Deciphering Abnormal Platelet Subpopulations in COVID-19, Sepsis and Systemic Lupus Erythematosus through Machine Learning and Single-Cell Transcriptomics

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Abstract

Single-cell transcriptomic profiling of peripheral blood mononuclear cells (PBMCs) in patients with COVID-19, sepsis, and systemic lupus erythematosus (SLE) has revealed insights into disease mechanisms. We hypothesize that the increased platelet population in PBMC fractions in severe cases represents activated platelet subpopulations responsible for disease outcomes in acute inflammation-driven diseases, suggesting potential new therapeutic strategies targeting these abnormal platelet subtypes. By collecting and integrating scRNAseq data from publicly available datasets on COVID-19, sepsis, and SLE and using machine learning techniques along with SingleR, Seurat, and Monocle analysis software, unique platelet subpopulations were identified. These subpopulations were found to correlate with disease severity and outcomes. Dynamic analysis revealed how these platelets behave and function under various conditions. Abnormal platelet subpopulations were found to overexpress genes related to endotheliopathy, potentially increasing the risk of disseminated intravascular coagulation in fatal patients, as well as genes modulating lymphocyte function, suggesting a broader role for platelets in abnormal inflammatory and immune responses.

Introduction

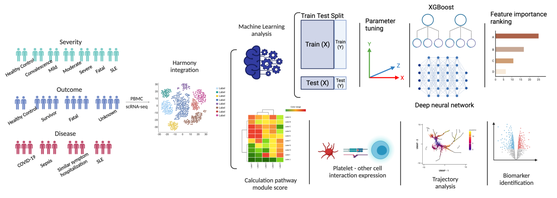


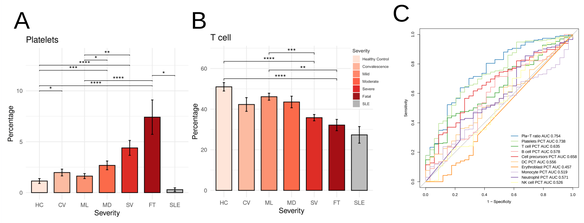
Figure 1. A schematic outline depicting the workflow for data collection from published literature and subsequent integrated analysis.

Group	Platelets
Healthy Controls (HC)	3,205
Convalescence (CV)	3,695
Mild (ML)	7,359
Moderate (MD)	4,330
Severe (SV)	198,005
Fatal (FT)	9,415
Systemic Lupus Erythematosus (SLE)	169
Outcomes	
Healthy Controls (HC) Outcome	3,205
Non-Survivors (NS)	9,415
Survivors (S)	25,750
Unknown Outcome	9,608
Diseases	
COVID-19	38,673
Hospitalized Patients with Similar Symptoms (SSH)	2,508
Sepsis	3,421
Systemic Lupus Erythematosus (SLE) Disease	169

Table 1. We gathered single-cell RNA-seq datasets of peripheral blood mononuclear cells (PBMCs) from COVID-19 patients[1-9], sepsis [10. 11], and systemic lupus erythematosus (SLE) [12] in order to study the peripheral immunological responses generated by various immune disorders. In the COVID-19 investigations, individuals with severe influenza, lung infections, and non-COVID-19 patients with similar symptoms were also included. They were all termed "hospitalized patients with similar symptoms" (SSH).

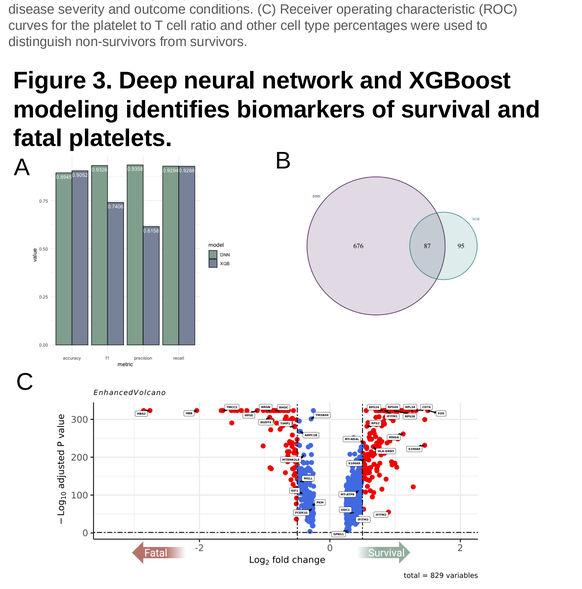
Results

Figure 2. The PBMC platelet-T cell ratio as the predictor of disease severity and separating non-survivors from survivors.



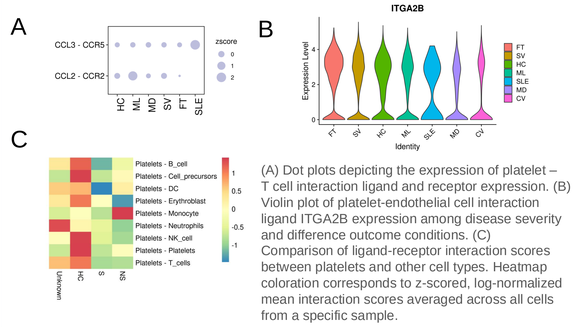
(A, B) Bar plots depicting the percentage of platelets and T cells in PBMCs under different disease severity and outcome conditions. (C) Receiver operating characteristic (ROC) curves for the platelet to T cell ratio and other cell type percentages were used to distinguish non-survivors from survivors.

Figure 3. Deep neural network and XGBoost modeling identifies biomarkers of survival and fatal platelets.



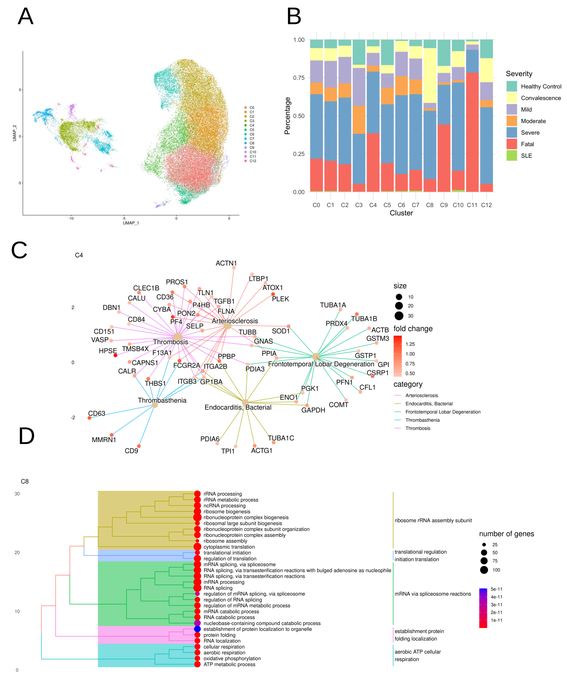
(A) Comparison of DNN and XGBoost Model Performance (B) VENN plot if DNN and XGB models containing only the features that are within the top 5% of importance or gain from their respective models. (C) Volcano plot depicting genes that are upregulated or downregulated when comparing platelets from survivors to those from fatal cases.

Figure 4 Interactions between platelets and other cells impacts.



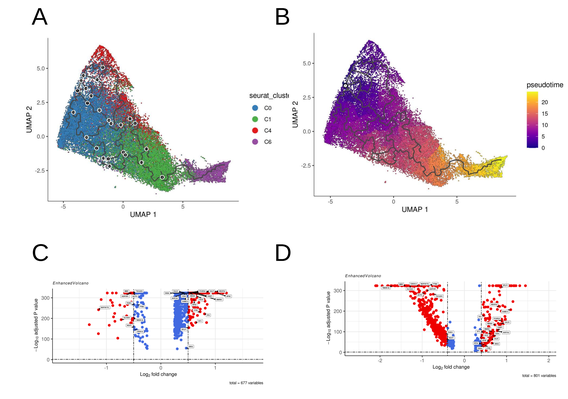
(A) Dot plots depicting the expression of platelet – T cell interaction ligand and receptor expression. (B) Violin plot of platelet-endothelial cell interaction ligand ITGA2B expression among disease severity and difference outcome conditions. (C) Comparison of ligand-receptor interaction scores between platelets and other cell types. Heatmap coloration corresponds to z-scored, log-normalized mean interaction scores averaged across all cells from a specific sample.

Figure 5. Platelet module signatures in patients have been related to convalescence, survival, and fatal.



(A) Cell cluster UMAP representation of all merged platelets. (B) Stacked density plot display platelets cluster proportion under different disease severity. (C) Gene-Concept Network display fatal cluster C4 up-regulated genes and enriched pathways in gene ontology (GO). (D) Tree plot display convalescence cluster C8 enriched pathways in GO.

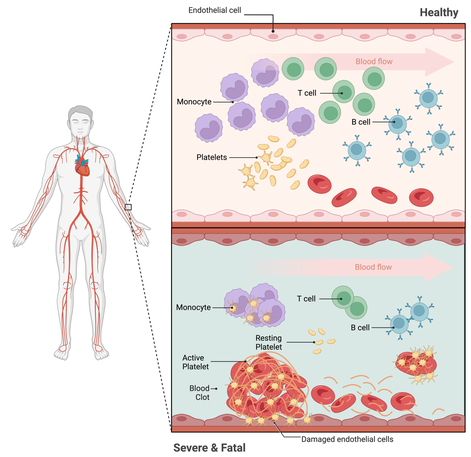
Figure 6. Platelet survival and fatal signatures to predict the dynamic in severe patients



(A, B) Pseudo-time plot of platelets from cluster C0, C1, C4 and C6 exhibiting trajectory fates. (C, D) Volcano plot display the genes constantly up/down-regulated in the direction of disease severity, proposed two gene list modules: fatal and survival modules.

Conclusions

- Integrative analysis highlights both common and unique features of platelets across different disorders (Fig. 1).
- We found that the platelet-to-T-cell ratio in PBMC was the strongest predictor for separating survivors from non-survivors (Fig. 2).
- For scRNA-seq platelet data, when compares the DNN and XGB machine learning models, showing the DNN excels in precision and F1 score while XGB has slightly higher accuracy and recall. Machine learning models assist in identifying biomarkers by uncovering the key features that are crucial for making accurate predictions. (Fig. 3)
- Severe to fatal diseases correlate with increased endothelial invasion by platelets. Platelets could influence lymphocyte activation, proliferation, and differentiation through interactions with other immune cells, implying that platelets can modulate lymphocyte function and contribute to inflammatory and immune responses (Fig. 4).
- Different platelet subgroups, particularly active coagulation, hypoxic, and quiescent clusters, are identified in non-surviving COVID-19 patients, suggesting targeted treatment approaches (Fig. 5).
- The identification of a precursor platelet cluster highlights the need for early intervention to prevent fatal platelet cluster formation (Fig. 6).
- Analysis of platelet clusters reveals distinct fatal and survival modules, suggesting different disease progression pathways (Fig. 6).



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Acknowledgements

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