Using Clinical Data and Cytokine Biomarkers to Predict Deep Vein Thrombosis After Rib Fractures

Ruowei Zhong, BS[1,2]; Renhua Li, PhD[1,3]; Fausto A. Bustos Carrillo, PhD[1,3]; Scott F. Grey, PhD[1,3]; Seth A. Schobel, PhD[1]; Eric A. Elster, MD[1,4]; Joseph S. Fernandez-Moure, MD[1,5]

[1] Uniformed Services University Surgical Critical Care Initiative (SC2i), Bethesda, MD; [2] Yale University, New Haven, CT; [3] Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD; [4] Walter Reed National Military Medical Center, Bethesda, MD; [5] Duke University School of Medicine, Duke University, Durham, NC

INTRODUCTION

Background: DVT is a major complication after rib fracture (RFx), but reliable early prediction tools remain limited. Prior work identified three RFx pattern groups and a 12-cytokine panel associated with post-RFx complications.

Hypothesis: Combining cytokine biomarkers with RFx patterns, demographic variables, and clinical data will improve early prediction of DVT after RFx.

Aims:

1. Evaluate associations among RFx groups, cytokine responses, and DVT.
2. Develop machine-learning models to predict post-RFx DVT.

METHODS

Study cohort and data:

- 142 RFx patients enrolled at Duke University Hospital, Grady Memorial Hospital, and Walter Reed Medical Center during 2014–2020.
- 431 longitudinal serum samples analyzed using the Meso Scale Discovery (MSD) platform.
- Clinical variables included demographics, RFx characteristics, injury factors, and complications.

Statistical analysis:

- Serum samples were divided into initial assessment data (I-data; n = 142) and follow-up data (F-data; n = 289) for model training and assessment, respectively.
- Hierarchical clustering identified cytokine profiles, and principal component analysis summarized pro- and anti-inflammatory cytokines (Pro-PC1 and Anti-PC1).
- A directed acyclic diagram (DAG) guided analyses of RFx1 and DVT, with cytokine PCs as potential mediators and age, sex, and ISS as potential confounders.
- Predictors were selected using bootstrap resampling, random forest importance scores, and recursive feature elimination.

RESULTS

Table 1. Characteristics of rib fracture patients with and without complications

Characteristic	With n = 73	Without n = 69	*P*
Age, mean (SD)	46.4 (17.7)	43.9 (15.9)	0.378
Sex, n (%)			0.789
Female	27 (37.0)	28 (40.6)	
Male	46 (63.0)	41 (59.4)	
Injury severity score, mean (SD)	34.4 (14.6)	24.5 (10.2)	<0.001
Fractured ribs by location, mean (SD)			
Rib location group 1	0.6 (0.8)	0.4 (0.6)	0.136
Rib location group 2	1.5 (1.3)	1.3 (1.1)	0.478
Rib location group 3	2.2 (2.0)	2.1 (1.7)	0.836
Total fractured ribs, mean (SD)	4.2 (3.0)	3.8 (2.5)	0.396
Complications			
DVT, n (%)	10 (13.7)	0 (0.0)	
Pneumonia, n (%)	6 (8.2)	0 (0.0)	
Acute lung injury, n (%)	28 (38.4)	0 (0.0)	
Acute kidney injury, n (%)	22 (30.1)	0 (0.0)	
Ventilator associated pneumonia, n (%)	17 (23.3)	0 (0.0)	
Sepsis, n (%)	13 (17.8)	0 (0.0)	
Count of complications, mean (SD)	2.7 (2.2)	0.0 (0.0)	
Total hospital days, mean (SD)	25.1 (17.0)	9.1 (8.2)	<0.001

Rib location group 1 includes 1st and 2nd ribs; group 2 includes 3rd - 5th, and 12th ribs, and group 3 includes 6th - 11th ribs.

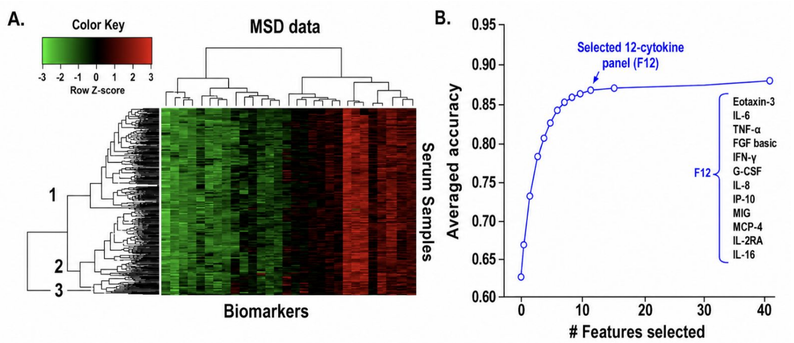
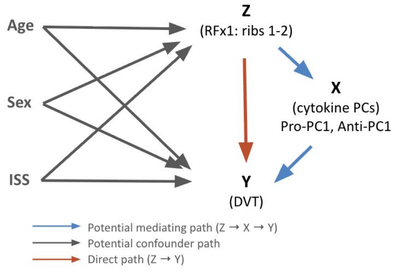


Figure 1. A. Unsupervised clustering of early serum cytokine measurements identified distinct inflammatory patterns associated with RFx-related complications. **B.** Recursive feature selection identified a 12-cytokine panel (F12) for DVT classification.

A. Causal DAG



B. Partial correlation analysis

Unadjusted association: Cor(Z,Y), p-value

	I-data	F-data
Pro-PC1	9.8e-02	5.8e-05
Anti-PC1	9.8e-02	5.8e-05

Adjusted association: Cor(Z,Y | X, age, sex, ISS), p-value

(Conditioning on cytokine PCs and clinical covariates simultaneously)

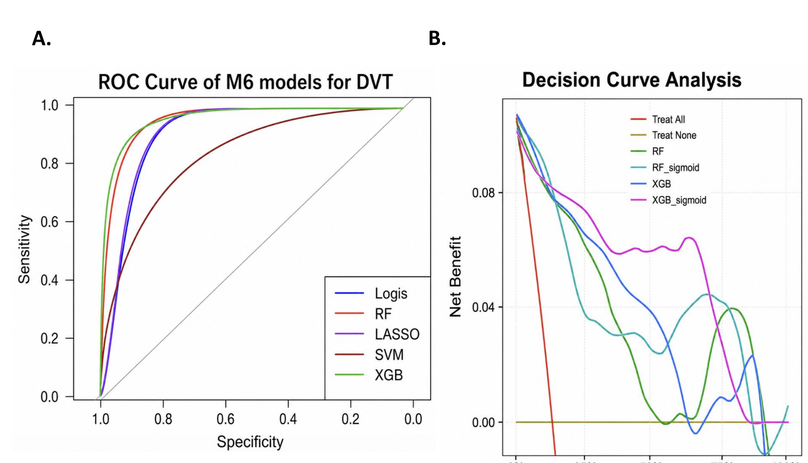
	I-data	F-data
Pro-PC1	1.6e-02	4.2e-09
Anti-PC1	6.3e-03	6.0e-13

Figure 2. A. Directed acyclic diagram (DAG) showing cytokine PCs as potential mediators and age, sex, and ISS as potential confounders. **B.** Partial correlation analysis of RFx1 and DVT. RFx1, defined as fractures of ribs 1–2, remained associated with DVT after adjustment for cytokine PCs, age, sex, and ISS.

Table 2. Model comparisons for DVT using different combinations of predictors

Model	Predictors	Best Model	AUC	Sensitivity	Specificity
M1	F12	XGB	0.76	0.74	0.70
M2	IL-2RA	XGB	0.68	0.84	0.52
M3	IL-2RA + RFx group1 + age + sex	XGB	0.91	0.97	0.78
M4	IL-2RA + RFx group2 + age + sex	XGB	0.95	0.97	0.83
M5	IL-2RA + RFx group3 + age + sex	XGB	0.96	1.00	0.89
M6	IL-2RA + total RFx class + age + sex	XGB	0.97	1.00	0.85

RFx groups were defined by location: group 1, ribs 1–2; group 2, ribs 3–5 and 12; and group 3, ribs 6–11.



C.

Model	AUC	Sensitivity	Specificity	Intercept	Slope
M6 XGB	0.971	1.000	0.845	-1.136	0.792
M6 XGB_Sigmoid	0.971	1.000	0.837	0.001	0.999
M6 RF	0.951	0.968	0.872	-0.876	1.000
M6 RF_Sigmoid	0.951	0.968	0.872	0.000	0.999

Figure 3. A. ROC curves for M6 models predicting DVT show strong discrimination, with XGB and RF achieving the highest AUCs (0.971 and 0.951, respectively), outperforming logistic, LASSO, and SVM models. **B.** Decision curve analysis demonstrates that XGB_sigmoid provided the highest net benefit across a broad range of threshold probabilities (approximately 10–75%), suggesting potential clinical utility for DVT risk stratification across varied decision thresholds. **C.** Calibration metrics show that sigmoid transformation improved calibration slopes toward 1.0 and reduced intercept deviation without changing AUC or sensitivity/specificity.

CONCLUSION

- A 12-cytokine panel identified distinct inflammatory patterns after RFx.
- RFx1, defined as fractures of ribs 1–2, remained associated with DVT after adjustment for cytokine PCs, age, sex, and ISS.
- IL-2RA, the alpha chain of the IL-2 receptor and a marker of immune activation, supported strong DVT prediction when combined with total RFx class, age, and sex.
- The M6 model showed strong discrimination and potential clinical utility for early DVT risk stratification.
- External validation in larger military and civilian trauma cohorts is needed to confirm the model's generalizability and clinical utility for early DVT risk prediction.

*SC2i is a consortium of Uniformed Services University of the Health Sciences, Walter Reed National Military Medical Center, Duke Health, Emory University School of Medicine, and Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.