Fig 2 Three Type of Gene Ontology, Biological Process, Cellular Component, and Molecular Functions are Given in this Figure. It Shows the Expression of Highly Varied DEGs in Different Components of Cells.

➢ *KEGG Pathway Enrichment Analysis:*

Pathway enrichment analysis can help in understanding biological classification and pathogenesis of disease. KEGG pathway was conducted on ShinyGO 0.80 using differentially expressed genes to find significant signalling pathways involved. KEGG pathway analysis revealed a correlation between differentially expressed genes in dataset GSE95233 linked to sepsis and a spectrum of infections. The KEGG analysis of GSE95233 revealed that the DEGs were related to various infections such as yersinia infection, spinocerebellar ataxia, salmonella infection, human immunodeficiency virus 1 infection, shigellosis, amyotrophic lateral sclerosis, Alzheimer disease (figure: 3).

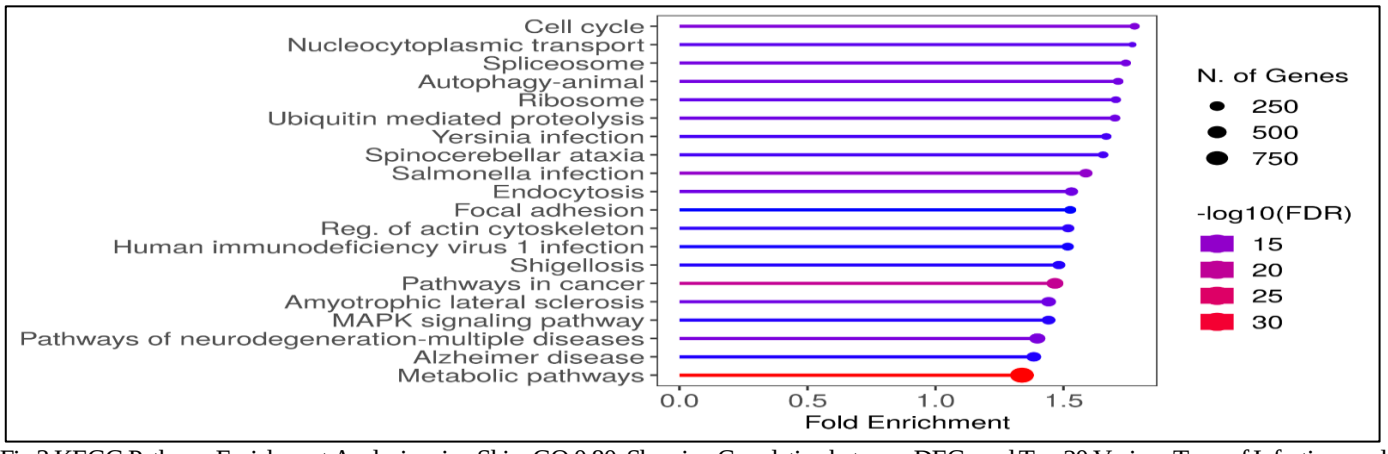

Fig 3 KEGG Pathway Enrichment Analysis using ShinyGO 0.80, Showing Correlation between DEGs and Top 20 Various Type of Infections and Disrupted Pathways. The Horizontal Axis Represent the Fold Enrichment Score and Vertical Axis is Showing Different Types of Infections and Pathways Associated with DEGs of GSE95233

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUL1726

➢ *PPI Network & Module Construction:*

The STRING database was utilized to identify a network of proteins (PPI) that interact based on genes whose expression levels significantly change under sepsis conditions (figure 4 (a)). Within this network, certain clusters of proteins, which are highly interconnected, were visualized using the MCODE plug-in in the Cytoscape software. These clusters are referred to as significant modules. The module in figure 4(b) had 26 nodes and 224 edges, it was the most noteworthy significant module. Another module in figure 4(c) had 5 nodes and 10 edges.

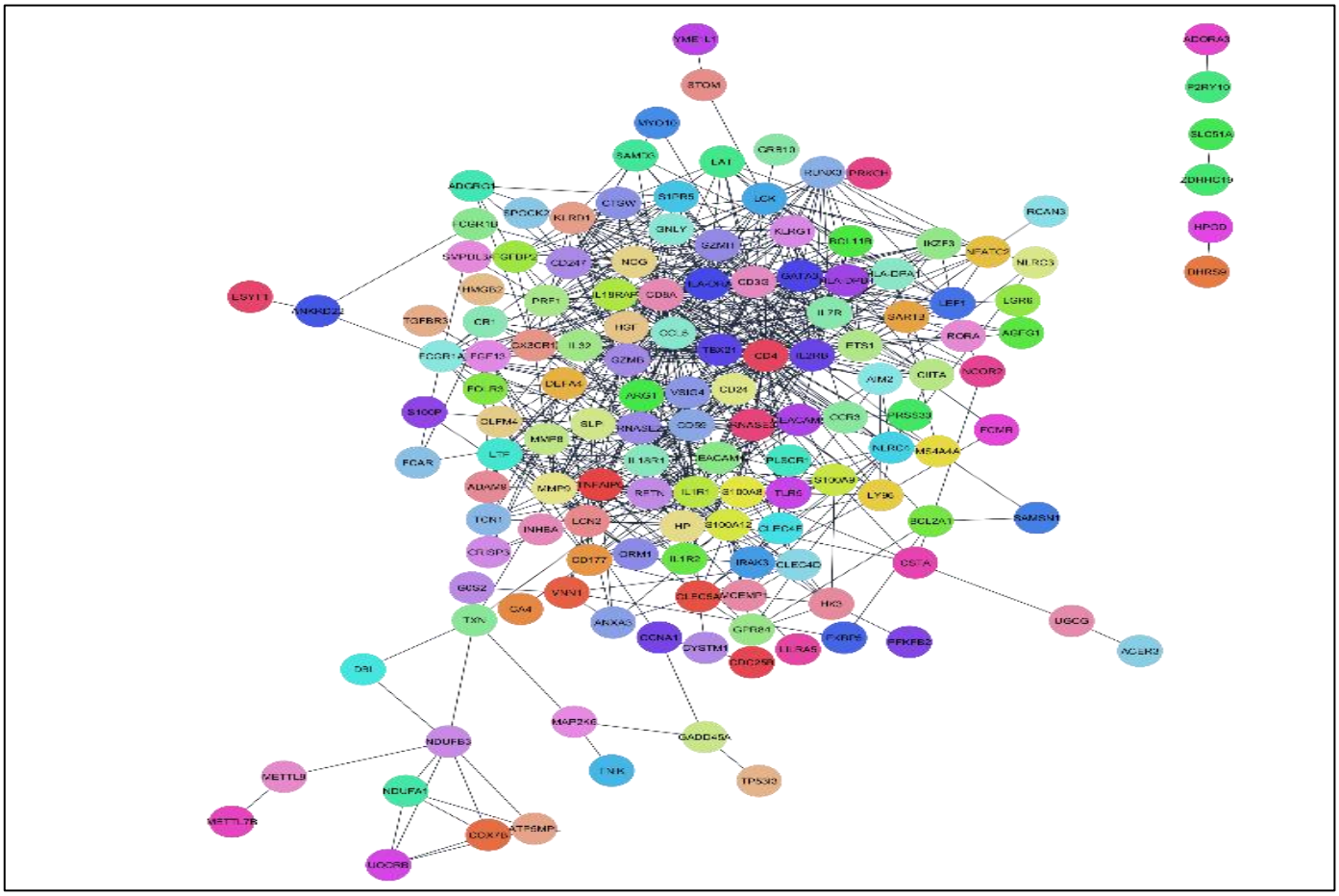

Fig 4(a) PPI Network of Intersecting DEGs Construced using STRING Database.

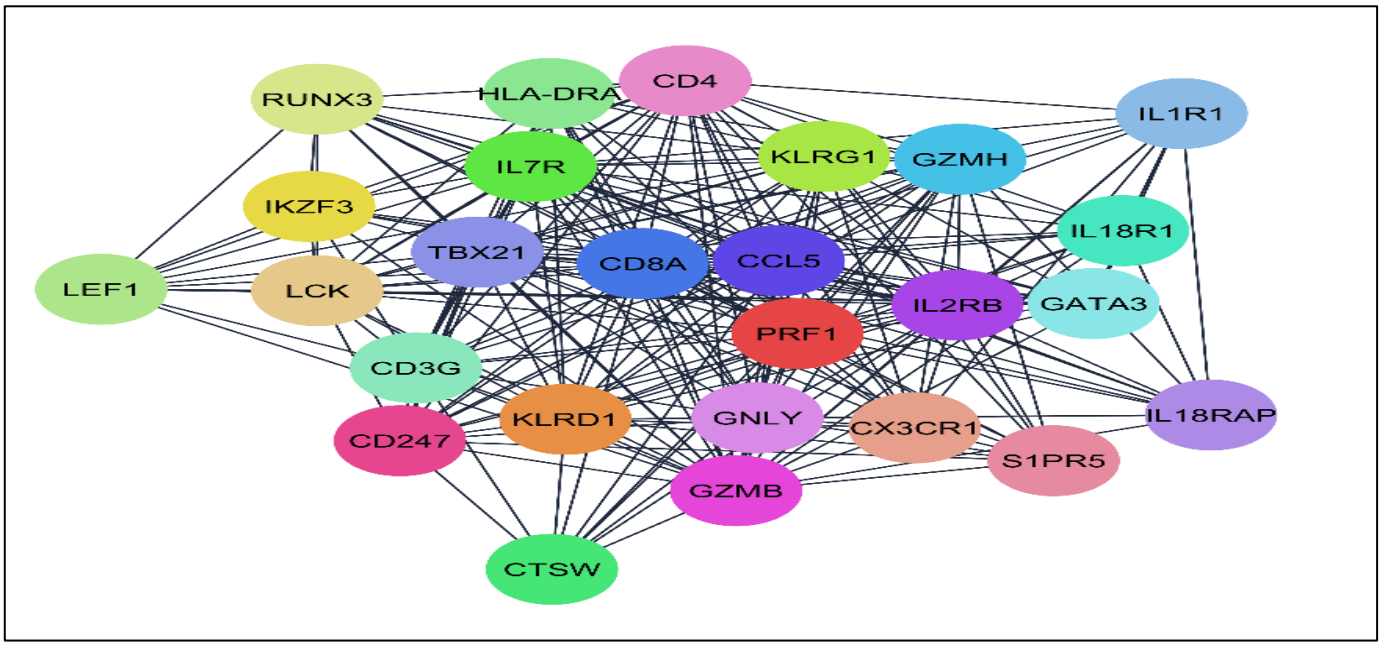

Fig 4 (b) Module Constructed using MCODE, it has 26 Nodes and 224 Edges.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUL1726

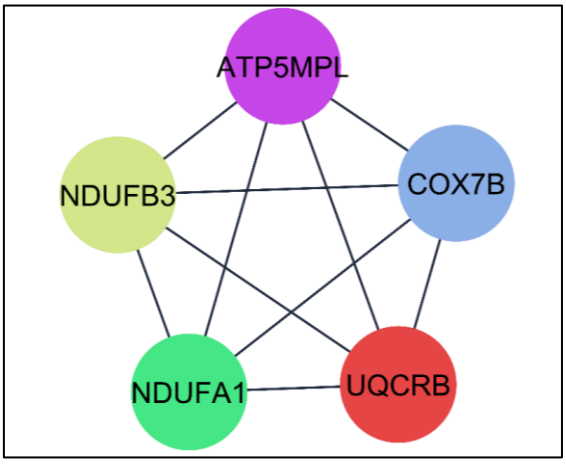

Fig 4 (c) Module had 5 Nodes and 10 Edges.

➢ *Hub Gene Screening:*

The PPI network from string was used to find some important hub genes. The CytoHubba plugin in Cytoscape was utilized and top 10 hub genes were selected, ranked with degree method. The interaction network of hub genes is shown in figure 5. Table 2 displays the collection of hub genes alongside with their respective abbreviations, functionalities, and the scores derived through CytoHubba calculations.

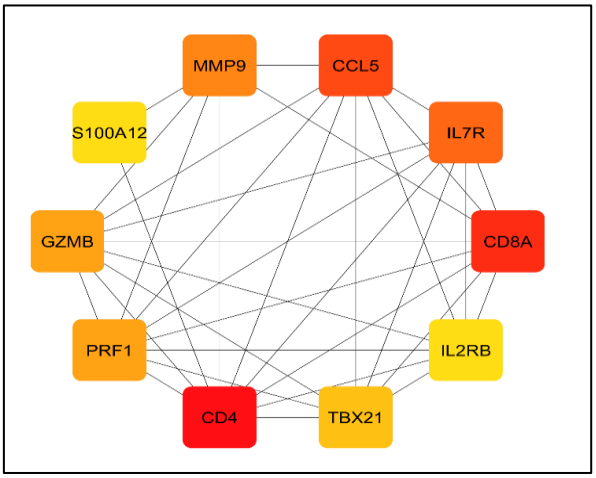

Fig 5 Interaction Network of Hub Genes Plotted using CytoHubba Plug-in of Cytoscape.

Table 2 Full Name, Score and Function of Abbreviation

No.	Abbreviation	Full Name	Score	Function
1	CD4	CD4 membrane glycoprotein of T lymphocytes.	65	Encodes the CD4 glycoprotein receptor of T lymphocytes.
2	CD8A	CD8 subunit alpha	56	Encodes the CD8A glycoprotein receptor of T lymphocytes.
3	CCL5	C-C Motif Chemokine Ligand 5	42	Chemoattractant for blood monocytes, memory T-helper cells and eosinophils. Causes the release of histamine from basophils and activate eosinophils.
4	IL7R	Interleukin 7 Receptor	35	Receptor for IL-7. Acts as a receptor for thymic stromal lymphopoietin (TSLP).
5	MMP9	Matrix Metallopeptidase 9	34	Local proteolysis of the extracellular matrix and in leukocyte migration.
6	GZMB	Granzyme B	32	Serine proteases released by cytotoxic T cells and natural killer (NK) cells. Play a crucial role in programmed cell death (apoptosis).
7	PRF1	Perforin 1	32	Encodes a protein that forms membrane pores which permit release of granzyme of target cells.
8	TBX21	T- box transcription factor TBX21	30	Lineage- defining transcription factor.
9	S100A12	S100 calcium-binding protein A12 (calgranulin C)	28	Regulation of inflammatory processes.
10	IL2RB	Interleukin-2 receptor subunit beta	28	Involved in receptor mediated endocytosis.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUL1726

IV. DISCUSSION

Bioinformatics is a multidisciplinary field that is consist of Biology, information science, statistics and many more. The research in life sciences is going data driven that's why bioinformatics plays an important role in analysing large, big data available in public databases. Sepsis represents the ultimate culmination of mortality resulting from infections and stands as a significant public health concern for healthcare systems globally [1]. The existing treatment protocol, which mainly includes antibiotics, fluid therapy, and organ support, has shown limited effectiveness in enhancing patient outcomes, resulting in ongoing high mortality rates ranging from 38.6% to 80%, varying based on the patient demographic and research findings [2]. Despite progress in medical interventions, sepsis continues to pose a significant challenge in clinical practice, persisting as a major contributor to global mortality rates, particularly evident in its high in-hospital fatality rates. Accounting for approximately 20% of worldwide mortality, sepsis stands out as one of the most critical conditions encountered in emergency departments [3] [4] [5]. An essential hurdle in the management of sepsis is the diversity found among patient populations, which includes a range of underlying conditions and immune responses. This variability presents a challenge in crafting treatment approaches that universally prove effective [6].

The increase in sepsis occurrences is linked to various factors, including an aging population, the heightened utilization of invasive surgical techniques, widespread administration of immunosuppressive drugs and chemotherapy, and the growing concern of antibiotic resistance [7]. Individuals with compromised immune systems, such as those battling HIV/AIDS, liver cirrhosis, or undergoing cancer therapies, are notably vulnerable to sepsis. According to a study conducted in a French ICU, these groups face an almost threefold (Odds Ratio 2.8) higher risk of developing sepsis [8].

Sepsis is distinguished by systemic inflammation, with clinical manifestations often involving variations in body temperature (fever or hypothermia), changes in white blood cell counts (leucocytosis and leukopenia), rapid heart rate (tachycardia), low blood pressure (hypotension), and increased breathing rate (hyperventilation). These symptoms, while common in sepsis, can also stem from non-infectious sources such as trauma or what is known as sterile inflammation. Their lack of specificity and sensitivity in detecting sepsis underscores the need for markers that facilitate early identification of sepsis and organ dysfunction, enabling prompt and targeted medical interventions. C-reactive protein (CRP) serves as a valuable indicator for identifying localized infections, while procalcitonin (PCT) shows promise in enhancing the diagnosis and treatment monitoring of individuals with sepsis and septic shock [9]. Additionally, tools such as the Sequential Sepsis-related Organ Failure Assessment (SOFA) score play a crucial role in evaluating the extent of organ dysfunction and forecasting the risk of mortality, thereby assisting in the prompt diagnosis and effective management [10].

It is important to note that systemic inflammation does not always stem from infections alone. Various conditions such as pancreatitis, trauma, or severe allergic reactions can present symptoms resembling those of sepsis. The EPIC II study offered significant revelations regarding the infectious origins of sepsis, highlighting the lungs as the predominant site of infection among patients from 75 countries [11]. These findings shed light on the urgency and intricacy of sepsis treatment, emphasizing the critical need for a comprehensive grasp of its underlying mechanisms. Sepsis is not a simple pathological condition; it presents with a range of physiological disturbances across different levels of human biology. This complex array of pathophysiological alterations, originating from and extending beyond the site of infection, calls for a comprehensive investigation into its pathogenesis and cellular mechanisms. This depth of understanding is vital not only for improving diagnostic precision and treatment effectiveness but also for advancing the prospects of personalized medicine in sepsis management.

The intricate nature of sepsis and the challenges in its treatment demand novel approaches, especially given the constraints of existing therapies. Even with the administration of broad-spectrum antibiotics, patients frequently encounter difficulties in clearing initial infections and remain vulnerable to secondary infections during their hospital stay. Strengthening immune function could play a crucial role in resolving primary infections and averting the life-threatening complications of secondary infections [12].

Modern treatment strategies and protocols have resulted in prolonged illnesses characterized by the prevalence of the immunosuppressive phase in sepsis. This trend is notably impacting the elderly population, with a considerable portion of sepsis cases and associated fatalities occurring in individuals aged 65 and above within advanced healthcare systems. The diminished effectiveness of the immune system in older adults, termed immunosenescence, coupled with the presence of comorbidities, significantly increases the susceptibility to sepsis and its mortality rates [13] [14].

Timely identification and effective management of sepsis stands as a pivotal factor in diminishing mortality rates among affected individuals. Discriminating between patients with sepsis and those manifesting systemic inflammatory responses due to non-infectious origins poses a significant challenge. The diagnosis of sepsis relies on a comprehensive approach encompassing medical history, thorough physical examinations, and various investigative procedures, including biomarker assessments, to enhance diagnostic precision. Prompt administration of antibiotics forms a fundamental aspect of sepsis management. However, judicious use of antimicrobial agents remains imperative to curb the rise of drug-resistant strains. Hence, bolstering diagnostic certainty aids in the appropriate initiation of antimicrobial treatment, with potential benefits in the de-escalation or cessation of antibiotics for critically ill patients, thereby mitigating resistance risks. Biomarkers emerge as valuable tools aiding in sepsis diagnosis, prognosis evaluation, and treatment adjustments. While numerous biomarkers exist, only a handful have earned recognition for their diagnostic capabilities, yet none have emerged as definitive indicators of sepsis diagnosis.

In present study we extracted the data from GSE95233 dataset available on NCBI database. We found that after applying logFC |>2| total 197 genes were differentially expressed out of which 68 were upregulated and 129 were downregulated. The significantly expressed genes were further used for gene annotation and pathway enrichment analysis. Results showed that DEGs in sepsis is involved in neutrophil degradation, neutrophil activation, T cell activation, lymphocyte differentiation, cytokine binding, immune receptor

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activity, RAGE receptor activity, NAD+ nucleosidase activity. KEGG pathway enrichment analysis revealed that sepsis was related to yersinia infection, spinocerebellar ataxia, salmonella infection, human immunodeficiency virus 1 infection, shigellosis, amyotrophic lateral sclerosis, Alzheimer disease. The monocyte-macrophage network forms a crucial component of the body's innate defence mechanism, significantly influencing the progression and manifestation of sepsis [15].

Protein- protein interaction network can enhance our understanding towards molecular mechanism of sepsis, DEGs were employed to analyse by PPI. PPI network revealed top 10 most important hub genes on basis of degree method, including CD4, CD8A, CCL5, IL7R, MMP9, GZMB, PRF1, TBX21, S100A12 and IL2RB.

CD4 is responsible for encoding the CD4 membrane glycoprotein found on T lymphocytes, a crucial component of the immune system. Acting as a partner to the T-cell receptor, CD4 aids in identifying antigens presented by antigen-presenting cells alongside class II MHC molecules. Functionally, the protein plays a pivotal role in kickstarting T-cell activation and could potentially contribute to secondary neuronal harm in infectious and immune-related disorders affecting the central nervous system. In studies it has shown that during a septic event/ the spontaneous decline in CD4 T cell numbers impacts various antigen-specific effector CD4 T cell groups in a random manner [16].

The integral membrane glycoprotein CD8A plays a crucial role in orchestrating immune responses, serving multiple functions in defending against both internal and external threats to the body's well-being. It has been found that CD8 T cells exhibit heightened proliferation in septic patients compared to healthy individuals, this increased proliferation alters the composition and tissue distribution of memory CD8 T cells [17]. CCL5 is a crucial regulator of the body's response to infection during sepsis. Studies have suggested that CCL5 influences the host's immune response by interacting with a receptor called CCR1. When CCL5 binds to CCR1, it increases NF-kB activation and CLP-induced inflammatory cytokine production [18]. The IL7R receptor emerges as a promising biomarker in individuals with septic shock, with its diminished expression noted in such patients, while those exhibiting a lower risk of mortality display heightened levels of IL7R expression [19]. Gene expression of MMP-9 has shown significant increase during CLP induced sepsis in rats [20]. GZMB has shown increased proportion in sepsis patient compared to healthy volunteers [21], although expression of granzyme family depends on cause of sepsis. The granule exocytosis mechanism represents a distinct pathway for the targeted intracellular transportation of proteins, through which lymphocytes deploy perforin alongside Gzms. Perforin (PRF1) acts as the conduit for granzymes, facilitating their entry into the cytosol of target cells to execute diverse effector roles, encompassing both cytotoxic and non-cytotoxic functions [22].

TBX21 serves as a transcriptional activator, driving the expression of a distinct cluster of genes essential for the specialized functions of Th1 cells. Meanwhile, S100A12, characterized by its ability to bind calcium and copper ions, assumes a pivotal role in the regulation of inflammatory responses. Its activities encompass the recruitment of leukocytes, enhancement of cytokine and chemokine production, and the precise modulation of leukocyte adhesion and migration within the intricate framework of the immune system. S100A12 has shown increased plasma level in septic shock patients, making it a promising biomarker [23]. The beta subunit of the interleukin-2 receptor (IL2RB) plays a crucial role in receptor-mediated endocytosis and transduction of mitogenic signals. It collaborates with IL15RA, contributing to the stimulation of neutrophil phagocytosis by interleukin-15 (IL-15) [24].

V. CONCLUSIONS

In conclusion, our study has identified a repertoire of crucial genes, namely CD4, CD8A, CCL5, IL7R, MMP9, GZMB, PRF1, TBX21, S100A12, and IL2RB, exhibiting notable expression patterns in individuals afflicted with sepsis and septic shock. These genes hold considerable promise as diagnostic biomarkers for sepsis, offering potential avenues for non-invasive diagnostic approaches and serving as plausible targets for future sepsis therapeutics. Furthermore, our findings shed light on the diverse array of bacterial and viral infections that may underlie the etiology of sepsis in affected patients, thereby enriching our understanding of this complex condition.

ACKNOWLEDGMENT

I would like to express my deepest gratitude to my family. Their constant support throughout this journey helped me to complete this project. I also want to than me for believing in me. I am also thankful to the Quick IsCool, for providing a good environment and their support throughout this project.

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