Medical Science Journal for Advance Research

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Vol. 7, No. 3, September 2026
*e-ISSN: 2774-4892*

# Transcriptomic Signatures of Right Ventricular Dysfunction and Systemic Complications in Advanced Heart Failure

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**ABSTRACT**

***Background:*** *Retinoid* ***Background*** *Heart failure (HF) is a complex syndrome where clinical stratification has historically relied on hemodynamic parameters, often overlooking the distinct molecular profile of the Right Ventricle (RV).* ***Methods:*** *This study used a multi-stage design, interrogating 109 human heart tissue samples (CAGE-seq) and validating findings in 29 Peripheral Blood Mononuclear Cell (PBMC) profiles from patients undergoing Mechanical Circulatory Support (MCS).* ***Results:*** *We identified robust correlations between gene expression and clinical phenotypes. Specifically, the lymphatic marker LYVE1 showed a strong positive correlation with the MELD-XI score ($r=0.64$, $p<0.01$) and the SOFA score ($r=0.39$, $p=0.041$), linking lymphatic activation to congestive hepatopathy. In the RV, TIMP4 expression was significantly higher in patients with moderate-to-severe dysfunction compared to mild cases (ANOVA $p=0.041$), also correlating with RV dimensions ($r=0.40$, $p<0.05$)4. A collagen switch was observed where COL21A1 correlated with adverse outcomes ($r=0.26$) while COL24A1 was protective. Furthermore, in patients with preserved RV function, elevated CDK1 was a significant predictor of 1-year mortality ($p=0.024$), serving as a hidden signal of cellular failure. Finally, IL12A showed significant upregulation in females compared to males ($p=0.035$), suggesting sex-specific inflammatory pathways.* ***Conclusions:*** *These findings offer a biologically relevant framework for monitoring and treating the systemic complications of HF which may be stratified at a molecular level.*

**Keywords: Heart Failure, Transcriptomics, Right Ventricular Dysfunction, Collagen Remodeling, LYVE1.**

**Article Information**

Received: July 31, 2026; Revised: August 29, 2026; Online: September 2026y

## INTRODUCTION

Clinical stratification of heart failure (HF) relies on Left Ventricular Ejection Fraction (LVEF). Therapies based on this hemodynamic framework have not improved survival rates in advanced HF. The failing heart is a heterogeneous organ composed of distinct cellular states and intercellular networks that vary by etiology and chamber [1–4].

Failure of the Right Ventricle (RV) drives morbidity and mortality in heart failure, yet lacks specific therapies. The RV is embryologically, structurally, and molecularly distinct from the Left Ventricle (LV), challenging its historical perception as a passive conduit [5,6]. The right ventricle's gene expression profile governs its response to pressure overload through different metabolic dependencies and immune priming. This specificity makes it difficult to translate findings from general heart failure into RV-specific clinical biomarkers. The molecular drivers of the transition from compensated RV hypertrophy to fatal dilation, or the hemostatic dysregulation seen in end-stage patients, are less well-defined than those of LV disease [7–9].

Therefore, the primary rationale for this study is to bridge the gap between broad molecular discovery and specific clinical utility. We hypothesized that specific differentially


https://doi.org/10.46966/msjar.v7i3.476
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expressed genes (DEGs) in end-stage heart failure are not merely passive markers of disease presence, but act as active drivers or indicators of specific clinical complications in high-risk populations [10–12]. For instance, dysregulation in genes governing extracellular matrix turnover or fatty acid oxidation may specifically predict echocardiographic evidence of RV dilation, while transcriptional reprogramming of the endothelium may underpin the bleeding risks and systemic inflammatory shock frequently observed in patients undergoing Mechanical Circulatory Support (MCS) [13,14].

We integrated heart failure transcriptomic data with clinical outcomes, PBMC profiles, and echocardiographic data from patients undergoing MCS. This orthogonal validation identified a dysregulated transcriptome. We correlated this transcriptome with clinical variables to isolate an expression signature that predicts right ventricular dysfunction and its systemic effects.

## METHODS

### Study Design

This study utilized a multistage validation design to identify transcriptomic signatures associated with specific heart failure complications. The workflow proceeded in two distinct phases a discovery phase to identify differentially expressed genes DEGs in failing human hearts and a validation phase to correlate these molecular candidates with granular clinical phenotypes specifically RV dysfunction, bleeding events and systemic organ failure scores in a distinct cohort of patients undergoing Mechanical Circulatory Support MCS.

### Discovery Phase Identification of Candidate Markers

The discovery phase used the CAGE-seq Cap Analysis of Gene Expression dataset identified as GSE150736 which was retrieved from the Gene Expression Omnibus GEO database https://www.ncbi.nlm.nih.gov/geo/. This comprehensive atlas encompasses 109 samples derived from 31 human hearts including tissues from both the right and left atria and ventricles. Libraries was prepared using ssCAGE or nAnT-iCAGE protocols and sequenced on the Illumina HiSeq 2500 system to map transcriptional start sites and promoter activity with high precision. Differential expression analysis was performed using the DESeq2 package https://bioconductor.org/packages/release/bioc/html/DESeq2.html to compare human failing heart tissue against healthy controls [15]. Candidate genes were shortlisted using a dual filter strategy requiring statistical stringency and mechanistic relevance. We applied a statistical threshold of an adjusted P-value p-adjusted less than 0.05 and an absolute Log2 Fold Change greater than 1.0. Following this functional enrichment analysis against Gene Ontology (GO), Reactome and KEGG databases was conducted using the Enrichr tool https://maayanlab.cloud/Enrichr/ to identify associated biological pathways [16].

### Validation Phase Clinical Correlation in MCS Cohort

For the clinical validation phase we utilized the RNA-seq dataset GSE104423 also obtained from the GEO database. This cohort consist of whole transcriptome profiles from peripheral blood mononuclear cells (PBMCs) collected from 29 advanced heart failure patients one day prior to undergoing Mechanical Circulatory Support (MCS) surgery Sequencing for this cohort was also performed on the Illumina HiSeq 2500 platform. This specific dataset was selected due to the availability of granular clinical metadata including RV function echocardiography SOFA scores MELD scores bleeding events and 1 year survival outcomes which were absent in the discovery dataset. Data processing began with the harmonization of raw gene count matrices with clinical metadata using GEO accession IDs to ensure accurate sample to phenotype mapping. To account for sequencing

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depth differences raw counts were normalized to Counts Per Million CPM, Log2(CPM + 1) transformation was subsequently applied to stabilize variance and normalize the distribution for parametric testing Expression vectors for the shortlisted candidate genes were then extracted for downstream statistical testing. Candidates were manually curated based on literature evidence linking them to three specific pathological axes ECM Remodeling as putative drivers of RV dilation Systemic Inflammation and Cytokine Shedding as putative drivers of organ shock and Mucosal or Vascular Integrity.

**Statistical Analysis Framework**

All statistical analysis were performed using Python v3.13 utilizing the pandas scipy.stats and seaborn libraries. Categorical associations between gene expression and clinical groups such were assessed using One way Analysis of Variance (ANOVA) and Independent T-tests. This approach determined if mean gene expression levels differed significantly between the stratified clinical groups testing hypotheses such as whether the downregulation of structural genes correlates with worse RV function grades. Continuous correlations between gene expression and clinical severity scores were evaluated using Spearman Rank Correlation. Since clinical scores like SOFA Sequential Organ Failure Assessment and MELD Model for End Stage Liver Disease are often ordinal or non normally distributed [17,18]. Spearman correlation provided a robust method to detect outliers and non linear monotonic relationships. This allowed us to test if the upregulation of inflammatory sheddase correlates positively with higher organ failure scores. Additionally stratified interaction analyses were conducted using grouped linear regression to detect interaction effects. This assessed whether the correlation between a gene and an outcome was dependent on a third variable such as gender or survival status distinguishing general risk factors from those specific to a sub population.

# RESULTS

**Datasets and Study Design**

We analyzed myocardial regulatory elements using the GSE150736 CAGE-sequencing atlas of 109 human hearts. To separate these local signals from systemic immune responses, we used the GSE104423 validation cohort containing PBMC transcriptomes from 29 advanced heart failure patients before mechanical circulatory support.

**3.2 Differential Gene Expression Between Failing Heart and Healthy Control**

Comparison of failing and healthy myocardial tissue revealed 393 upregulated and 371 downregulated genes (Figure 1A). The failing heart induced genes associated with immunity and structural remodeling. These included chemokines (CCL24, CXCL1, CXCL10, CCL5, CCL3), immune receptors (IL2RG, IL2RB, IL12A, CD3E), specific collagen isoforms (COL24A1, COL14A1), and matrix-modifying enzymes like COLGALT2. The tissue suppressed genes for electromechanical coupling and metabolic homeostasis. Downregulated transcripts included cytoskeleton and gap junction components (CDK1, TUBA3C, TUBA3E, TUBB2A, TUBB2B) and enzymes for catecholamine and tyrosine metabolism (PNMT, ADH1C, ADH1B), suggesting a loss of metabolic specialization.

**Functional Enrichment Analysis**

Pathway enrichment analysis across GO, KEGG, and Reactome databases showed gene expression changes skewed toward immune activation and structural remodeling (Figure 1B-D). Co-expression of ligands (CCL24, CXCL10) and their receptors drove enrichment of cytokine and chemokine signaling pathways that recruit leukocytes to the myocardium (KEGG: hsa04060, GO:0070098). Upregulation of T-cell receptor (CD3E) and signaling genes (STAT4, IL12A) enriched Th1 and Th2 cell differentiation pathways, while Reactome analysis linked gene changes to collagen

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formation and active extracellular matrix turnover. Downregulated pathways suggested cardiomyocyte de-differentiation. A loss of tubulin and CDK1 expression lowered Gap junction function and formed an arrhythmogenic substrate. Suppressed Tyrosine metabolism also produced the metabolic rigidity and limited adrenergic signaling (PNMT) characteristic of failing myocardium.

**Shortlisting Biomarkers for Systemic Validation**

Further, having established the baseline transcriptomic disturbances within the failing myocardium, we wanted to assess whether these local signals were confined to the tissue or reflected in the systemic circulation. We used a PBMC validation cohort to find non-invasive surrogates for myocardial remodeling because cardiac biopsies are impractical for routine monitoring. Our approach required detecting specific immune and fibrotic signatures present in peripheral blood.

**Venous Congestion and Lymphatic Activation**

Myocardial expression of lymphatic and extracellular matrix remodeling markers correlated with cardiorenal dysfunction severity. The lymphatic endothelial activation marker LYVE1 was the strongest signal in the validation cohort. LYVE1 expression positively correlated with the MELD-XI score ($r=0.64$, $p<0.01$), a surrogate for congestive hepatopathy in heart failure (Supplementary Figure 1E).

LYVE1 expression correlated with the SOFA score ($r=0.39$, $p=0.041$) and was higher in patients with moderate-to-severe RV dysfunction than in those with preserved function. These results link lymphatic activation to both multi-organ failure severity and right-sided hemodynamic burden (Figure 2, Supplementary Figure 1A, 1F).

In survivors, lymphatic activation correlated with organ failure severity, but non-survivors showed a disrupted pattern suggesting lymphatic exhaustion (Supplementary Figure 1C). Furthermore, sex-stratified analysis indicated that while the association between LYVE1 and congestive hepatopathy (MELD-XI) was robust across both sexes, females exhibited a more distinct linear trajectory (Supplementary Figure 1G), a trend that was also maintained in the response to general organ failure (Supplementary Figure 1D).

**Extracellular Matrix Remodeling and Right Ventricular Dysfunction**

Parallel to the lymphatic response, the tissue inhibitor of metalloproteinases 4 (TIMP4) emerged as a significant correlate of RV pathology. TIMP4 expression correlated significantly with the MELD-XI score ($r=0.47$, $p<0.05$) and quantitative metrics of RV dimension ($r=0.40$, $p<0.05$), Figure 2. ANOVA confirmed that TIMP4 was differentially expressed based on RV functional status, with significantly higher transcript abundance observed in patients with moderate-to-severe RV impairment compared to those with normal or mild impairment ($p=0.041$), Figure 5A. In the normal/mild cohort TIMP4 expression was negligible, whereas the moderate/severe group displayed a marked transcriptional activation, consistent with a profibrotic matrix stabilization response to chronic wall stress.

**Differential Remodeling Profiles**

Collagen isoforms showed opposing associations with organ failure progression. COL21A1 expression correlated positively with late-stage organ failure (TP5 SOFA: $r=0.28$) and adverse outcomes ($r=0.26$), suggesting its upregulation promotes pathologic fibrosis and ventricular stiffening. COL24A1 showed the strongest negative correlation with late-stage organ failure (TP5 SOFA: $r=-0.37$), indicating it facilitates adaptive matrix turnover. Lower baseline COL14A1 levels associated with higher initial severity (TP1 MELD: $r=-0.22$), suggesting a loss of fibril-regulatory collagens marks the acute decompensated state (Figure 3).

**Immune-Inflammatory Signatures and Adaptive Immunity**

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In the PBMC validation cohort, disease severity correlated with higher levels of eosinophil and neutrophil-recruiting chemokines. CCL24 (Eotaxin-2) showed the strongest correlation with the MELD-XI score ($r=0.67$, $p<0.01$). We propose a mechanism where systemic liver congestion causes a pro-fibrotic inflammatory response that connects hepatic and cardiac pathology. This was accompanied by a significant correlation between the neutrophil chemoattractant CXCL1 and MELD-XI ($r=0.50$, $p<0.01$), indicating a mixed inflammatory milieu in patients with severe cardio-hepatic syndrome, Figure 4.

Prognostically, sustained adaptive immune activation appeared detrimental. Genes associated with T-cell and NK cell signaling, specifically IL2RG ($r=0.49$, $p<0.01$) and IL2RB ($r=0.42$, $p<0.05$), were significantly correlated with adverse clinical outcomes. Beyond survival, this adaptive immune activation tracked with hemodynamic severity; IL2RG levels were significantly elevated in patients with moderate-to-severe RV dysfunction compared to those with preserved function (Figure 6B), suggesting that T-cell/NK-cell cytokine signaling tracks with the progression of right heart failure. Elevated IL2RG specifically served as a detectable by echo cardio negative prognostic marker (Log2 CPM > 7.5 associated with mortality), supporting the cytokine hypothesis where chronic immune system overactivation mediated by the common gamma chain receptor family contributes to myocardial depression and adverse outcomes (Figure 6C, 6D).

**Molecular Risk in Preserved RV Function**

Stratification of the validation cohort by RV function revealed a critical insight where severe RV dysfunction is a known risk factor, transcriptomic analysis identified a high-risk molecular profile specifically in patients with normal/mild RV impairment. In patients with preserved RV function, elevated CDK1 expression was a significant predictor of 1-year mortality ($p=0.024$). As CDK1 is a regulator of mitosis its upregulation in this context likely reflects abortive cell cycle re-entry or aggressive fibroblast proliferation, signaling cellular failure before organ-level mechanical failure is detectable by echocardiography, Figure 6E. Similarly, CD3E ($p=0.027$) and CD2 ($p=0.022$) were significantly upregulated in non-survivors within the normal/mild RV group. This suggests an immunological uncoupling from mechanical function where an active adaptive immune response acts as a synergistic drastic effector in patients who appear hemodynamically stable (Figure 6F, 6G).

**Markers of Acute Inflammation and Organ Failure Severity**

The metalloproteinase ADAM19 was identified as a severity-dependent marker associated with acute physiological decline. ADAM19 transcript levels showed a moderate, statistically significant positive correlation with the SOFA score ($r=0.41$, $p=0.029$), Figure 2. The relationship between ADAM19 and organ failure was modified by RV function, where patients with preserved RV function exhibited a linear, steep upregulation of ADAM19 in response to rising SOFA scores, whereas those with severe RV dysfunction showed a blunted slope with a higher basal expression, indicative of a saturated stress response (Supplementary Figure 4A). Unlike LYVE1, which appeared to be a compensatory marker, ADAM19 expression followed a maladaptive pattern where the higher expression levels were associated with 1-year mortality (Supplementary Figure 4B). This specific blunting of the stress response in severe RV dysfunction was similarly observed when correlating ADAM19 with indices of hepatic congestion; patients with moderate-to-severe RV impairment maintained elevated protease expression regardless of MELD-XI scores, contrasting with the linear response seen in patients with preserved RV function (Supplementary Figure 4C). Males had higher

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baseline ADAM19 expression and more variability than females, though both sexes increased expression with SOFA scores (Supplementary Figure 4D).

**Demographic and Sex-Specific Expression Profiles**

IL1RL1 (ST2) expression increased with age (r=0.45, p=0.017) independent of hemodynamics, but this effect was exclusive to survivors and absent in non-survivors (Supplementary Figure 2A). This age-dependent increase was exacerbated in patients with severe RV dysfunction, likely reflecting the cumulative burden of inflammaging and mechanical strain (Supplementary Figure 2B). Additionally, sex-specific profiling revealed that the age-dependent increase in ST2 expression was markedly more pronounced in females, suggesting a distinct, steeper trajectory of 'inflammaging' in the female heart failure population (Supplementary Figure 2C).

Furthermore, sex-stratified analysis revealed significant dimorphisms. While the global correlation with SOFA was non-significant (r=-0.14), sex-stratified analysis showed that females upregulated BDNF in response to increasing organ failure, potentially as a compensatory neuro-cardiac mechanism, whereas males exhibited a mal-adaptive downregulation of BDNF with worsening clinical status (Supplementary Figure 5). Additionally, analysis of the IL12A gene (encoding the p35 subunit of IL-12) revealed a statistically significant upregulation in females compared to males (p=0.035; Median Log2 CPM approx. 0.42 vs 0.24), (Figure 6A). As IL-12 is a key driver of Th1 adaptive immunity, this elevation suggests a heightened inflammatory baseline in female heart failure patients, potentially linked to the microvascular inflammation phenotype often observed in HFpEF or autoimmune susceptibility (Supplementary Figure 5).

Similar sexual dimorphism was observed in the regulation of lymphatic and mucosal integrity genes. In response to late-stage organ failure (TP5 SOFA), females exhibited a downregulation of LYVE1, whereas males maintained elevated expression levels (Supplementary Figure 1B).

**Divergent Transcriptional Trajectories and Clinical Outcomes**

Global correlation analyses masked interactions between gene expression, clinical severity, and one-year survival for FCGBP and TIMP4. Stratification by mortality showed opposing FCGBP responses despite a negligible aggregate correlation with the SOFA score (r=-0.12, p=0.545). Survivors downregulated FCGBP as organ failure worsened. Non-survivors showed a paradoxical upregulation with rising SOFA scores, suggesting failed resolution of mucosal or systemic inflammation (Supplementary Figure 3A). Early-stage failure (TP1 SOFA) also produced sex-specific FCGBP responses, with females downregulating the gene and males upregulating it (Supplementary Figure 3B).

TIMP4 expression showed a failure-to-compensate pattern. Surviving patients had an age-dependent upregulation of TIMP4 (r>0.3). Non-survivors failed to mount this response, exhibiting flat or negative expression trends despite advancing age and disease severity (Figure 5G). This failure to resolve inflammation in non-survivors appeared at baseline. Survivors had a negative correlation between FCGBP and initial TP1 SOFA scores, but non-survivors showed a positive trend consistent with early mucosal barrier compromise (Supplementary Figure 3C). Elevated FCGBP also tracked with higher MELD-XI scores in non-survivors with congestive hepatopathy, linking mucosal barrier breakdown to fatal cardio-hepatic outcomes (Supplementary Figure 3D).


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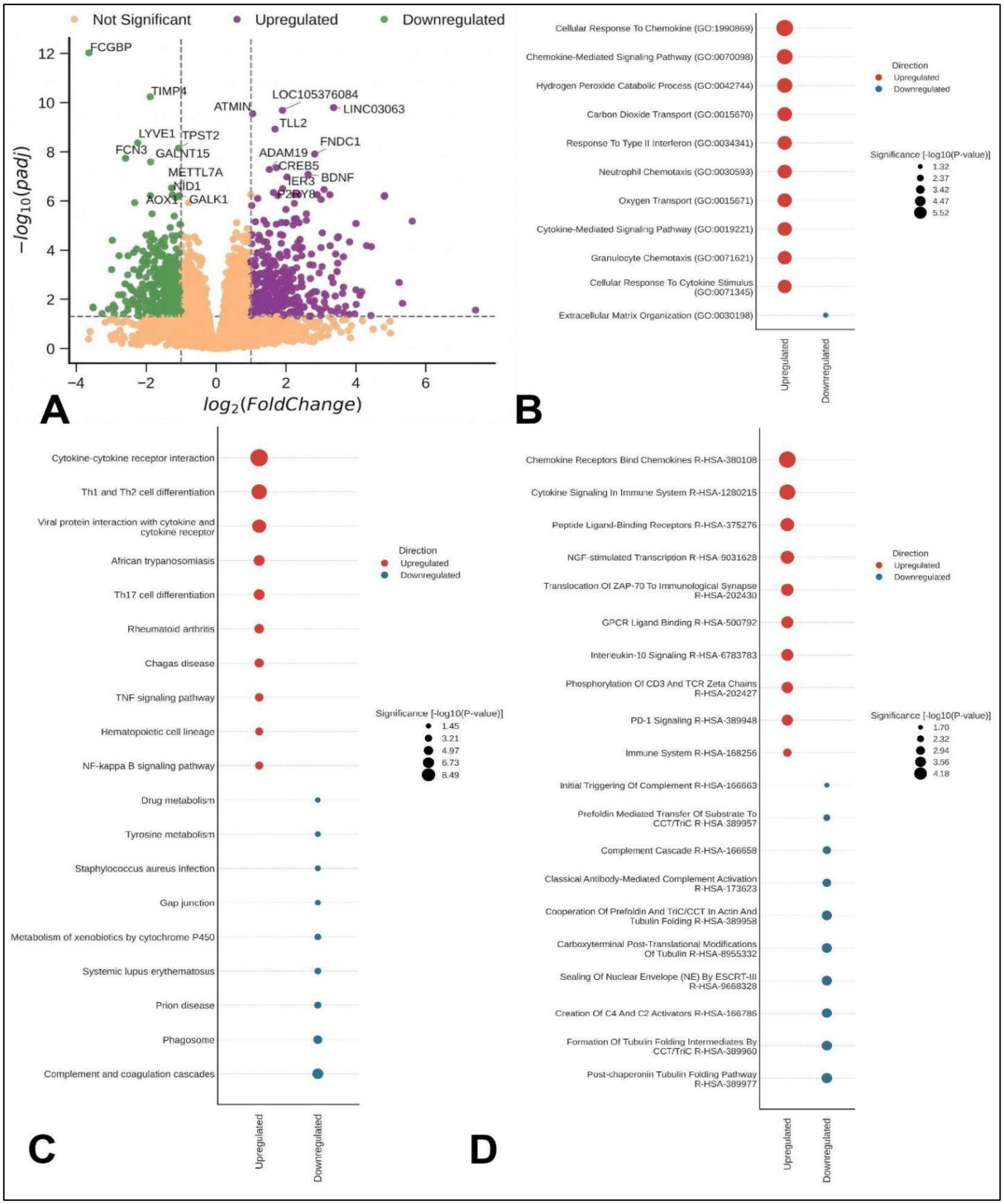



**Fig 1. (A) Gene expression differed between failing human hearts and healthy controls. Upregulated genes encoded immune (CCL24, CXCL10) and matrix (TIMP4, ADAM19) proteins. Downregulated genes were involved in metabolism and structure (PNMT, CDK1). (B-D) Functional analysis showed upregulated genes were enriched for chemokine signaling and cytokine-receptor interactions.**

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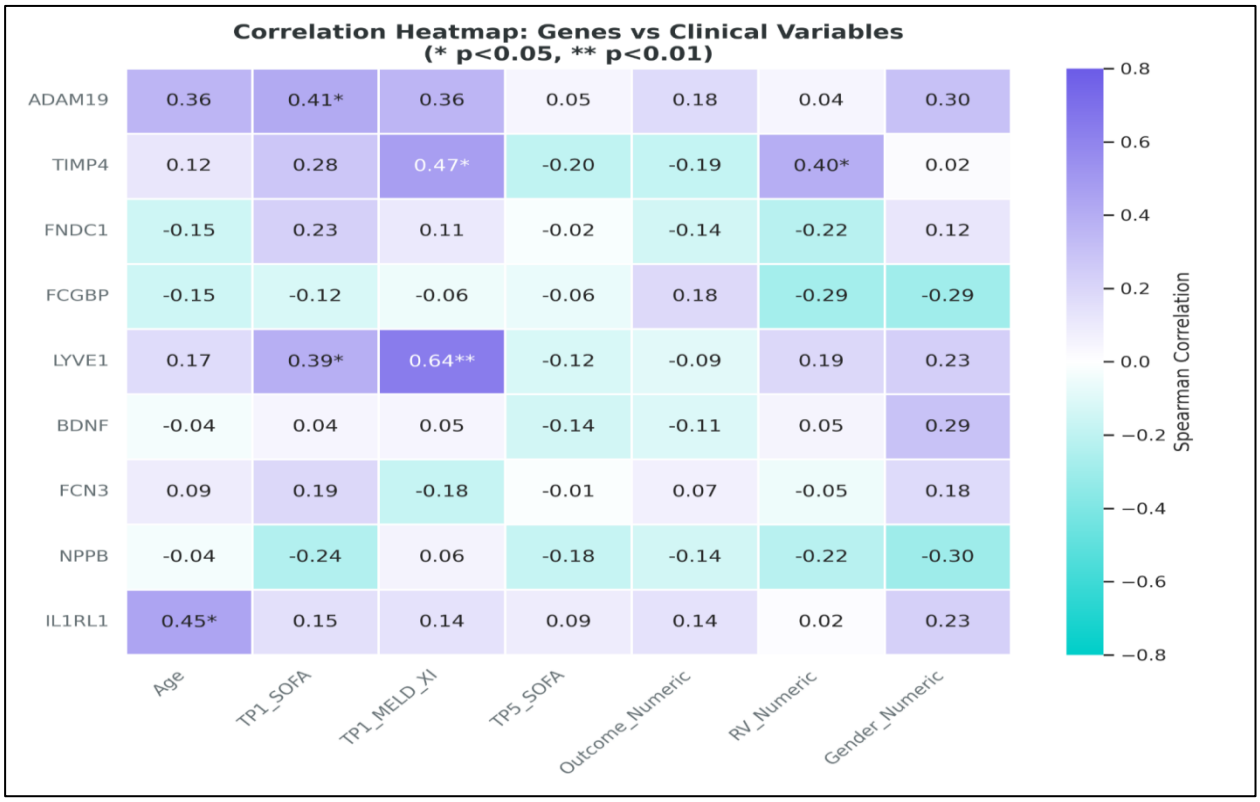



**Fig 2. Spearman rank correlation coefficients (r) link structural and lymphatic gene expression to clinical severity in the validation cohort.** *LYVE1 expression positively correlates with hepatic congestion (TP1_MELD_XI, r=0.64) and organ failure (TP1_SOFA, r=0.39). TIMP4 expression correlates with RV dimensions and MELD-XI scores. All reported correlations are significant at p<0.05.*

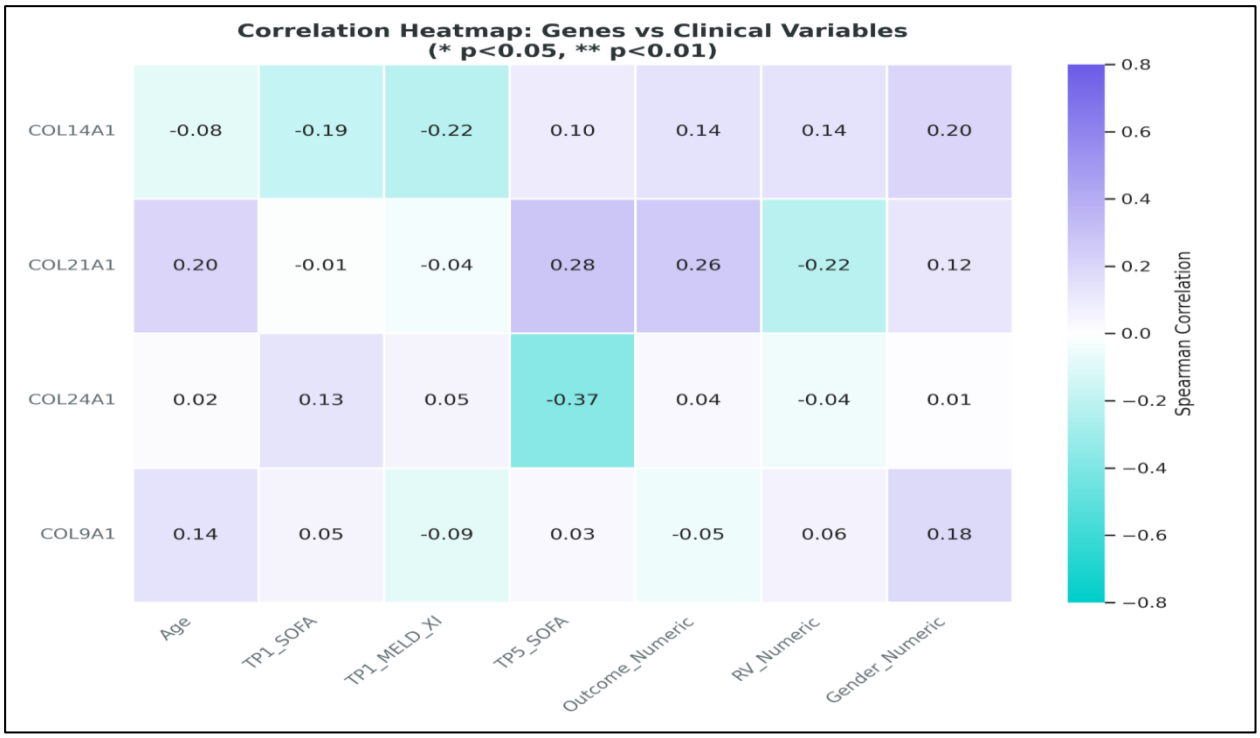



**Fig 3. High COL21A1 expression correlates with late-stage organ failure (TP5_SOFA).** *COL24A1 expression shows a negative correlation with organ failure severity. These opposing patterns, combined with an association between low COL14A1 and high initial severity, suggest a "collagen switch".*

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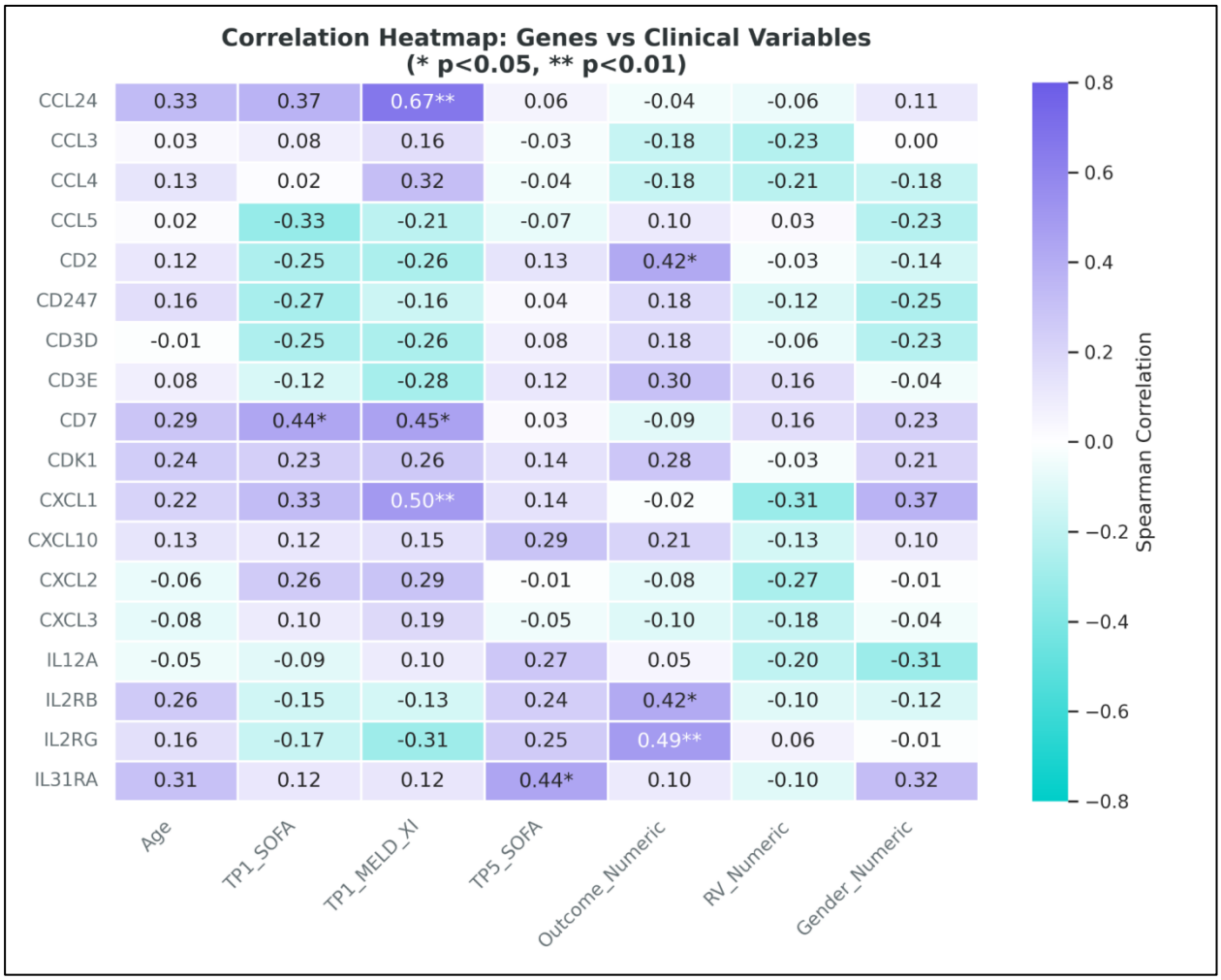



**Fig4. A chemokine cluster (CCL24, CXCL1) correlated with congestive hepatopathy (MELD-XI).** *Separately, adaptive immune markers (IL2RG, CD2) correlated with adverse clinical outcomes and late-stage organ failure*.

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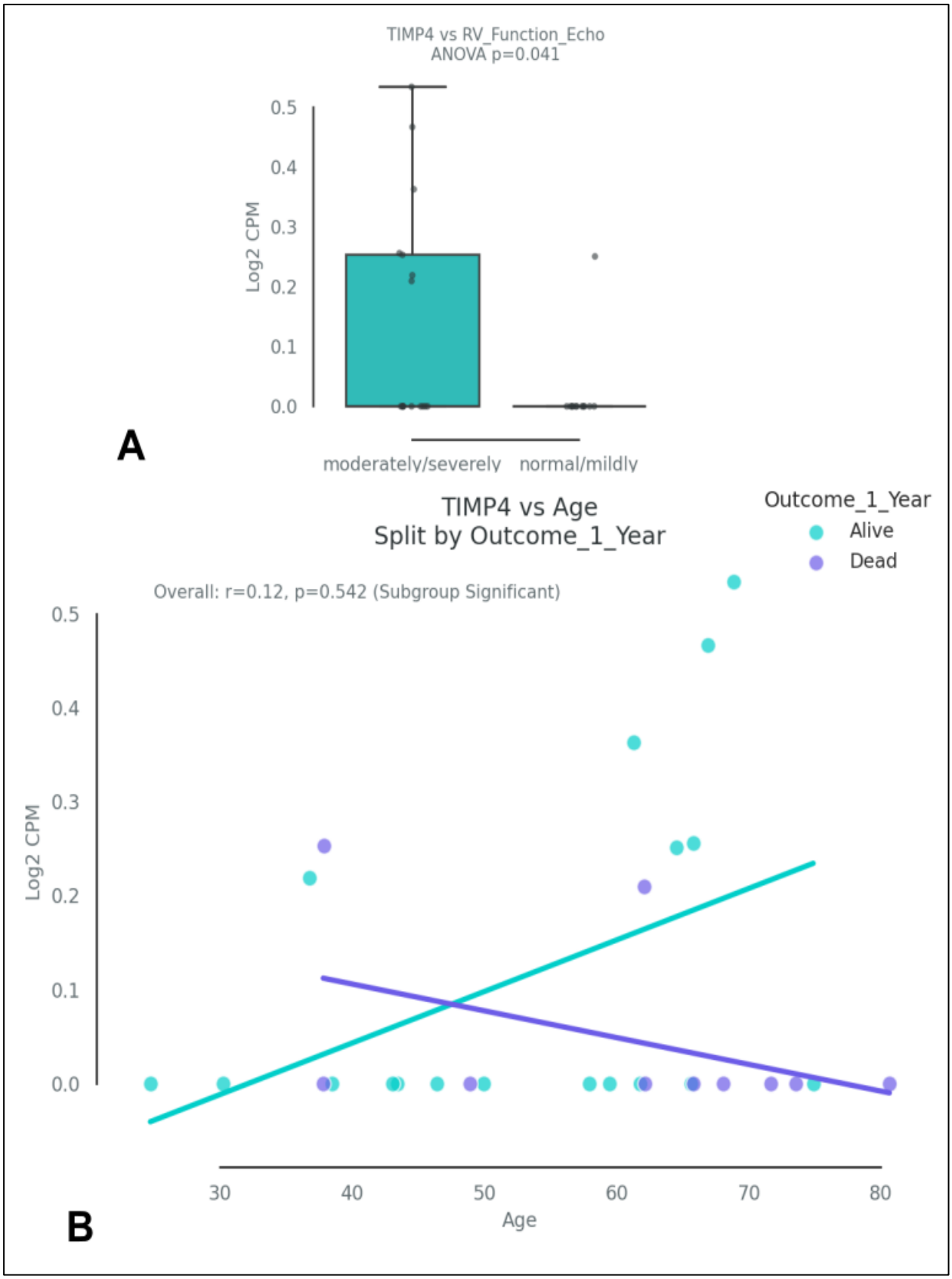



**Fig5. TIMP4 Expression and Clinical Interaction Analysis.** *(A) Patients with moderate-to-severe RV dysfunction have significantly higher TIMP4 expression (ANOVA p=0.041). (B) TIMP4 expression increases with age in survivors but not in non-survivors, a 'Failure-to-Compensate' phenotype.*

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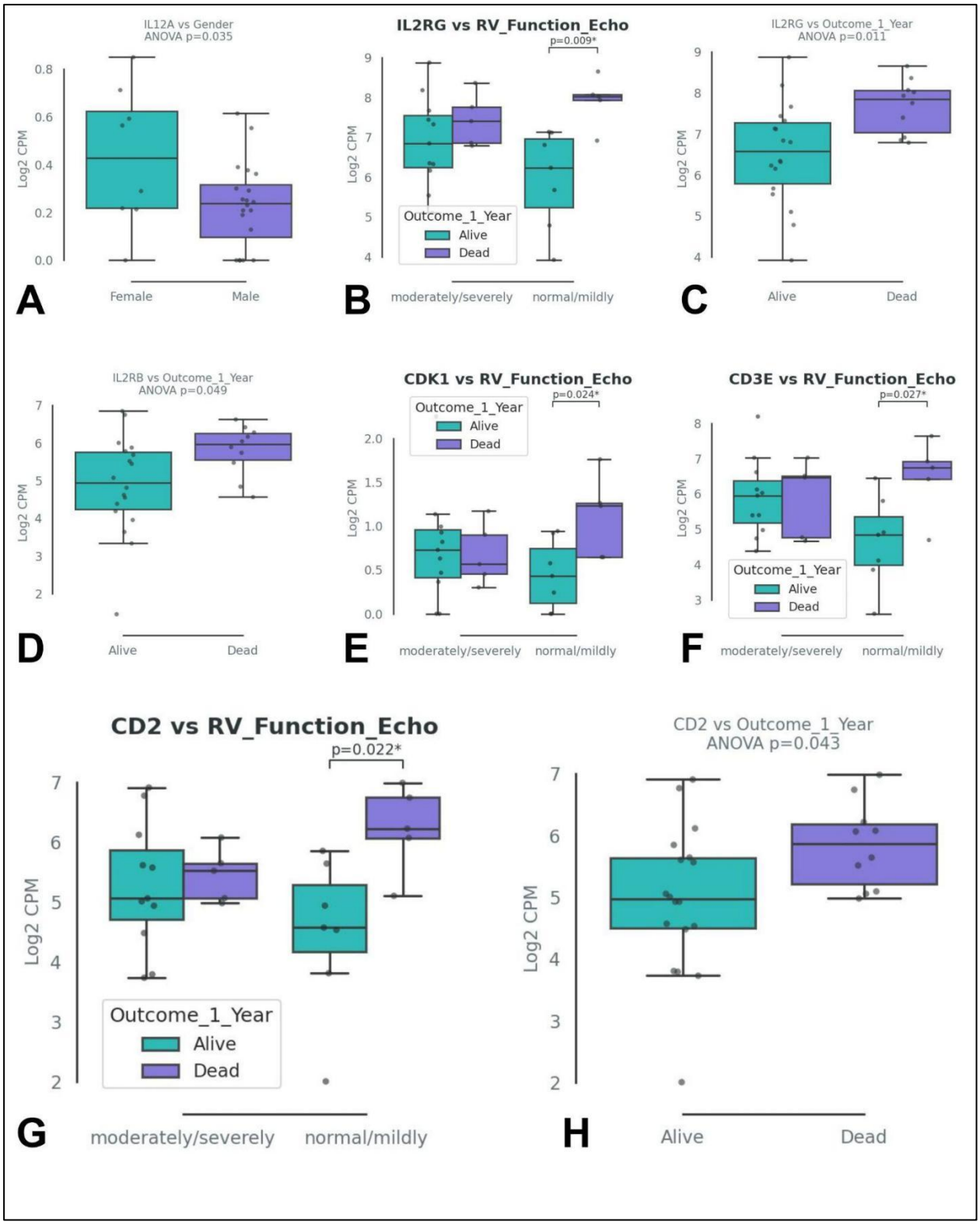



**Fig 6. Higher IL2RG and CD2 expression correlated with non-survival.** *In patients with preserved right ventricular function, non-survivors had elevated CDK1, CD3E, and CD2 levels, suggesting an immunological response uncoupled from hemodynamic status, while females showed higher IL12A expression.*

## DISCUSSION

Our findings demonstrates that the failing heart may not merely be a pump in mechanical decline and rather the epicenter of a complex, multi-systemic clinical syndrome characterized by distinct molecular signatures that precede and predict clinical deterioration. Linking myocardial CAGE-seq and peripheral blood RNA-seq profiles identified a dysregulated transcriptome that stratifies risk beyond

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hemodynamic parameters. This transcriptome reveals a collagen switch, questioning the view of fibrosis as uniformly detrimental. We observed a diametrical divergence between collagen isoforms, where COL21A1 tracked with adverse outcomes and organ failure, while COL24A1 exhibited a protective profile, which has been shown in osteoblastic differentiation previously [19]. The upregulation of COL21A1, a FACIT collagen involved in fibril organization, likely contributes to maladaptive ventricular stiffening and a locking of the ECM that prevent functional recovery. On contrast, the association of COL24A1 with better outcomes suggest a fetal or regenerative matrix program that retain the plasticity necessary for adaptation to mechanical unloading. Furthermore, the RV-specific upregulation of TIMP4 highlights the distinct fibrotic response of the right ventricle to pressure overload, observation perfectly aligns with the earlier discussion about the RV unique molecular signature and fibrotic response. The RV-specific upregulation of TIMP4 is a key finding that reinforces the idea that RV fibrosis is fundamentally different from the left ventricle's response to stress [20].

Crucially, the inability of non-survivors to upregulate TIMP4 with advancing age suggest a failure-to-compensate phenotype, where the loss of matrix stabilization mechanisms precipitate rapid decompensation. Plasma TIMP4 levels rise with age in healthy individuals and correlate with left ventricular collagen accumulation and remodeling. While this increase is part of normal aging, aged mice lacking TIMP4 show impaired cardiac function. This loss of function demonstrates a protective role for TIMP4 in the aging heart. Multiple animal models of heart failure (such as those induced by aorta-vena cava fistula) show significant downregulation of TIMP4 gene and protein expression [21,22]. These findings implies that therapeutic strategies must move beyond broad anti-fibrotic suppression to the targeted modulation of specific matrix components.

Beyond the myocardium, our results elucidate the lymphatic-hepatic axis as a critical driver of the cardio-hepatic syndrome. The lymphatic marker LYVE1 correlates with the MELD-XI score, providing a transcriptomic link between right-sided hemodynamic burden and peripheral lymphatic remodeling [23]. The elevation of LYVE1 in patients with RV dysfunction likely reflect compensatory lymphangiogenesis or endothelial shedding in response to severe venous congestion where is caused by RV dysfunction leads to fluid accumulation (edema) in tissues, which drastically increases interstitial fluid pressure. LYVE1-expressing lymphatic endothelial cells expand to clear excess fluid and immune cells. This compensatory network restores fluid balance and resolves inflammation, but is insufficient in end-stage heart failure [24–27].

Upregulation of CCL24 and CXCL1 recruits both eosinophils and neutrophils to drive hepatic injury [28,29]. The correlation of CCL24 with hepatic dysfunction suggests a fibrotic cycle. Macrophages responding to hepatic congestion release CCL24, which acts through the CCR3 receptor to reinforce myocardial fibrosis. CXCL1 recruits neutrophils that release proteases and reactive oxygen species, further destabilizing tissue architecture. Consequently, LYVE1 and CCL24 emerges as potential liquid biopsy candidates for monitoring the progression of congestive hepatopathy before irreversible liver fibrosis occurs.

We also identified a critical dysregulation in proteolytic signaling mediated by ADAM19, which serve as a severity-dependent marker of acute physiologic decline. While ADAM19 expression generally tracked with the SOFA score, stratification by RV function revealed a saturated stress response in patients with severe RV impairment. Unlike patients with preserved RV function who mounted a linier upregulation of ADAM19 in response to worsening organ

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failure, those with severe RV dysfunction exhibited high basal expression with a blunted slope. ADAM19 is highly expressed in the endocardial cushions and Cono truncal region of the developing heart, structures that form the heart valves and the membranous ventricular septum. Its absence leads to ventricular septal defects (VSD) and abnormal, stenotic valves. The pattern of ADAM19 expression varies with the type of heart failure. In patients with severe RV impairment, the stress response involving ADAM19 appears saturated, contrasting with the linear upregulation seen in patients with preserved RV function. This indicates a more complex and exhausted physiological state in severe RV dysfunction [30,31].

This proteolytic exhaustion suggests that the homeostatic mechanisms in end-stage RV failure are overwhelmed. Observed saturation suggests ADAM19 cannot increase reparative Neuregulin-1 signaling while its inflammatory shedding of TNFA continues [32]. ADAM19 saturation contributes to the refractory shock and hemostatic dysregulation in this population. A high-risk molecular profile identifies patients with preserved RV function previously considered stable. In this group, CDK1 expression predicts mortality, suggesting cellular failure precedes mechanical dysfunction. Elevated CDK1 in terminally differentiated tissue indicates either abortive cell cycle re-entry or aggressive fibroblast proliferation. Combined with increased T-cell markers (CD3E, CD2), this profile shows that active cell death and immune surveillance drive mortality despite preserved pump function, creating a feedback loop of cellular stress, immune activation, and structural damage [33–35]. This shows the limitations of imaging alone and suggests that transcriptomic profiling can identify a hidden high-risk cohort requiring earlier intervention.

The paradoxical upregulation of the mucosal barrier gene FCGBP in non-survivors suggests a failed attempt to repair intestinal damage from chronic hypoperfusion. Survivors resolve this signal as organ failure stabilizes, while persistent expression in non-survivors is consistent with unresolved endotoxemia [36,37]. FCGBP (Fc fragment of IgG binding protein), a large secreted glycoprotein in the gut mucosal barrier, supports immune defense and maintains epithelial integrity. Higher IL12A expression in females suggests an elevated Th1-mediated inflammatory baseline. This sex-specific profile provides a mechanism for the greater prevalence of certain autoimmune phenotypes and HFpEF in women. Animal models show IL12A directly contributes to pathogenic heart scarring, as its deficiency lowers pressure-induced cardiac inflammation, hypertrophy, and fibrosis [38,39].

Females responded to worsening SOFA scores by upregulating BDNF, which preserved myocardial bioenergetics. Males instead downregulated BDNF, increasing their vulnerability to ischemic injury and cell death [40,41]. Expression of the fibrosis marker IL1RL1 (ST2) increased with age only in females, indicating women have a greater age-related fibrotic risk and inflammaging profile than men [42].

This study shows biological signals predict organ-specific risks and mortality in advanced heart failure more accurately than hemodynamic metrics. The authors connect LYVE1 expression to congestive hepatopathy, a collagen switch (COL21A1 versus COL24A1) to remodeling outcomes, and CDK1 to cellular failure in hemodynamically preserved hearts. These sex-specific molecular signatures were validated in a mechanical circulatory support cohort and suggest that therapies should target distinct biological pathways. The study's observational design and focus on end-stage heart failure patients limits the generalizability of its findings. The associations between transcriptomic signatures (LYVE1, CDK1) and clinical outcomes are correlational, with biological mechanisms inferred from prior

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literature rather than directly demonstrated. Using circulating PBMCs as a surrogate for organ pathology is an assumption that requires validation in larger, prospective, and more diverse populations. Collectively, these findings support a biological characterization of a failing heart, offering a new framework for monitoring and treating the systemic complications of advanced heart failure.

## CONCLUSION

This study provides a comprehensive transcriptomic evaluation that challenges the traditional hemodynamic-centric view of advanced heart failure. We demonstrated that the failing heart is the epicenter of a multi-systemic syndrome, identified by novel biomarkers such as LYVE1 which tracks the lymphatic-hepatic axis and liver congestion. The identification of a divergent collagen switch highlights that not all fibrosis is uniform, distinguishing maladaptive stiffness driven by COL21A1 from the regenerative potential of COL24A1. Perhaps most concerning is the high-risk molecular profile found in patients with apparently stable RV function, where CDK1 signals fatal cellular stress before it is detectable by echocardiography. Additionally, the significant sexual dimorphism observed in inflammatory markers like IL12A reinforces the urgent need for sex-stratified precision medicine. While further validation in larger cohorts is needed, these findings offer a biologically grounded framework for monitoring and treating the systemic complications of HF.

**Funding**

This research received no external funding.

**Data Availability**

The datasets analyzed in this study are publicly available in the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) repository under accession numbers GSE150736 and GSE104423. Additional data generated during the current study are available in manuscript body and supplementary files

**Declarations**

**Ethics Approval and Consent to Participate**

This study was based exclusively on publicly available transcriptomic datasets obtained from the NCBI Gene Expression Omnibus (GEO) database. No new human participants or animals were directly involved in this research; therefore, institutional ethical approval and informed consent were not required.

**Competing Interests**

The authors declare that they have no competing interests.

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