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Original Article

NAMPT-associated gene signature in the prediction of severe sepsis

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Abstract: Objective: Sepsis is a life-threatening condition of severe organ dysfunction induced by uncontrolled infection and dysregulated host response. However, standardized clinical biomarkers for sepsis are needed to improve patient care, especially in intensive care units (ICUs). Nicotinamide phosphoribosyltransferase (NAMPT) regulates the activity of nicotinamide adenine dinucleotide (NAD)-dependent enzymes and modulates multiple metabolic pathways. Elevated NAMPT gene expression is a risk factor in the pathogenesis and development of sepsis, which is strongly linked to patient morbidity and ICU mortality. At present, there is no identified NAMPT gene signature for prognosis of sepsis patients. Methods: By analyzing gene expression profiles in peripheral blood mononuclear cells, this study was designed to establish a NAMPT-associated biomarker that effectively predicts survival in sepsis patients. Results: We obtained 19 common genes by intersecting NAMPT-associated genes and sepsis survival-related genes, and this 19-gene signature is significantly enriched in metabolic pathways and NF-κB pathways related to sepsis development. Notably, this 19-gene NAMPT signature was able to discriminate high-risk sepsis from low-risk sepsis in both discovery and validation cohorts. Furthermore, we confirmed that this 19-gene NAMPT signature performed significantly better for sepsis prognosis than random gene sets with 19 genes. Conclusions: We identified a novel NAMPT gene signature with effective prognostic power for sepsis. Further studies focusing on these biomarkers may also provide an early intervention system for sepsis treatment.

Keywords: NAMPT, gene signature, sepsis

Introduction

Sepsis is a life-threatening condition of severe organ dysfunction induced by uncontrolled infection and dysregulated host response. Sepsis-induced shock is responsible for high mortality in intensive care unit (ICU) patients: the life of approximately one in three patients is threatened by sepsis [1, 2]. Adequate intervention at the early stage of sepsis can notably improve the survival rate of patients with severe sepsis. Thus, early diagnosis and accurate prognosis are essential for care of sepsis patients [3].

Several scoring criteria for predicting clinical outcome of sepsis, such as the sequential organ failure assessment (SOFA), quick SOFA (qSOFA) score, host systemic inflammatory response syndrome (SIRS) and early warning scores (EWS), have been developed and are currently utilized. However, these scores are often cumbersome to calculate and difficult to externally validate in heterogeneous ICU populations [4]. Contemporary available individual biomarkers for sepsis typically include proinflammatory cytokines, procalcitonin (PCT), C-reactive protein (CRP), or anti-inflammatory cytokines, among others [5, 6]. Nevertheless, these biomarkers are highly variable and inadequately standardized. Because of these limitations, the need for a reliable and consistent sepsis biomarker remains high.

Nicotinamide phosphoribosyltransferase (NAMPT) has been identified as a risk factor in the development of sepsis [7]. NAMPT has both intra- and extracellular forms [8]. Intracellular NAMPT (iNAMPT) is a crucial enzyme in the nicotinamide adenine dinucleotide (NAD) biosyn-

Table 1. The NAMPT-related gene signature

Gene Name	Log (Fold Change)
ALDH18A1	1.3383
BST1	-1.0022
CFD	0.7968
ERO1 L	-0.6556
GSR	-0.6131
IDH2	0.6126
KYNU	0.6943
LCN2	-0.7511
PARP1	0.8638
PEPD	0.8571
POU2F2	1.3669
PPARG	-0.9355
PTGS2	0.7048
QPRT	0.7197
RETN	-1.6697
SARM1	0.853
SIRT5	-1.4172
SREBF1	0.6352
TLR4	-0.5983

thetic pathway [9] that regulates the activity of NAD-dependent enzymes such as sirtuins while also modulating lipid and glucose metabolism, apoptosis, inflammation, stress response, and the immune system. eNAMPT is an extracellular form of NAMPT that acts as a cytokine and has also been identified as a pre-B-cell colony enhancing factor [10]. A positive correlation has been found between NAMPT and other markers (peripheral blood mononuclear cells or PBMCs, CRP, and PCT) for sepsis [11]. High gene or protein expression levels of NAMPT are commonly associated with severe sepsis and increased likelihood of ICU mortality among high-risk sepsis patients [12].

In recent years, gene expression profiles in blood or tissue samples have been successfully utilized to discover new biomarkers for numerous diseases. Gene expression profiling provides concurrent assessment of multiple genes by utilizing next-generation sequencing-based techniques such as microarray or RNA sequencing (RNA-seq) to identify gene clusters that illustrate a coordinated pattern of gene expression [13]. Gene expression profiling has also resulted in the discovery of several gene expression biomarkers of possible diagnostic and prognostic importance in sepsis. Whole blood samples of patients with sepsis can be obtained and monitored more conveniently than tissue samples.

This study aimed to use a genomic classification model to generate a NAMPT-associated gene signature as a new method to predict the survival of patients with severe sepsis. This is a novel and important step toward individualized treatment for sepsis patients.

Materials and methods

Microarray datasets

We searched the ArrayExpress and Gene Expression Omnibus (GEO) databases, and two ArrayExpress datasets (E-MTAB-4421 and E-MTAB-4451) meeting the following criteria were included in our study: 1) RNA samples extracted from human peripheral blood mononuclear cell (PBMC) samples. 2) Microarray datasets with clinical information. 3) Sample count > 100.

E-MTAB-4421, involving 265 sepsis patients with clinical information, was assigned as the discovery cohort. Samples from survivors were assessed at 4 weeks after intensive care unit (ICU) admission. E-MTAB-4451, including 106 sepsis survivors (Supplementary Table 1), was assigned as the validation cohort. RNA samples were obtained by quickly isolating PBMCs.

Sepsis survival-related genes

The R packages “limma” (version 3.13) and “gcrma” (version 3.13) were used to detect DEGs between SHR and SLR in the discovery cohort, which were considered to be sepsis survival-related genes.

Risk score

The risk score uses a linear combination of gene expression values and corresponding weight values in NAMPT-GS. The formula for the risk score is:

$$risk\ score = \sum_{i=1}^{n} W_i \left(\frac{e_i - \mu_i}{s_i} \right)$$

where n represents the count of genes included in NAMPT-GS for each dataset, Wi shows the

Table 2. Weight value of the NAMPT-related gene signature

Genes	Weight
ALDH18A1	1
BST1	-1
CFD	1
ERO1 L	-1
GSR	-1
IDH2	1
KYNU	1
LCN2	-1
PARP1	1
PEPD	1
POU2F2	1
PPARG	-1
PTGS2	1
QPRT	1
RETN	-1
SARM1	1
SIRT5	-1
SREBF1	1
TLR4	-1

weight value of each gene (see **Table 2**), ei shows the expression level of each gene, and μi and si are the corresponding mean and standard deviation value for the ITH gene among whole samples.

Enrichment analysis

To analyze the identified genes at the biological pathway level, database for annotation, visualization and integrated discovery (DAVID) v6.8 (https://david.ncifcrf.gov/tools.jsp), an online biological and functional annotation database, was used to provide interpretation of gene ontology and signaling pathways for our gene lists.

Protein-protein interaction network

STRING (https://string-db.org) [14] is an online database (version 11.0b) used for evaluating PPI information for a list of proteins. To estimate PPI relationships, the 19 identified genes were mapped by STRING, and interactions with a combined score of over 0.4 were selected to generate a PPI network. The PPI network information was downloaded and visualized in Cytoscope (version 3.8.2).

Statistical analyses

Statistical calculations in this study were executed in R language. R packages (ade4 and pROC) were used to generate PCA plots and ROC curves. A false discovery rate (FDR) < 0.05 was considered significant in this study.

Results

After searching the GEO and Array Express databases, E-MTAB-4421 (https://www.ebi.ac.uk/arrayexpress/experiments/E-MTAB-4421/) [15] with 265 patients was selected as the discovery cohort in our study. Transcriptomic analysis of PBMCs from patients of the E-MTAB-4421 dataset defined two distinct clusters associated with different 14-day mortality. Ward's method, Euclidean distance, and k-means were utilized to establish the proper clustering. Our grouping method was based on these two clusters, with 108 sepsis patients with higher mortality assigned to the high-risk sepsis (SHR) group and the other 157 assigned to the low-risk sepsis (SLR) group. Compared to SLR, SHR displayed functional differences in T-cell activation, cell death, and apoptosis.

In the discovery cohort, a total of 2722 differentially expressed genes (DEGs) were identified between the SHR and SLR groups with the following cutoffs: fold change |FC| > 1.5 and false discovery rate (FDR) < 5%. We defined these DEGs as sepsis survival-related genes in this study. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis showed metabolic pathways, T-cell receptor signaling pathways, Th17 differentiation, and NF-κB signaling pathways (**Figure 1A**) to be enriched among these 2722 genes. We also performed gene set enrichment analysis (GSEA) on the discovery cohort, revealing some signaling pathways, such as cell adhesion molecules and pyrimidine metabolism, to be downregulated in SHRs (**Figure 1B**).

The STRING database 14 (https://string-db.org) combines all known and predicted interactions between proteins, comprising both direct molecular interactions and biological associations. We obtained all NAMPT-associated genes from the STRING database.

A total of 131 genes were identified as NAMPT-associated genes (minimum interaction score

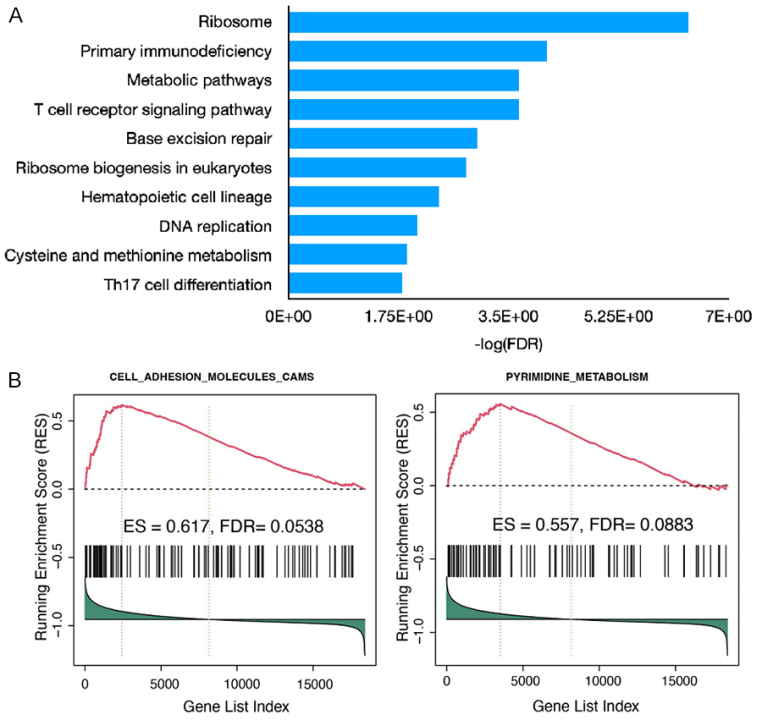

Figure 1. Sepsis survival-related genes. A. Enriched pathways among sepsis survival-related genes. B. Gene set enrichment analysis in discovery cohort.

0.4; Supplementary Table 2). Several metabolic pathways, such as nicotinate and nicotinamide metabolism, nonalcoholic fatty liver disease, and purine metabolism, were enriched among the NAMPT-associated genes, validating the key role of NAMPT-associated genes in the regulation of cellular metabolism (**Figure 2A**). Immune pathways such as the interleukin-17 (IL-17) signaling pathway, cytokine-cytokine receptor interaction, and JAK-STAT signaling pathway were also enriched among NAMPT-associated genes. These results are consistent with NAMPT's biologic functions (**Figure 2A**).

We generated a protein and protein interaction (PPI) network and corresponding clusters to confirm interactions between these 131 genes. The PPI network identified 3 main clusters among the 131 genes (**Figure 2B**). Metabolic pathways such as nicotinate and nicotinamide metabolism, nonalcoholic fatty liver disease, and purine metabolism were enriched in Cluster 1; other metabolic pathways such as arginine and proline metabolism as well as the AMP-activated protein kinase (AMPK) signaling pathway were enriched in Clusters 2 and 3 (**Figure 2C**).

To develop a method that can evaluate the probability of a clinical outcome in each sepsis patient from the transcriptome data we analyzed, a risk score was established using a formula consisting of linear combinations of the included genes, whereby a higher risk score correlates with a worse prognosis and survival rate. We examined the risk score of the single gene encoding NAMPT and found that the corresponding risk score for SHR was significantly higher than the corresponding risk score for SLR in both the discovery (P = 4e-15) and validation (P = 1.1e-06) cohorts (**Figure 3A**). However, the area under the receiver operating characteristic (ROC) curve (AUC) value of the single NAMPT gene for both the discovery (AUC: 0.66) and validation (AUC: 0.63) cohorts was relatively low (**Figure 3B**). Single biomarkers have the characteristics of poor sensitivity and/or specificity in estimating the severity of sepsis. Moreover, a biomarker comprising a single gene cannot sufficiently reveal the status of a patient's disease. Hence, we next attempted to utilize NAMPT-associated genes to establish a new biomarker containing multiple genes.

By intersecting the 131 NAMPT-related genes and the 2722 sepsis survival-related genes, we identified 19 overlapping genes (**Figure 4A**). These 19 genes were used as our NAMPT-related gene signature for sepsis (NAMPT-SG) in this study (**Table 1**), with the same pattern of variation in the discovery and validation cohorts (Supplementary Figures 1, 2). Hypergeometric testing confirmed that this overlap was statistically significant (p value < 0.05), suggesting that NAMPT-associated genes are significantly enriched among sepsis survival-related genes. Signaling pathways such as nicotinate and nicotinamide metabolism, metabolic pathways and the NF-κB signaling pathway, among others (**Figure 4B**), were found to be significantly enriched among these 19 genes. We generated a heatmap that indicated that these 19 genes

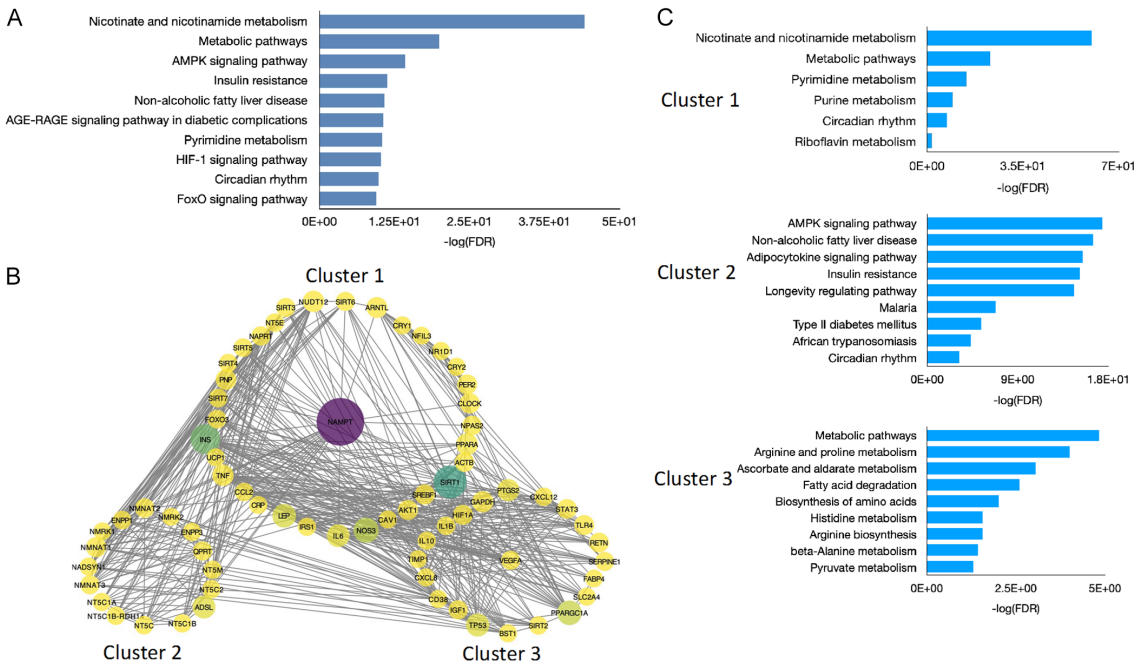

Figure 2. NAMPT-related genes. A. Enriched pathways among NAMPT-related genes. B. Protein and protein interaction network for NAMPT-related genes. C. Enriched pathways among three clusters from NAMPT-related genes.

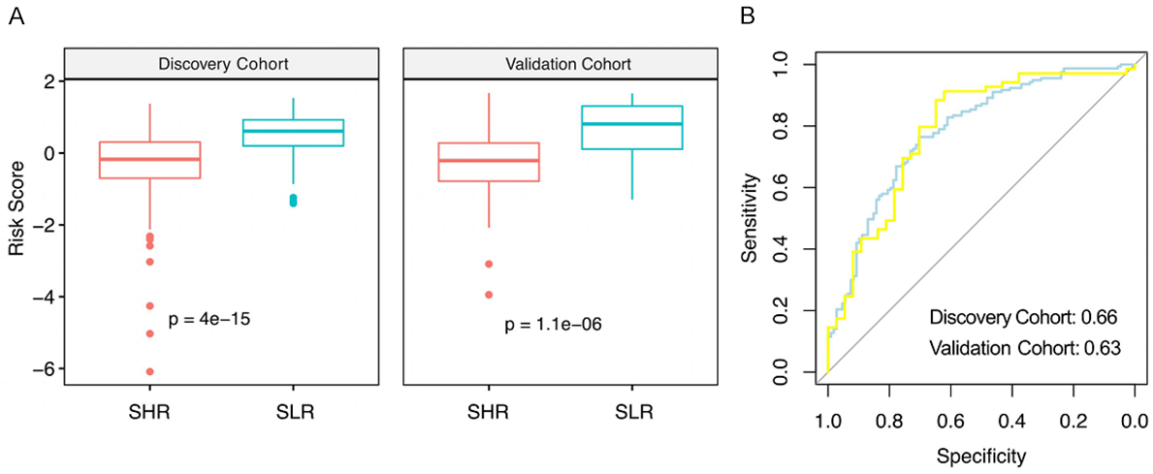

Figure 3. NAMPT single gene-based sepsis risk score differentiates non-survivors from survivors in both the discovery and validation cohort. A. Box plot of the risk scores in non-survivors and survivors. B. ROC curves of the NAMPT single gene signature in distinguishing non-survivors from survivors.

(NAMPT-SG) can discriminate SHR from SLR in the discovery cohort (**Figure 4C**).

Our results confirm that the NAMPT gene signature shows robust interaction with sepsis survival-related genes. More specifically, the results suggest that NAMPT-SG establishes a link between NAMPT-associated proteins, signaling pathways and sepsis prognosis. Risk scores were significantly increased in the SHR group in both the discovery (p value < 2e-16) and validation (p value = 5.8e-13) cohorts (**Figure 5A**), affirming that NAMPT-SG can estimate clinical outcome in sepsis.

Validation of the NAMPT-SG categorization was performed by determining the dataset's capability to distinguish between groups. Excellent

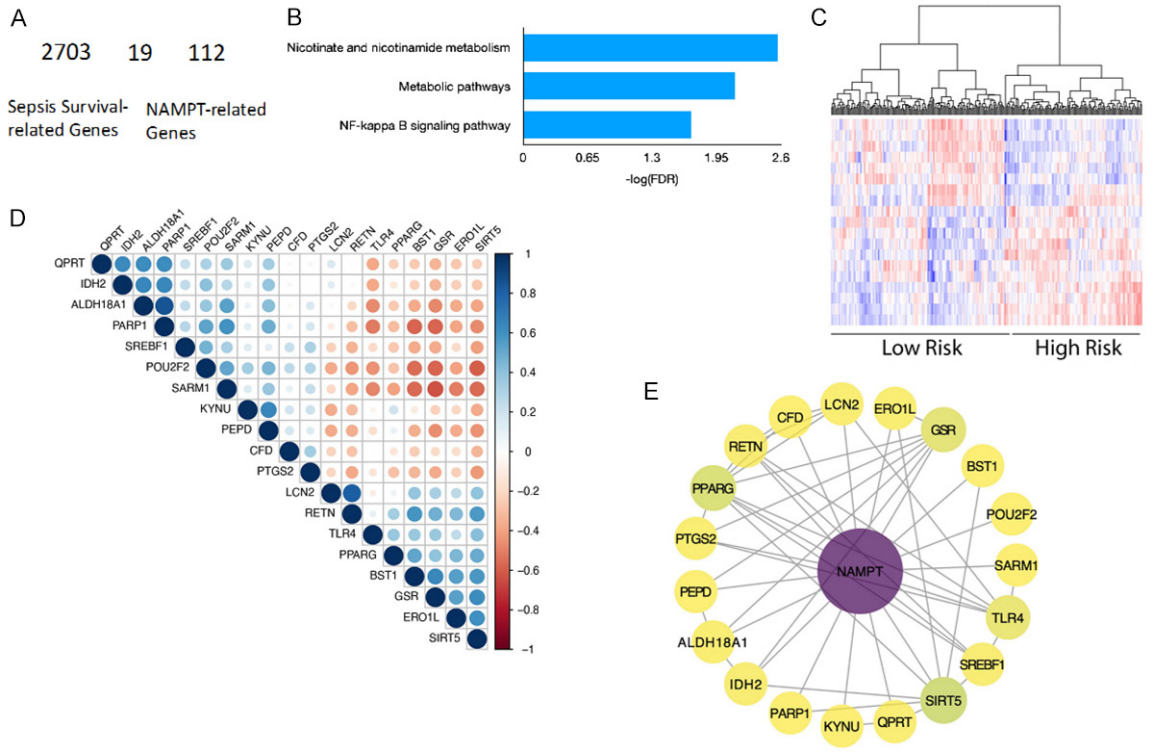

Figure 4. The NAMPT-related sepsis gene signature. A. Venn plot of intersection of sepsis survival-related genes with NAMPT-related genes. B. Enriched KEGG pathways among 19 genes. C. Heatmap shows gene expression of sepsis survival-related genes in the discovery cohort. D. Pearson correlations matrix in discovery cohort. E. Protein and protein interaction network for 19 genes.

AUC values for both the discovery (AUC: 0.98) and validation (AUC: 0.88) cohorts were obtained (**Figure 5B**). NAMPT-GS demonstrated excellent ability in classifying sepsis patients based on the sum of AUC values relative to random gene sets with 19 genes from whole protein-coding genes or survival-associated genes (**Figure 5C**). Additionally, we conducted principal component analysis (PCA) on our 19-gene expression model to reduce its dimensionality and examine the similarity between each sample. In both the discovery and validation cohorts, PCA showed that the 19 genes can entirely or mostly differentiate SHR from SLR patients (**Figure 5D**).

An additional whole blood sample dataset with sepsis (GSE54514) was added for comparison and validation. Six genes of NAMPT-SG and the overall risk score for each patient were significantly higher in sepsis non-survivors (Supplementary Figures 3, 4), which indicates that our NAMPT-SG can be verified using the clinical samples of other studies.

Discussion

Sepsis is a systemic inflammatory response syndrome to infection with a mortality rate of up to 40%. Sepsis with signs of shock (e.g., hypotension, fever, altered mental status) indicates disruption of normal metabolic function that requires stabilization in a critical care setting [16], with prompt and adequate treatment. Due to its multiple functions, NAMPT has been associated with multiple human health disorders, including sepsis. Various studies have demonstrated that NAMPT is a genetic risk factor in sepsis [17, 18], highlighting it as a valuable biomarker for clinicians. Discovering NAMPT-based gene signatures in sepsis will uncover previously unknown biological characteristics of the pathogenesis of this condition. We utilized two microarray datasets from the Array Express database involving PBMC samples from sepsis patients with survival details to determine a NAMPT gene signature. This study provides the following results: (1) discovery of a NAMPT-associated gene signature that

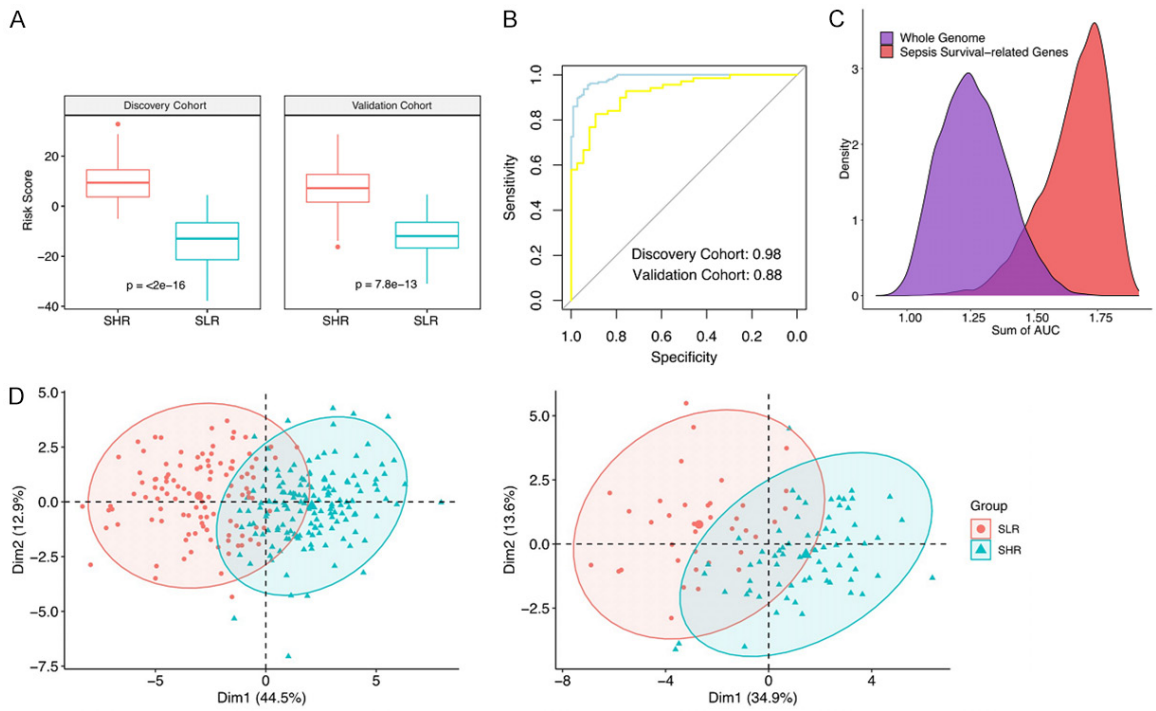

Figure 5. The 19-gene signature-based sepsis risk score discriminates non-survivors from survivors. A. Box plot of the risk scores in non-survivors and survivors. B. ROC curves of the 19-gene signature in discriminating non-survivors from survivors. C. Predictive power of the NAMPT-related gene signature in the discovery and validation cohort compared with random 19-gene. D. PCA plot of NAMPT gene signature for the discovery cohort and validation cohort.

can differentiate high-risk from low-risk sepsis patients at the gene expression level; (2) enriched signaling pathways including metabolism and immune response signaling pathways among our gene signature links NAMPT biological processes with severe sepsis.

Biomarkers for the diagnosis or prognosis of sepsis might provide better targeted early intervention, thus lowering the risk of morbidity and mortality in patients with the highest risk. To date, lactic acid is the most regularly used biomarker to determine sepsis, with other biomarkers employed to increase or decrease lactate's predictive value, as elevated lactate alone is nonspecific. High-throughput gene expression profiling technologies such as microarrays and RNA sequencing generate a large gene expression dataset that can be utilized for the discovery of biomarkers. Gene signatures from gene expression profiling have enormous potential for disease diagnosis, prevention, prognosis, and treatment. These gene signatures can also be used for discovering key genes and pathways related to the development of diseases.

Several metabolic signaling pathways were found to be enriched in NAMPT-GS, including NF-κB. Understanding the role of metabolic disorders in the development of sepsis can provide better knowledge or potential new therapies for sepsis patients. NF-κB activation is associated with systemic inflammation [19]. Inhibition of the NF-κB pathway ameliorates vascular derangement, inhibits proinflammatory gene expression, decreases intravascular procoagulation, and ameliorates microvascular endothelial leakage. These pathways identified by our NAMPT gene signature show that this gene signature can both experimentally estimate the outcome of sepsis patients and reveal underlying molecular mechanisms in the pathologic processes of sepsis.

Jia et al. first reported that NAMPT in whole blood from severe sepsis patients is increased compared with that in mild patients. Bajwa et al. [20] showed that the NAMPT-1001T > G variant allele is strongly associated with developing acute respiratory distress syndrome (ARDS). NAMPT in peripheral blood plays a vital role in sepsis progression. Our NAMPT-

associated gene signature expands the molecular mechanisms of how NAMPT affects sepsis progression.

In summary, our results demonstrate that the 19-gene NAMPT signature we generated has value in clinical evaluations and disease monitoring for patients with sepsis and may ultimately improve contemporary sepsis treatment methods.

Disclosure of conflict of interest

None.

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Supplementary Table 1. Summary of sepsis patients included in the discovery and validation cohorts

	Discovery Cohort (n=265)	Validation Cohort (n=106)
Age (years)	62 (16)	69 (14)
Male Percentage (%)	55	79
APACHE II score	18 (7)	23 (9)
SOFA score	6 (4)	7 (4)

Supplementary Table 2. NAMPT-associated genes

Gene Name
ACTB
ADIPOQ
ADIPOR1
ADIPOR2
ADSL
AGT
AKT1
ALDH18A1
ALDH7A1
ALDH9A1
ANKFY1
APLN
ARNTL
ASS1
BGLAP
BST1
CAV1
CCL2
CD38
CERS4
CFD
CISD1
CLOCK
CRP
CRY1
CRY2
CXCL12
CXCL8
CYBB
CYP4A22
ENPP1
ENPP3
ERO1L
FABP4
FGF21
FNDC5
FOXO1
FOXO3
GAPDH
GCG

GHRL
GSR
H6PD
HAAO
HIF1A
HNRNPH1
IDH2
IGF1
IL10
IL1B
IL6
IL7
INS
IRS1
ITLN1
KYNU
LCN2
LEP
LEPR
LTA4H
METRNL
MLXIPL
MRPL10
MT-ND1
MVD
NADK
NADSYN1
NANS
NAPRT
NFIL3
NMNAT1
NMNAT2
NMNAT3
NMRK1
NMRK2
NNMT
NOS3
NPAS2
NR1D1
NT5C
NT5C1A
NT5C1B
NT5C2
NT5E
NT5M
NUDT12
NUDT15
PARP1
PEPD

PER2
PER3
PGBD5
PNP
POU2F2
PPARA
PPARG
PPARGC1A
PTGS2
QPRT
RARRES2
RBP4
RETN
SARM1
SERPINA12
SERPINE1
SIRT1
SIRT2
SIRT3
SIRT4
SIRT5
SIRT6
SIRT7
SKP1
SLC2A4
SOD2
SREBF1
STAT3
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TNF
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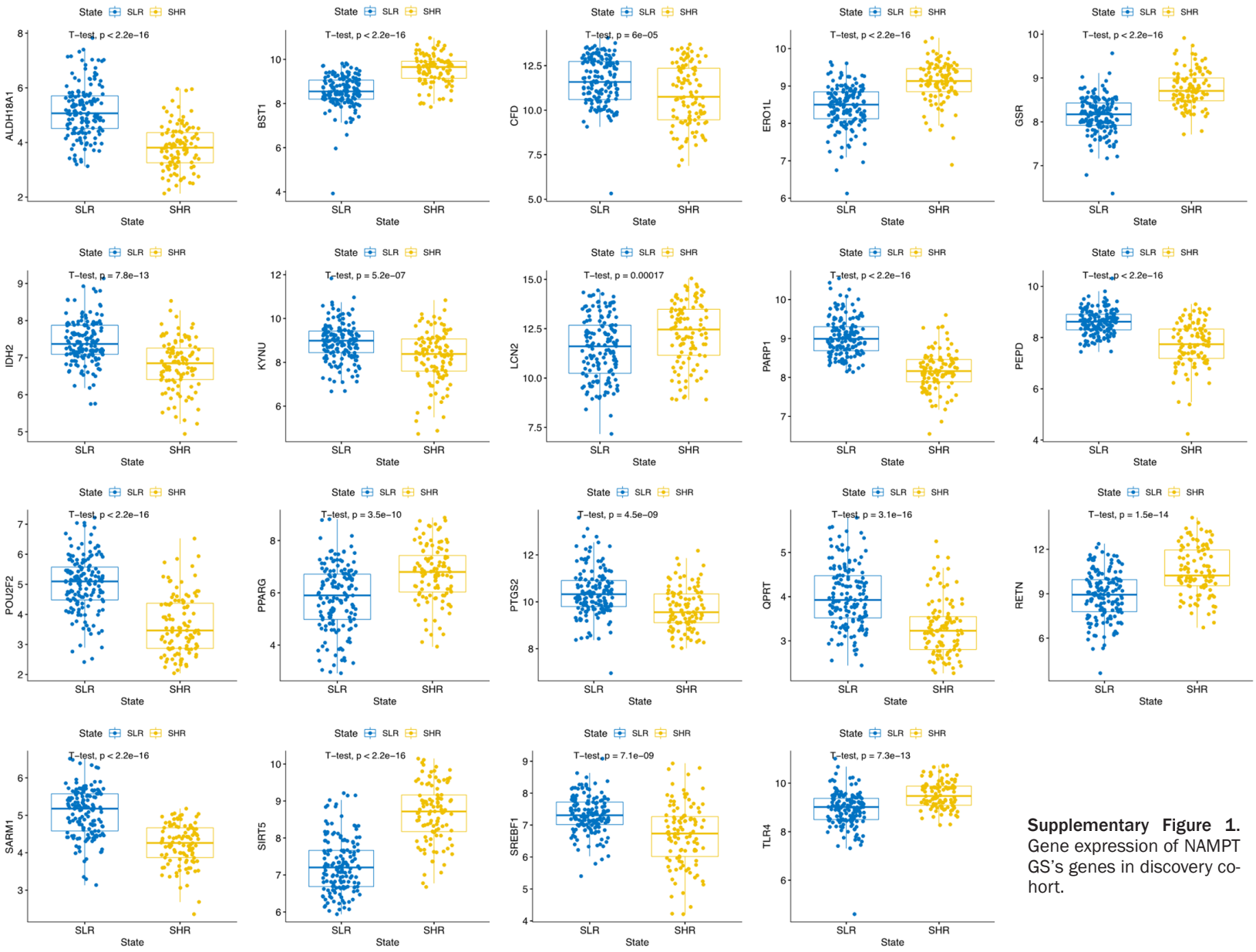
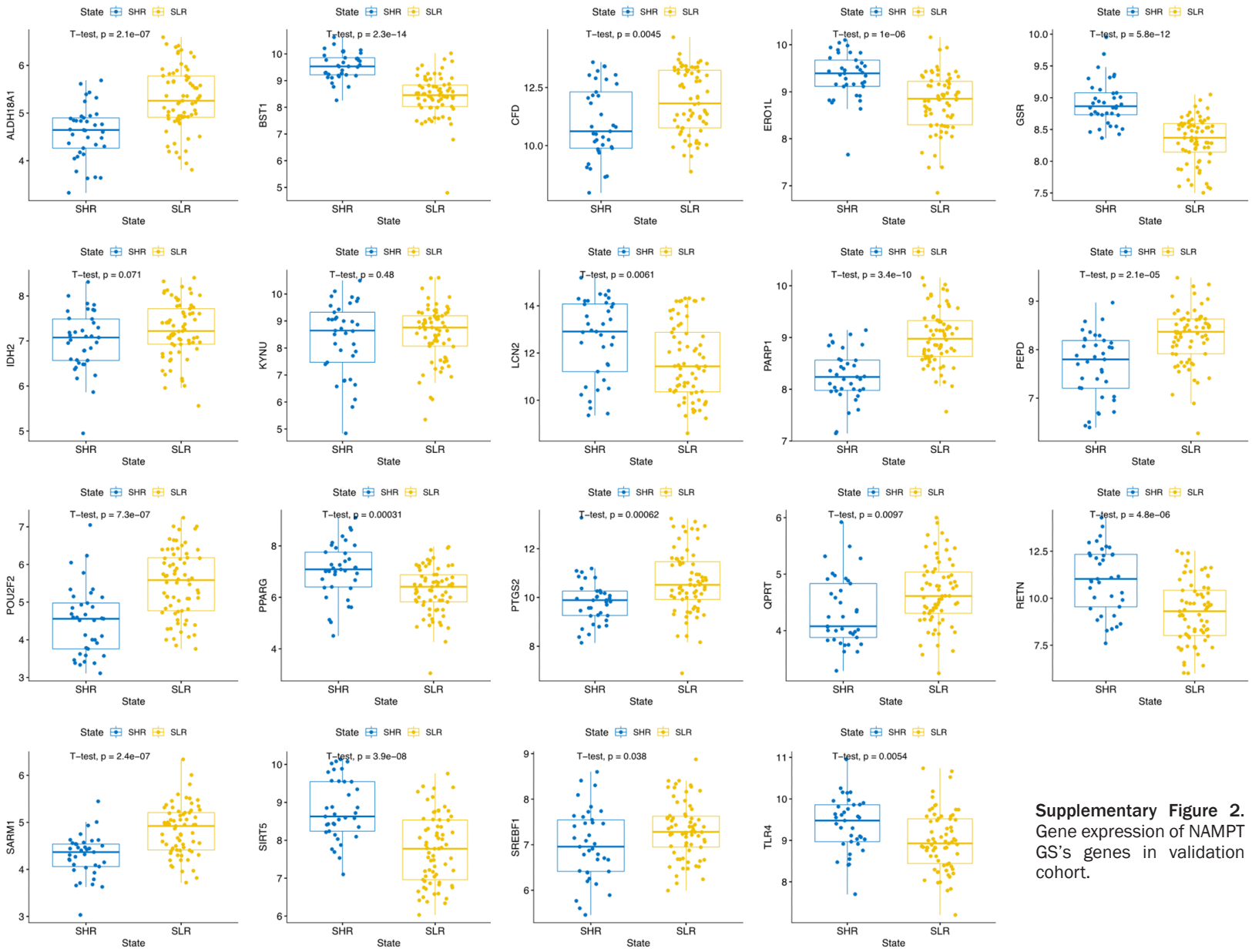
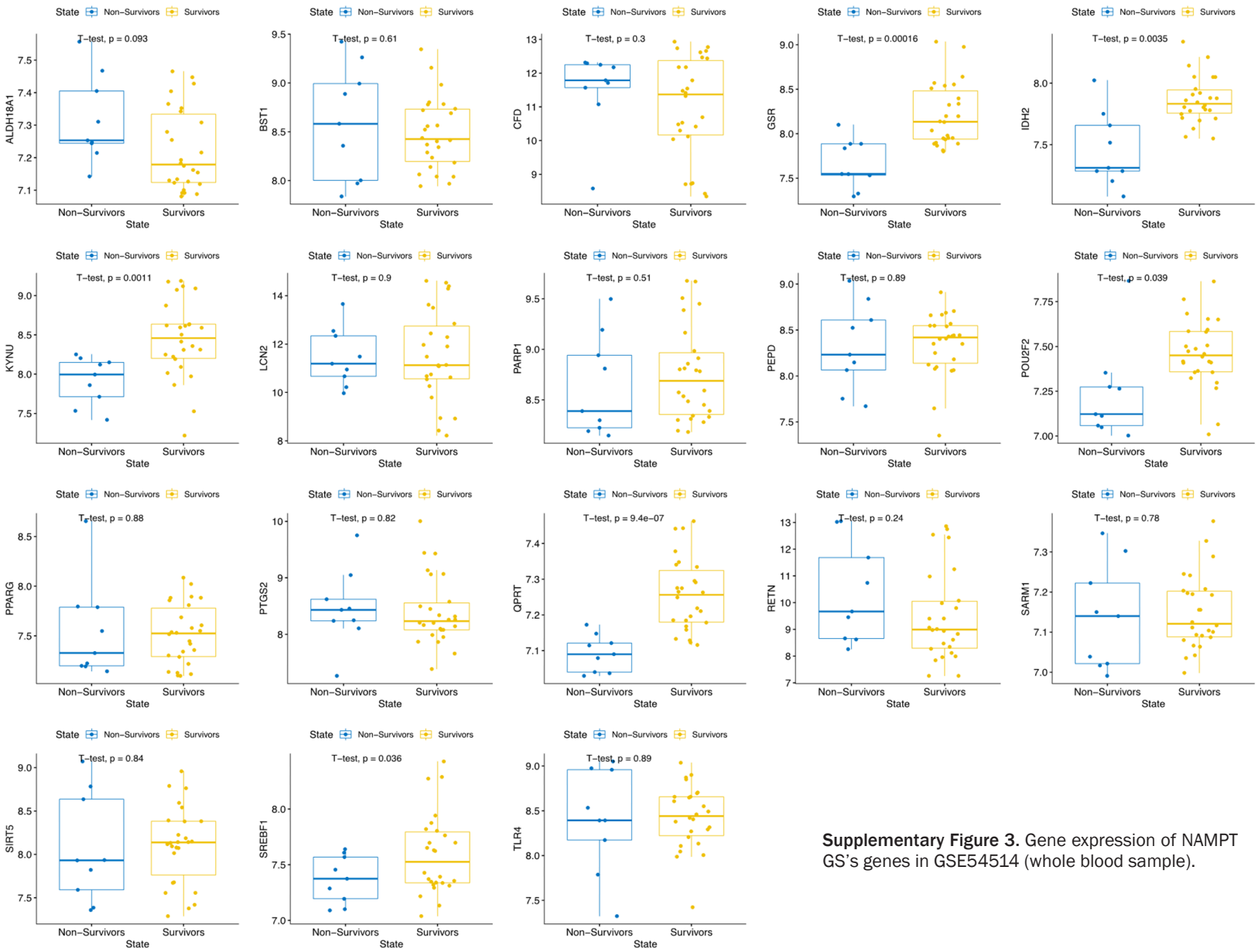
UCP2
UGT2B15
VEGFA
WARS
YARS



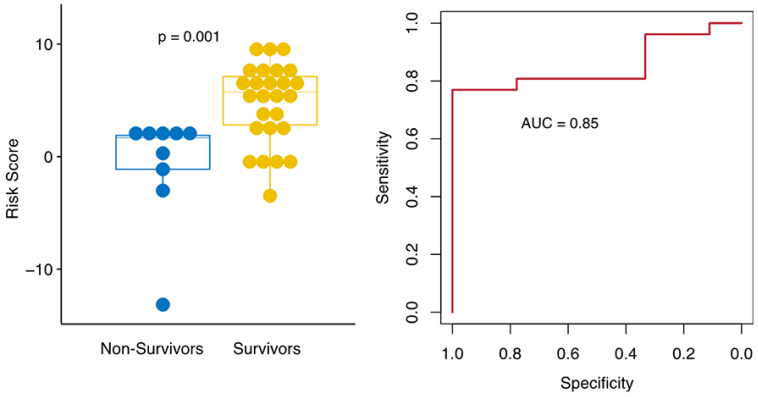
Supplementary Figure 1. Gene expression of NAMPT GS's genes in discovery cohort.



Supplementary Figure 2. Gene expression of NAMPT GS's genes in validation cohort.



Supplementary Figure 3. Gene expression of NAMPT GS's genes in GSE54514 (whole blood sample).



Supplementary Figure 4. Risk score of NAMPT-GS in GSE54514.