



Peak Thromboinflammatory Biomarkers and ICU Mortality in Severe Viral Pneumonia

I Made Prema Putra^{1*}, Made Wirga Wirgunatha¹, Putu Ugi Sugandha¹,
I Made Harry Pranata¹, Putu Eka Nantha Kusuma¹,
I Gusti Ngurah Mahaalit Aribawa¹, I Gusti Agung Gede Utara Hartawan¹,
Putu Agus Surya Panji¹, Made Wiryana¹

1. Department of Anesthesiology and Intensive Therapy, Faculty of Medicine, Universitas Udayana - Udayana University Hospital, Denpasar, Indonesia

*corresponding author

DOI: 10.55497/majanestcricar.v44i3.515

ABSTRACT

Introduction: Risk stratification in severe viral pneumonia requiring intensive care may benefit from integrating clinical variables and thromboinflammatory biomarkers. This study aim to evaluated the association of peak D-dimer, C-reactive protein (CRP), fibrinogen, and interleukin-6 (IL-6) with ICU mortality.

Method: This retrospective cohort study used secondary data from confirmed SARS-CoV-2-related severe viral pneumonia patients admitted to the ICU from July to August 2021. Peak biomarker values during ICU care were analyzed with baseline clinical covariates. The primary outcome was ICU mortality. Bivariable testing, logistic regression using log-transformed biomarkers, and receiver operating characteristic analysis were performed.

Results: Forty-one patients were included; 32 (78.0%) died. Median D-dimer and CRP were higher among non-survivors, but biomarker differences did not reach statistical significance. Mechanical ventilation was strongly associated with mortality (96.3% vs 42.9%; $p < 0.001$) and remained significant in an adjusted model (OR 60.20; 95% CI 3.52-1029.34; $p = 0.005$). The clinical model yielded an AUC of 0.712, while adding biomarkers increased AUC to 0.788.

Conclusion: In this small ICU cohort, peak thromboinflammatory biomarkers showed directional risk signals but were not statistically significant independent predictors. Requirement for mechanical ventilation was the strongest clinical marker of ICU mortality.

Keywords: D-dimer, ICU mortality, interleukin-6, severe viral pneumonia, thromboinflammation



Biomarker Tromboinflamasi Puncak dan Mortalitas ICU pada Pneumonia Viral Berat

**I Made Prema Putra^{1*}, Made Wirga Wirgunatha¹, Putu Ugi Sugandha¹,
I Made Harry Pranata¹, Putu Eka Nantha Kusuma¹,
I Gusti Ngurah Mahaalit Aribawa¹, I Gusti Agung Gede Utara Hartawan¹,
Putu Agus Surya Panji¹, Made Wiryana¹**

1. Departemen Anestesiologi dan Terapi Intensif, Fakultas Kedokteran, Universitas Udayana – Rumah Sakit Universitas Udayana, Denpasar, Indonesia

*penulis korespondensi

DOI: 10.55497/majanestcricar.v44i3.515

ABSTRAK

Pendahuluan: Stratifikasi risiko pada pneumonia viral berat di ICU memerlukan integrasi parameter klinis dan biomarker tromboinflamasi. Penelitian ini bertujuan untuk mengevaluasi hubungan nilai puncak D-dimer, C-reactive protein (CRP), fibrinogen, dan interleukin-6 (IL-6) dengan mortalitas ICU.

Metode: Studi kohort retrospektif ini menggunakan data sekunder pasien pneumonia viral berat terkonfirmasi yang dirawat di ICU pada Juli-Agustus 2021. Nilai puncak biomarker selama perawatan ICU dianalisis bersama kovariat klinis dasar. Luaran primer adalah mortalitas ICU. Analisis dilakukan dengan uji bivariat, regresi logistik, transformasi log biomarker, dan area under the receiver operating characteristic curve (AUC).

Hasil: Sebanyak 41 pasien dianalisis; 32 pasien (78,0%) diantaranya meninggal. Median D-dimer dan CRP lebih tinggi pada kelompok meninggal dibandingkan hidup, tetapi perbedaan biomarker tidak mencapai kemaknaan statistik. Penggunaan ventilator berhubungan kuat dengan mortalitas (96,3% vs 42,9%; $p < 0,001$) dan tetap bermakna pada model yang disesuaikan (OR 60,20; 95% CI 3,52-1029,34; $p = 0,005$). Model klinis memiliki AUC 0,712, sedangkan penambahan biomarker meningkatkan AUC menjadi 0,788.

Simpulan: Pada studi kohort ini, biomarker tromboinflamasi puncak menunjukkan kecenderungan risiko tetapi tidak menjadi prediktor independen yang bermakna. Kebutuhan ventilator merupakan penanda klinis terkuat untuk mortalitas ICU.

Kata Kunci: D-dimer, interleukin-6, mortalitas ICU, pneumonia viral berat, tromboinflamasi

INTRODUCTION

Severe viral pneumonia requiring intensive care is frequently characterized by respiratory failure, systemic inflammation, endothelial dysfunction, and coagulation activation. These mechanisms may interact as thromboinflammation, in which inflammatory signaling and coagulation activation amplify each other and contribute to organ failure.^{1,2} In Indonesia, national ICU outcome data remain limited, and recent claims-based evidence has emphasized the need for locally generated critical care data to contextualize ICU length of stay and mortality patterns.³

In critical care practice, D-dimer, CRP, fibrinogen, and IL-6 are commonly available biomarkers that represent complementary biological domains: fibrinolysis and coagulation activation, systemic inflammation, acute-phase response, and cytokine-driven inflammation. Prior ICU studies and meta-analytic evidence have reported associations between these markers and mortality, although their incremental value beyond clinical severity indicators varies across cohorts.⁴⁻⁹

Prediction studies should report not only statistical association but also model performance, including discrimination and calibration, to clarify whether biomarkers add useful prognostic information beyond routine clinical variables.¹⁰⁻¹² This study aimed to evaluate the prognostic association of peak thromboinflammatory biomarkers with ICU mortality and to explore whether biomarker information improved model discrimination when added to routinely available clinical covariates.

METHOD

This was an observational analytic study using a retrospective cohort design. The study used secondary data from patients with confirmed SARS-CoV-2-related severe viral pneumonia admitted to the ICU during July-August 2021. The study was conducted in the Department of Anesthesiology and Intensive Therapy, Faculty of Medicine, Universitas Udayana - Udayana University Hospital, Denpasar, Bali, Indonesia. The reporting approach followed the key

principles of transparent prognostic model reporting.^{10,11}

The target population was all severe or critical confirmed SARS-CoV-2 pneumonia patients receiving intensive care during the study period. Total sampling was used because the study was based on a fixed retrospective dataset from a limited study period. Patients were eligible if they had a documented final ICU outcome and available data for the main biomarker analysis. Patients with invalid or duplicate records, unclear final outcome, or very early referral out without ascertainable outcome were excluded. After data cleaning, 41 complete cases were included in the final analysis. No formal a priori sample size calculation was performed; therefore, the study was interpreted as an exploratory analysis intended to generate local evidence and hypotheses for larger multicenter validation studies.

The primary predictors were peak D-dimer, peak CRP, peak fibrinogen, and peak IL-6. Peak was defined as the highest recorded value during ICU treatment in the available dataset. Clinical covariates included age, sex, body mass index (BMI), diabetes mellitus, hypertension, and selected clinical variables such as mechanical ventilation, thrombolytic treatment with alteplase, and computed tomography pulmonary angiography (CTPA). The primary outcome was ICU mortality, coded as survivor or non-survivor. Secondary descriptive outcomes included ICU length of stay and total hospital length of stay. Numerical data were assessed for distribution and summarized as mean $\pm$ standard deviation or median (interquartile range [IQR]) as appropriate. Categorical data were summarized as number and percentage. Between-group comparisons used the independent t-test or Mann-Whitney U test for numerical variables and the chi-square or Fisher exact test for categorical variables. Biomarkers were consistently expressed as natural log-transformed variables in logistic regression (ln-D-dimer, ln-CRP, ln-fibrinogen, and ln-IL-6) because of skewed distributions. Univariable and multivariable logistic regression models were reported as odds ratios (ORs), 95% confidence intervals (CIs), and p-values. Discrimination was assessed using the area under the receiver operating characteristic

curve (AUC). Formal calibration testing and internal validation were not performed because the small number of observations and survivors could have resulted in unstable estimates. This limitation was considered when interpreting model performance. Statistical significance was defined as a two-sided $p < 0.05$.

This study was approved by the Research Ethics Committee, Faculty of Medicine, Universitas Udayana, Indonesia (No. 0605/UN14.2.2.VII.14/LT/2026; protocol No. 2026.03.1.0191; 13 February 2026). Patient identifiers were removed from the retrospective secondary dataset.

RESULTS

Of the 90 screened ICU records, 41 patients met the eligibility criteria and were included in the final analysis (Figure 1). The overall ICU mortality was 78.0% (32/41). Table 1 summarizes numerical characteristics according to survival status. Non-survivors had higher median peak D-dimer and CRP levels than survivors, but the differences were not statistically significant. ICU and hospital lengths of stay were longer among survivors, reflecting early mortality among many non-survivors.

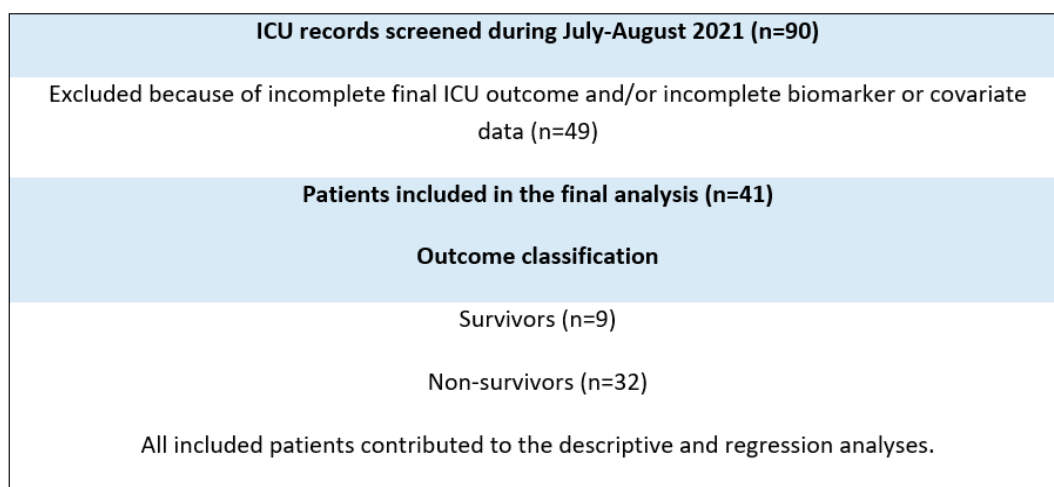


Figure 1. Study flow diagram

Table 1. Numerical characteristics according to ICU survival status

Variables	Survivors (n=9)	Non-survivors (n=32)	p-value
Age, years, median (IQR)	59.0 (33.0-62.0)	57.5 (52.0-65.3)	0.440
ICU length of stay, days, median (IQR)	11.0 (6.0-13.0)	5.5 (3.8-8.3)	0.023
Hospital length of stay, days, mean $\pm$ SD	16.33 $\pm$ 8.59	8.53 $\pm$ 5.01	0.001
Height, cm, median (IQR)	170.0 (162.0-170.0)	165.0 (165.0-170.0)	0.820
Weight, kg, median (IQR)	75.0 (70.0-85.0)	70.0 (67.3-75.0)	0.196
BMI, kg/m ² , mean $\pm$ SD	29.26 $\pm$ 7.89	25.58 $\pm$ 2.85	0.203
D-dimer, median (IQR)	3410 (1148-5310)	7014 (1837-10000)	0.168
CRP, median (IQR)	82.9 (59.8-212.7)	230.7 (91.7-300.0)	0.114
Fibrinogen, median (IQR)	476.1 (409.3-999.0)	422.9 (358.7-522.8)	0.243
IL-6, median (IQR)	26.4 (21.8-35.5)	33.2 (16.6-88.7)	0.671

Table 2. Categorical variables and ICU mortality

Variable	Category	Survivor n (%)	Non-survivor n (%)	p-value
Sex	Female	2 (22.2)	7 (77.8)	1.000
	Male	7 (21.9)	25 (78.1)	
Vaccination status	Unvaccinated	5 (18.5)	22 (81.5)	0.692
	Vaccinated	4 (28.6)	10 (71.4)	
Diabetes mellitus	No	6 (23.1)	20 (76.9)	1.000
	Yes	3 (20.0)	12 (80.0)	
Hypertension	No	5 (27.8)	13 (72.2)	0.471
	Yes	4 (17.4)	19 (82.6)	
Asthma	No	9 (23.1)	30 (76.9)	1.000
	Yes	0 (0.0)	2 (100.0)	
Mechanical ventilation	No	8 (57.1)	6 (42.9)	<0.001
	Yes	1 (3.7)	26 (96.3)	
Alteplase	No	5 (33.3)	10 (66.7)	0.248
	Yes	4 (15.4)	22 (84.6)	
CTPA	No	7 (20.0)	28 (80.0)	0.597
	Yes	2 (33.3)	4 (66.7)	

Table 3 presents logistic regression results. In univariable models using natural log-transformed biomarkers, ln-D-dimer and ln-CRP showed positive point estimates for mortality, whereas ln-fibrinogen showed an inverse point estimate; however, the single-biomarker associations did

not reach statistical significance. In the adjusted clinical model, no baseline clinical covariate was independently associated with mortality. In the model including mechanical ventilation, ventilator use remained the dominant predictor of ICU mortality.

Table 3. Logistic regression and model discrimination for ICU mortality

Model/predictor	OR (95% CI)	p-value	AUC
Univariable ln-D-dimer	1.68 (0.84-3.35)	0.142	-
Univariable ln-CRP	1.60 (0.77-3.35)	0.211	-
Univariable ln-fibrinogen	0.20 (0.03-1.43)	0.109	-
Univariable ln-IL-6	1.08 (0.60-1.94)	0.805	-
Univariable mechanical ventilation	34.67 (3.62-332.36)	0.002	-
Clinical model: age, sex, BMI, DM, hypertension	-	-	0.712
Biomarker model: ln-D-dimer, ln-CRP, ln-fibrinogen, ln-IL-6	-	-	0.747
Clinical + biomarker model	-	-	0.788
Clinical + mechanical ventilation model	-	-	0.924
Adjusted mechanical ventilation effect	60.20 (3.52-1029.34)	0.005	-

DISCUSSION

This retrospective ICU cohort showed three main findings. First, ICU mortality was high, consistent with the severe clinical phenotype represented in this dataset and with the broader need to describe ICU outcomes in Indonesia using local data.³ Second, peak D-dimer, CRP, and IL-6 were numerically higher among non-survivors, but the associations were not statistically significant in this small cohort. Third, mechanical ventilation was strongly associated with mortality and was the most practical clinical marker of severity. Clinically, these findings suggest that thromboinflammatory biomarkers may describe disease biology, but the need for invasive mechanical ventilation remains more immediately applicable for bedside risk recognition in this dataset.

The direction of the D-dimer and CRP findings is biologically plausible. Severe viral pneumonia may involve systemic inflammation, endothelial activation, coagulation pathway activation, and fibrinolysis, and previous studies have shown that D-dimer, CRP, and IL-6 can be associated with ICU mortality or disease severity.^{4-9,13} However, the lack of statistical significance in this study should not be interpreted as evidence of no association; rather, it likely reflects limited sample size, few survivors, and the heterogeneity of biomarker timing.

The inverse point estimate for fibrinogen deserves cautious interpretation. Fibrinogen is an acute-phase protein and a coagulation substrate, and its concentration may vary according to timing, inflammation, consumption, anticoagulation, and disease trajectory. A single peak value may not capture clinically relevant kinetics. Recent biomarker literature also emphasizes that serial changes, combined indices, and dynamic patterns may be more informative than isolated measurements in critically ill patients.^{5,8}

The increase in AUC from 0.712 in the clinical model to 0.788 after adding biomarkers suggests potential incremental discrimination, but this difference is exploratory. Because the dataset included only 41 patients and 9 survivors, the multivariable model is prone to overfitting. Following prediction-model reporting principles, the AUC should be viewed as

apparent discrimination rather than a validated performance estimate.^{10,11} Future studies should use a larger multicenter cohort, prespecified predictor handling, internal validation with bootstrapping, and external validation before clinical implementation.

Mechanical ventilation was strongly associated with mortality in both unadjusted and adjusted analyses. This finding is expected because invasive ventilation is a marker of advanced respiratory failure and overall severity; large ICU cohorts have consistently reported worse outcomes among patients with severe respiratory failure requiring intensive care and ventilatory support.^{14,15} For etiologic inference, ventilation may act as a mediator between disease severity and death rather than a baseline confounder. Therefore, the adjusted association should be interpreted mainly as a severity marker, not as evidence that ventilation itself independently caused mortality.

From a risk-stratification perspective, discrimination alone is insufficient; calibration is also essential before a model can be recommended for individual prognostic prediction.¹⁶ In small datasets, adding several candidate predictors can produce unstable coefficients, optimistic AUC estimates, and limited transportability.¹⁷ Therefore, the present findings should be used to support clinical interpretation and future study design rather than direct bedside prediction. The observed direction of higher D-dimer among non-survivors is consistent with the broader literature linking coagulation activation with poor outcome, although the non-significant result in this cohort underscores the need for adequately powered validation.¹⁸

This study has several limitations. The sample size was small, and the number of survivors was limited, reducing statistical power and precision. A formal a priori sample size calculation was not performed because the study used total sampling from a fixed retrospective dataset. The study used retrospective secondary data, so residual confounding and information bias are possible. Biomarker timing was represented by peak values rather than standardized sampling points or trajectories. Physiologic severity scores,

organ support intensity, anticoagulation details, and treatment changes were not fully captured. Calibration and internal validation were not performed because of the limited number of observations and survivors. These limitations mean that the findings should be considered hypothesis-generating rather than definitive.

CONCLUSION

In this retrospective ICU cohort of severe SARS-CoV-2-related viral pneumonia, peak thromboinflammatory biomarkers showed directional prognostic signals but were not statistically significant independent predictors of ICU mortality. Mechanical ventilation was the strongest and most practical clinical marker of death, and biomarker addition modestly increased apparent model discrimination. Larger, prospectively standardized studies with adequate sample size, calibration assessment, and internal or external validation are needed to determine whether dynamic thromboinflammatory biomarker profiles can improve risk stratification beyond routine clinical severity markers.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENT

The authors thank the Department of Anesthesiology and Intensive Therapy, Faculty of Medicine, Universitas Udayana/Udayana University Hospital, for supporting access to anonymized secondary data for academic analysis.

REFERENCES

1. World Health Organization. Clinical management of COVID-19: living guideline. Geneva: World Health Organization; 2025.
2. Ma L, Willey J. The interplay between inflammation and thrombosis in COVID-19: mechanisms, therapeutic strategies, and challenges. *Thromb Update*. 2022;8:100117. doi:10.1016/j.tru.2022.100117.
3. Putra IMP, Sudiantara PH, Aryawangsa AAN, Panji PAS, Senapathi TGA. Trends in ICU length of stay and in-hospital mortality in Indonesia: A national health insurance claims analysis, 2019-2024. *J Crit Care*. 2026;94:155523. doi:10.1016/j.jcrc.2026.155523.
4. Milenkovic M, Hadzibegovic A, Kovac M, Jovanovic B, Stanisavljevic J, Djikic M, et al. D-dimer, CRP, PCT, and IL-6 levels at admission to ICU can predict in-hospital mortality in patients with COVID-19 pneumonia. *Oxid Med Cell Longev*. 2022;2022:8997709. doi:10.1155/2022/8997709.
5. Arturi F, Melegari G, Giansante A, Giuliani E, Bertellini E, Barbieri A. COVID-19 Biomarkers for Critically Ill Patients: A Compendium for the Physician. *Neurol Int*. 2023 Jul 23;15(3):881-95. doi: 10.3390/neurolint15030056.
6. Popadic V, Klasnja S, Milic N, Rajovic N, Aleksic A, Milenkovic M, et al. Predictors of Mortality in Critically Ill COVID-19 Patients Demanding High Oxygen Flow: A Thin Line between Inflammation, Cytokine Storm, and Coagulopathy. *Oxid Med Cell Longev*. 2021 Apr 20;2021:6648199. doi: 10.1155/2021/6648199.
7. Eljilany I, Elzouki AN. D-dimer, fibrinogen, and IL-6 in COVID-19 patients with suspected venous thromboembolism: a narrative review. *Vasc Health Risk Manag*. 2020;16:455-62. doi:10.2147/VHRM.S280962.
8. Hafez W, Nasa P, Khairy A, et al. Interleukin-6 and the determinants of severe COVID-19: A retrospective cohort study. *Medicine (Baltimore)*. 2023;102(45):e36037. doi:10.1097/MD.00000000000036037.
9. Nugroho J, Wardhana A, Maghfirah I, Mulia EPB, Rachmi DA, A'yun MQ, et al. Relationship of D-dimer with severity and mortality in SARS-CoV-2 patients: a meta-analysis. *Int J Lab Hematol*. 2021;43(1):110-5. doi:10.1111/ijlh.13336.
10. Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. *Ann Intern Med*. 2015;162(1):55-63. doi:10.7326/M14-0697.
11. Moons KGM, Altman DG, Reitsma JB, Ioannidis JPA, Macaskill P, Steyerberg EW, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis

- or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med.* 2015;162(1):W1-W73. doi:10.7326/M14-0698.
12. Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E, et al. Prediction models for diagnosis and prognosis of COVID-19: systematic review and critical appraisal. *BMJ.* 2020;369:m1328. doi:10.1136/bmj.m1328.
 13. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood.* 2020;135(23):2033-40. doi:10.1182/blood.2020006000.
 14. COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. *Intensive Care Med.* 2021;47(1):60-73. doi:10.1007/s00134-020-06294-x.
 15. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. *JAMA Intern Med.* 2020;180(10):1345-55. doi:10.1001/jamainternmed.2020.3539.
 16. Van Calster B, McLernon DJ, van Smeden M, Wynants L, Steyerberg EW. Calibration: the Achilles heel of predictive analytics. *BMC Med.* 2019;17(1):230. doi:10.1186/s12916-019-1466-7.
 17. Riley RD, Ensor J, Snell KIE, Harrell FE Jr, Martin GP, Reitsma JB, et al. Calculating the sample size required for developing a clinical prediction model. *BMJ.* 2020;368:m441. doi:10.1136/bmj.m441.
 18. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost.* 2020;18(4):844-847. doi:10.1111/jth.14768.