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INFLAMMATORY, COAGULATION, AND THROMBO-INFLAMMATORY BIOMARKERS ASSOCIATED WITH IN-HOSPITAL MORTALITY IN HOSPITALISED PATIENTS WITH COVID-19

INFLAMATORNI, KOAGULACIONI I TROMBOINFLAMATORNI BIOMARKERI POVEZANI SA INTRAHOSPITALNIM MORTALITETOM KOD HOSPITALIZOVANIH BOLESNIKA SA COVID-19

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Summary

Background: Early risk stratification in hospitalised patients with coronavirus disease 2019 is clinically important, where management relies on routinely available laboratory data. This study evaluated the association of conventional inflammatory, coagulation, hematologic, and oxygenation-related parameters, together with derived thrombo-inflammatory indices, with in-hospital mortality.

Methods: This retrospective single-centre cohort study included 78 hospitalised patients with reverse transcription polymerase chain reaction-confirmed coronavirus disease 2019 and documented in-hospital outcomes. Variables included oxygen saturation, leukocyte differential parameters, C-reactive protein, D-dimer, ferritin, lactate dehydrogenase, urea, and creatinine. Derived indices included neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, systemic inflammation response index, D-dimer-to-lymphocyte ratio, C-reactive protein-to-lymphocyte ratio, and an exploratory scaled thrombo-inflammatory hypoxemia-lymphopenia index. Group comparisons, receiver operating characteristic analysis, and age-adjusted logistic regression were performed.

Results: Of the 78 patients, 66 survived, and 12 died. Non-survivors had lower oxygen saturation and higher

Kratak sadržaj

Uvod: Rana procena rizika kod hospitalizovanih pacijenata sa koronavirusnom bolešću 2019 ima veliki klinički značaj, posebno u uslovima kada se lečenje zasniva na rutinski dostupnim laboratorijskim parametrima pri prijemu. Ova studija ispitivala je povezanost konvencionalnih inflamatornih, koagulacionih, hematoloških i oksigenacionih parametara, zajedno sa odabranim izvedenim tromboinflamatornim indeksima, sa intrahospitalnim mortalitetom.

Metode: Retrospektivna, jednocentrična kohortna studija obuhvatila je 78 odraslih hospitalizovanih pacijenata sa RT-PCR potvrđenoim kovidom i dokumentovanim intrahospitalnim ishodom. Analizirani su prijemni parametri, uključujući saturaciju kiseonikom, diferencijalnu leukocitnu formulu, C-reaktivni protein, D-dimer, feritin, laktat-dehidrogenazu, ureu i kreatinin, kao i izvedene tromboinflamatorne indekse. Primenjene su komparativne analize grupa, analiza ROC krive i logistička regresija korigovana za starost.

Rezultati: Od 78 pacijenata, 66 je preživelo, a 12 je umrlo. Preminuli su imali nižu prijemnu saturaciju kiseonikom, više vrednosti C-reaktivnog proteina, D-dimera, feritina, laktat-dehidrogenaze i neutrofila, kao i niže vrednosti limfocita. Od izvedenih indeksa, više vrednosti kod preminulih pokazali su neutrofilno-limfocitni odnos, sis-

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C-reactive protein, D-dimer, ferritin, lactate dehydrogenase, neutrophil percentage and count, and lower lymphocyte percentage and count. Among the derived indices, the neutrophil-to-lymphocyte ratio, systemic immune-inflammation index, systemic inflammation response index, D-dimer-to-lymphocyte ratio, C-reactive protein-to-lymphocyte ratio, and the exploratory scaled thrombo-inflammatory hypoxemia-lymphopenia index were higher in non-survivors. C-reactive protein, D-dimer, neutrophil-to-lymphocyte ratio, D-dimer-to-lymphocyte ratio, C-reactive protein-to-lymphocyte ratio, and the exploratory scaled thrombo-inflammatory hypoxemia-lymphopenia index remained associated with mortality in age-adjusted models.

Conclusion: In hospitalised patients with coronavirus disease 2019, in-hospital mortality was associated with higher systemic inflammation, greater coagulation activation, more pronounced lymphopenia, and lower oxygen saturation. Routine laboratory biomarkers and derived thrombo-inflammatory indices may support early mortality-oriented risk stratification.

Keywords: biomarkers, C-reactive protein, COVID-19, D-dimer, mortality, prognosis

temski imuno-inflamatorni indeks, sistemski inflamatorni odgovor indeks, odnos D-dimera i limfocita, odnos C-reaktivnog proteina i limfocita i eksploratorni skalirani trombоinflamatorni hipoksemijsko-limfopenijski indeks. Ovi parametri ostali su povezani sa mortalitetom i u modelima korigovanim za starost.

Zaključak: Intrahospitalni mortalitet je bio povezan sa izraženijom sistemskom inflamacijom, većom aktivacijom koagulacije, naglašenijom limfopenijom i nižom prijemnom zasićenošću krvi kiseonikom. Rutinski laboratorijski biomarkeri i odabrani izvedeni trombоinflamatorni indeksi mogu pomoći u ranoj proceni rizika od smrtnog ishoda.

Ključne reči: biomarkeri, C-reaktivni protein, COVID-19, D-dimer, mortalitet, prognoza

Introduction

Coronavirus disease 2019 (COVID-19) shows marked clinical variability, from mild self-limited disease to severe pneumonia, acute respiratory distress syndrome, multiorgan failure, and death. Although it was initially viewed mainly as a respiratory infection, severe COVID-19 is now understood as a multisystem disorder characterised by dysregulated inflammation, endothelial damage, hematologic disturbances, and activation of coagulation pathways. In hospitalised patients, these features make early risk assessment particularly important (1, 2).

Early reports from hospitalised adult cohorts showed that adverse COVID-19 outcomes were linked not only to older age and greater clinical severity at presentation, but also to abnormalities in routine laboratory parameters. In the Wuhan cohort, older age and increased admission D-dimer were among the strongest factors associated with in-hospital death. Likewise, coagulation abnormalities, particularly markedly elevated D-dimer values, were reported more frequently in patients with fatal outcomes (1, 2).

Because routine laboratory tests are low-cost, rapidly obtainable, and routinely measured at hospital admission, they have been widely investigated as tools for outcome assessment in COVID-19. In addition to conventional biomarkers such as C-reactive protein, ferritin, lactate dehydrogenase, and D-dimer, CBC-derived inflammatory indices have also been investigated as accessible markers of clinical risk. Admission systemic immune-inflammation index has been associated with in-hospital mortality in COVID-19 patients, while other studies have suggested prognostic relevance for indices such as NLR, MLR, and SIRI (3, 4). Likewise, studies evaluating hemogram parameters together with CRP have supported the association of admission inflammation-related biomarkers with mortality in hospitalised COVID-19 patients (5).

Recent evidence indicates that routine blood-based laboratory tests may help identify hospitalised patients with SARS-CoV-2 infection who are at increased risk of death, supporting their use in real-world risk stratification (6).

However, the prognostic role of conventional inflammatory and coagulation markers relative to derived thrombo-inflammatory indices has not been fully clarified in real-world hospital cohorts. This question is particularly relevant in settings where clinical decision-making depends largely on routinely available laboratory data rather than advanced biomarker panels. Recent hospital-based studies from different settings, including Serbia and Peru, have shown that abnormalities in admission CRP, D-dimer, LDH, and oxygenation-related parameters are associated with mortality in hospitalised COVID-19 patients (7–9). At the same time, increasing attention has been given to ratio-based and composite biomarkers that combine multiple biological domains. In particular, the D-dimer-to-lymphocyte ratio has been evaluated as a mortality-related marker in hospitalised COVID-19 patients, while other composite laboratory indices have been proposed as exploratory tools for outcome assessment (10–12). Even so, evidence on the comparative and potentially complementary value of these derived indices remains limited, especially in single-centre real-world hospital datasets.

This study evaluated the association of routine inflammatory, coagulation, hematologic, and oxygenation-related admission parameters with in-hospital mortality in hospitalised patients with COVID-19. In addition to conventional biomarkers, we examined selected derived inflammatory and thrombo-inflammatory indices to explore whether they might provide complementary prognostic information in routine clinical practice.

Materials and Methods

Study design and participants

This retrospective single-centre cohort study was conducted at Hospital »Sveti Vračevi«, Bijeljina, Bosnia and Herzegovina, using routinely collected hospital data from December 2020 to April 2021. The study database was assembled retrospectively from hospital medical records and the Department of Haematology and Biochemistry's laboratory information system. Demographic characteristics, type of oxygen support, and routine laboratory parameters were retrieved from available records. The study was approved by the Ethics Committee of the Hospital »Sveti Vračevi«, Bijeljina (approval No. 4315-6-3/22, dated 07 April 2022) and was conducted in accordance with the Declaration of Helsinki.

The original dataset included 78 adult patients hospitalised in the COVID wards of the Hospital »Sveti Vračevi«, Bijeljina. Eligibility criteria for the present study were age >18 years, a positive SARS-CoV-2 RT-PCR test, hospitalisation at the study centre, and availability of admission laboratory data and documented in-hospital outcome.

Variables, outcome, and derived indices

The outcome of the present study was in-hospital mortality. Admission variables evaluated in the present analysis included age, oxygen saturation (SpO_2, %), leukocyte count, neutrophil percentage, neutrophil count, lymphocyte percentage, absolute lymphocyte count, monocyte count, platelet count, C-reactive protein (CRP), D-dimer, ferritin, lactate dehydrogenase (LDH), urea, and creatinine. ICU admission, mechanical ventilation, and length of hospitalisation were also analysed as indicators of in-hospital course according to outcome.

Routine laboratory work-up in the source dataset included blood gas analysis, complete blood count with differential leukocyte count, inflammatory markers, selected biochemical markers, and renal and liver function parameters. Haematology analyses were performed on the Cell-Dyn Ruby analyser (Abbott), biochemical and immunochemical analyses on the Alinity ci platform (Abbott), and blood gas analyses on the ABL 800 Flex analyser (Radiometer). Oxygen saturation was determined by amperometric measurement, complete blood count with leukocyte differential by flow cytometry, CRP and D-dimer by immunoturbidimetric methods, ferritin by chemiluminescent microparticle immunoassay, LDH by an IFCC-based spectrophotometric enzymatic method, and creatinine by the kinetic Jaffe method. Samples with marked haemolysis, lipemia, or icterus were excluded according to routine laboratory quality criteria.

In addition to conventional laboratory biomarkers, the following derived inflammatory and thrombo-inflammatory indices were calculated from admission laboratory data: neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), D-dimer-to-lymphocyte ratio (DLR), monocyte-to-lymphocyte ratio (MLR), aggregate index of systemic inflammation (AISI), and C-reactive protein-to-lymphocyte ratio (CLR). These indices were defined as follows:

NLR = neutrophil count/lymphocyte count

PLR = platelet count/lymphocyte count

SII = platelet count × neutrophil count/lymphocyte count

SIRI = neutrophil count × monocyte count/lymphocyte count

DLR = D-dimer/lymphocyte count

MLR = monocyte count/lymphocyte count

AISI = neutrophil count × monocyte count × platelet count/lymphocyte count

CLR = CRP/lymphocyte count

An exploratory composite index, the scaled thrombo-inflammatory hypoxemia-lymphopenia index ($TIHLI_3$), was also calculated as:

$TIHLI_3$ = (CRP × D-dimer)/(lymphocyte count × SpO_2 × 1000)

CRP was expressed in mg/L, D-dimer in ng/mL, lymphocyte count in $\times 10^9$/L, and SpO_2 in %. $TIHLI_3$ was evaluated as an exploratory composite index intended to integrate systemic inflammation, coagulation activation, lymphopenia, and hypoxemia.

Statistical analysis

The distribution of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables with non-normal distribution were presented as median (Q1–Q3), while categorical variables were presented as n (%). Group comparisons be-

tween survivors and non-survivors were performed using the Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate.

Receiver operating characteristic (ROC) analysis was used to assess the discriminatory performance of conventional biomarkers and derived indices for in-hospital mortality. Area under the ROC curve (AUC) values with 95% confidence intervals were calculated. Exploratory cut-off values were determined using the Youden index, and corresponding sensitivity and specificity were reported. In addition, pairwise comparisons of the leading dependent ROC curves were performed using the DeLong method.

Because of the limited number of fatal events, regression analyses were considered exploratory. Separate age-adjusted logistic regression models were fitted for selected biomarkers and derived indices to examine their association with in-hospital mortality while minimising overfitting. Odds ratios were expressed per 1-standard deviation increase in the predictor. CRP, D-dimer, NLR, DLR, CLR, and $TIHLI_3$ were log-transformed before standardisation. An exploratory combined logistic regression model including age, CRP, D-dimer, and admission SpO_2 was also constructed for in-hospital mortality. Model performance was summarised using AUC with 95% confidence interval.

Finally, Spearman's rank correlation analysis was used to examine interrelationships among the leading laboratory biomarkers and derived indices associated with mortality. A two-sided $p<0.05$ was considered statistically significant. All statistical analyses were performed using MedCalc Statistical Software, version 23.5.1 (MedCalc Software Ltd, Ostend, Belgium).

Results

A total of 78 hospitalised adult COVID-19 patients with available admission laboratory data and documented in-hospital outcome were included in the final prognostic analysis. Of these, 66 patients survived, and 12 died, corresponding to an in-hospital mortality rate of 15.4%.

As presented in *Table I*, non-survivors had lower admission oxygen saturation than survivors. In addition, they were more likely to require intensive care and mechanical ventilation during hospitalisation, whereas age, sex, and length of hospitalisation did not differ significantly between the groups.

According to *Table II*, non-survivors presented with significantly higher CRP, D-dimer, ferritin, and LDH levels than survivors. They also had higher neutrophil percentage and absolute neutrophil count, lower lymphocyte percentage and absolute lymphocyte count, and higher values of NLR, SII, SIRI, DLR, CLR, and $TIHLI_3$, whereas monocyte count did not differ significantly between the groups.

As shown in *Table III*, $TIHLI_3$, CRP, DLR, CLR, and D-dimer showed the best discriminatory performance for in-hospital mortality. Among conventional biomarkers, CRP had the highest AUC, whereas among derived indices $TIHLI_3$ and DLR performed best. Neutrophil percentage, lymphocyte percentage, and NLR also showed good discrimination, while ferritin, SpO_2, LDH, SIRI, absolute lymphocyte count, and SII showed moderate predictive performance.

As shown in *Table IV*, CRP, D-dimer, NLR, DLR, CLR, and $TIHLI_3$ remained significantly associated with in-hospital mortality in separate age-adjusted models. Overall, both conventional biomarkers and derived thrombo-inflammatory indices showed a significant age-adjusted association with fatal outcome.

Table I Demographic characteristics and in-hospital course according to in-hospital mortality.

Variable	Total (n=78)	Survivors (n=66)	Non-survivors (n=12)	p
Age, years	63.5 (56.0–73.8)	62.0 (54.3–72.8)	69.5 (63.0–75.8)	0.086
Male sex, n (%)	56 (71.8)	46 (69.7)	10 (83.3)	0.492
SpO2 on admission, %	91.0 (87.0–95.0)	92.9 (88.0–95.1)	85.0 (79.5–88.6)	0.003
ICU admission, n (%)	35 (44.9)	24 (36.4)	11 (91.7)	<0.001
Mechanical ventilation, n (%)	4 (5.1)	0 (0.0)	4 (33.3)	<0.001
Length of hospitalisation, days	11.0 (8.0–19.0)	11.0 (8.0–21.0)	10.0 (7.3–13.5)	0.361

Continuous variables are presented as median (Q1–Q3) and categorical variables as n (%). Group comparisons were performed using the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. SpO_2, peripheral oxygen saturation; ICU, intensive care unit.

Table II Laboratory biomarkers and derived indices according to in-hospital mortality.

Variable	Survivors (n=66)	Non-survivors (n=12)	p
A. Conventional laboratory biomarkers			
CRP, mg/L	44.0 (14.5–102.8)	144.0 (117.5–234.5)	<0.001
D-dimer, ng/mL	428.0 (289.2–1020.8)	2501.0 (1144.0–3201.5)	<0.001
Ferritin, ng/mL	494.3 (321.0–1032.0)	1433.0 (665.5–3239.2)	0.006
LDH, U/L	289.0 (236.0–409.0)	463.0 (395.0–586.8)	0.013
Leukocytes, $\times 10^9$/L	8.8 (6.1–11.8)	11.9 (8.1–14.7)	0.071
Neutrophils, %	81.9 (74.1–86.6)	90.1 (86.5–91.4)	0.002
Lymphocytes, %	10.7 (6.7–17.7)	4.9 (2.7–8.2)	0.002
Absolute lymphocytes, $\times 10^9$/L	0.89 (0.68–1.31)	0.57 (0.36–0.67)	0.018
Neutrophils, $\times 10^9$/L	7.34 (4.63–9.93)	10.34 (9.16–12.65)	0.013
Monocytes, $\times 10^9$/L	0.50 (0.31–0.73)	0.45 (0.34–0.85)	0.601
Platelets, $\times 10^9$/L	268.5 (182.0–337.8)	206.0 (153.2–268.8)	0.102
Urea, mmol/L	6.5 (4.5–9.3)	6.5 (5.6–12.4)	0.499
Creatinine, µmol/L	76.5 (65.3–94.5)	72.0 (60.5–90.0)	0.529
B. Derived inflammatory/thrombo-inflammatory indices			
NLR	7.71 (4.13–12.92)	18.46 (14.05–34.08)	0.003
PLR	284.9 (172.4–462.6)	438.3 (274.9–524.0)	0.115
SII	2207.1 (1039.2–3588.8)	4623.6 (2597.8–5663.0)	0.018
SIRI	3.57 (1.57–7.43)	9.71 (6.03–17.38)	0.014
DLR	521.9 (306.8–1138.5)	4253.6 (3298.9–5842.8)	<0.001
MLR	0.48 (0.33–0.90)	0.97 (0.63–1.46)	0.052
AISI	1114.3 (289.9–2073.6)	2228.3 (1047.6–3419.3)	0.081
CLR	50.23 (16.69–120.4)	349.7 (288.5–630.1)	<0.001
TIHLI3	0.245 (0.079–1.112)	9.795 (4.838–18.137)	<0.001

Data are presented as median (Q1–Q3). p values were calculated using the Mann–Whitney U test. Derived indices are presented as unitless ratios or composite indices. CRP, C-reactive protein; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; DLR, D-dimer-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; AISI, aggregate index of systemic inflammation; CLR, C-reactive protein-to-lymphocyte ratio; $TIHLI_3$, scaled thrombo-inflammatory hypoxemia-lymphopenia index.

Table III ROC analysis of conventional biomarkers and derived indices for prediction of in-hospital mortality.

Marker	AUC	95% CI	Youden cut-off	Sensitivity	Specificity
TIHLI3	0.886	0.782–0.996	>4.964	80.0%	89.1%
CRP, mg/L	0.879	0.787–0.972	>116.0	81.8%	86.4%
DLR	0.867	0.729–0.986	>3084.8	80.0%	87.9%
CLR	0.844	0.666–1.000	>277.9	80.0%	93.9%
D-dimer, ng/mL	0.842	0.739–0.944	>1018.0	81.8%	74.2%
Neutrophils, %	0.812	0.669–0.955	>88.7	70.0%	81.8%
Lymphocytes, %	0.811	0.664–0.957	≤5.4	70.0%	86.4%
NLR	0.794	0.596–0.992	>16.56	70.0%	86.4%
Ferritin, ng/mL	0.761	0.614–0.908	>1421.0	63.6%	80.0%
SpO_2 on admission, %	0.784	0.641–0.929	≤90.5	90.9%	67.2%
LDH, U/L	0.745	0.572–0.919	>391.0	80.0%	71.4%
SIRI	0.744	0.574–0.914	>5.786	80.0%	68.2%
Absolute lymphocytes, $\times 10^9$/L	0.734	0.520–0.949	≤0.68	80.0%	72.7%
SII	0.733	0.536–0.931	>4448.3	60.0%	84.8%

Data are presented as the area under the ROC curve (AUC) with 95% confidence intervals calculated using the DeLong method. Cut-off values were determined using the Youden index and should be interpreted as exploratory. Sensitivity and specificity are reported for the corresponding cut-off values. Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; CRP, C-reactive protein; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; DLR, D-dimer-to-lymphocyte ratio; CLR, C-reactive protein-to-lymphocyte ratio; $TIHLI_3$, scaled thrombo-inflammatory hypoxemia-lymphopenia index; SpO_2, peripheral oxygen saturation.

Table IV Age-adjusted logistic regression analysis for in-hospital mortality.

Predictor	Adjusted OR	95% CI	p
CRP	11.49	2.33–56.74	0.003
D-dimer	3.05	1.51–6.19	0.002
NLR	3.06	1.26–7.43	0.014
DLR	3.44	1.50–7.87	0.004
CLR	5.73	1.74–18.94	0.004
TIHLI3	4.18	1.79–9.78	0.001

Separate exploratory age-adjusted logistic regression models were fitted for each biomarker. Odds ratios are presented per 1-standard deviation increase in the predictor. CRP, D-dimer, NLR, DLR, CLR, and TIHLI3 were log-transformed before standardisation. Because of the limited number of fatal events, these models should be interpreted as exploratory age-adjusted association models.

Table V Exploratory combined logistic regression model for in-hospital mortality.

Predictor	Adjusted OR	95% CI	p
Age	1.84	0.60–5.71	0.288
CRP	9.21	1.60–53.12	0.013
D-dimer	2.04	0.84–4.93	0.116
SpO_2 on admission	0.52	0.24–1.11	0.089
Model performance			
n	Deaths	AUC	95% CI
78	12	0.911	0.830–0.991

The exploratory combined model included age, log-transformed CRP, log-transformed D-dimer, and admission SpO_2. Odds ratios are presented per 1-standard deviation increase in the predictor. AUC was calculated from the fitted logistic regression model. Because of the limited number of fatal events, the model should be regarded as exploratory and requires validation in independent cohorts. OR, odds ratio; CI, confidence interval; CRP, C-reactive protein; SpO_2, peripheral oxygen saturation; AUC, area under the receiver operating characteristic curve.

An exploratory combined logistic regression model including age, CRP, D-dimer, and admission SpO_2 was constructed to examine the joint association of inflammatory, coagulation-related, and oxygenation parameters with in-hospital mortality (*Table V*). The model showed high apparent discrimination, with an AUC of 0.911 (95% CI 0.830–0.991). Within the model, CRP remained the only statistically significant variable. Although D-dimer did not retain statistical significance in the full model, its inclusion improved the model's overall discriminatory performance. Because of the limited number of fatal events, this combined model should be interpreted as exploratory and requires validation in larger independent cohorts.

Pairwise comparison of the leading ROC curves showed no statistically significant difference between $TIHLI_3$ and CRP, $TIHLI_3$ and D-dimer, or CRP and D-dimer, whereas the comparison between $TIHLI_3$ and DLR showed borderline significance. Spearman correlation analysis demonstrated marked intercorrelation among the leading derived indices, with $TIHLI_3$ showing strong positive correlations with CLR, DLR, CRP, and D-dimer, and weaker inverse correlations with SpO_2 and absolute lymphocyte count.

Discussion

In this single-centre retrospective cohort of hospitalised COVID-19 patients, in-hospital death was associated with heightened systemic inflammation, increased coagulation activation, more marked lymphopenia, and lower admission oxygen saturation. Among conventional biomarkers, CRP and D-dimer showed the strongest association with mortality, while derived indices, including DLR, CLR, and the exploratory $TIHLI_3$, also showed substantial discriminatory ability.

An important result of the present analysis was the strong association between CRP and D-dimer and fatal in-hospital outcomes. Both markers were higher in non-survivors, achieved high AUC values, and remained associated with mortality in age-adjusted analyses. This is biologically plausible because severe COVID-19 reflects the combined effects of inflammatory dysregulation and coagulation activation. Our findings therefore align with both early studies highlighting D-dimer and coagulation abnormalities in fatal cases and more recent hospital cohorts and evidence syntheses identifying CRP, D-dimer, low oxygen saturation, LDH, and related routine laboratory abnormalities as markers of mortality risk in hospitalised patients (1, 2, 5, 7–9, 13–19).

Our findings also support the prognostic relevance of lymphopenia and neutrophil-to-lymphocyte imbalance. Non-survivors had lower lymphocyte counts and higher neutrophil percentages, and NLR remained associated with mortality in age-adjusted analysis. This is in keeping with the concept that severe COVID-19 reflects an imbalance between heightened innate immune activation and weakened adaptive immune response. Previous studies have similarly indicated that NLR, SII, and related hematologic indices help distinguish survivors from non-survivors and may support early clinical risk assessment. In particular, admission SII has been reported as a predictor of in-hospital mortality, while NLR, d-NLR, MLR, and SIRI have also been associated with mortality or severity in COVID-19 (3–5, 20–22).

Another relevant finding of this study was the performance of derived thrombo-inflammatory indices, especially DLR and CLR. These ratios combine a conventional biomarker with lymphocyte count, thereby capturing both inflammatory or coagulation-related burden and immune dysregulation. In our analysis, both DLR and CLR showed good discrimination for mortality. They remained associated with a fatal outcome after age adjustment. This supports the idea that composite ratios derived from routine laboratory parameters may contribute complementary prognostic information, even in small hospital cohorts. In line with this, recent DLR-focused studies have suggested that the ratio may help identify COVID-19 patients at higher risk of death, while related ratio-based biomarker studies have reinforced the potential value of combined laboratory measures (6, 10, 11, 23–25). However, because such indices overlap biologically and mathematically with established markers, they should be interpreted as supportive rather than definitive evidence of added predictive value.

$TIHLI_3$ was of particular interest because it integrates CRP, D-dimer, lymphocyte count, and oxygen saturation, combining four key aspects of severe COVID-19 biology: inflammation, coagulation activation, lymphopenia, and hypoxemia. In this cohort, $TIHLI_3$ showed strong mortality discrimination and remained associated with death in age-adjusted analysis. However, pairwise ROC comparisons did not demonstrate clear superiority of $TIHLI_3$ over CRP or D-dimer, suggesting that its performance should be interpreted as comparable rather than definitively superior to that of the leading conventional markers. This finding nonetheless supports the concept that adverse outcomes in COVID-19 are driven by interacting biological pathways rather than by isolated laboratory abnormalities. Similar attempts to construct composite laboratory indices for mortality assessment have also been reported (12, 23–25). However, because $TIHLI_3$ is a newly introduced exploratory index without external validation, it should be interpreted as hypothesis-generating rather than as a clinically established prognostic tool (1, 2, 6, 7, 12).

The exploratory combined model, including age, CRP, D-dimer, and oxygen saturation, showed high apparent discrimination, supporting the joint association of inflammatory, coagulation-related, and oxygenation markers with fatal outcome in this cohort. However, given the limited number of fatal events, this finding should be interpreted cautiously. The model is best regarded as an exploratory analysis of internal performance rather than as a definitive multivariable prediction model, and it requires validation in larger independent cohorts. At the same time, the correlation analysis demonstrated marked intercorrelation among the leading derived indices, particularly between $TIHLI_3$, CLR, DLR, CRP, and D-dimer, indicating that these markers capture overlapping but not identical aspects of the adverse biological profile associated with fatal outcome.

From a practical clinical standpoint, the present findings suggest that routinely measured admission laboratory parameters may be useful for early mortality-oriented risk assessment in hospitalised COVID-19 patients. CRP, D-dimer, ferritin, LDH, complete blood count parameters, and oxygen saturation are low-cost, quickly obtainable, and available even in hospitals without access to advanced biomarker platforms. This is especially relevant in routine care settings, where management decisions often rely on standard admission laboratory evaluation. Consistent with these findings, a recent Cochrane review and multiple hospital-based cohorts have shown that routine blood-based laboratory tests may help identify patients with SARS-CoV-2 infection who are at increased risk of death, although their performance is not uniform across studies and clinical settings (6, 15, 17–19, 22, 26).

Several limitations should be considered when interpreting these findings. First, the study used a retrospective, single-centre design, which may limit the generalizability of the results. Second, the number of fatal events was limited, and the regression estimates should therefore be interpreted with caution. Third, biomarker assessment was restricted to admission values rather than serial measurements obtained during hospitalisation. Fourth, neither the exploratory combined model nor the newly proposed $TIHLI_3$ index underwent external validation. Finally, because several derived indices share mathematical components, particularly lymphocyte count, they should be regarded as complementary summary measures rather than as representations of fully independent biological pathways.

The study also has important strengths. It used real-world hospital data, focused on in-hospital mortality as a clinically meaningful outcome, and evaluated both conventional and derived biomarkers through ROC and age-adjusted regression analyses. The findings were also internally consistent, as markers of inflammation, coagulation activation, lymphopenia, and hypoxemia all pointed toward the same adverse prognostic pattern. This convergence supports the biological plausibility of the findings and reinforces their potential relevance to routine hospital practice.

Conclusion

Among hospitalised COVID-19 patients, in-hospital mortality was most strongly associated with CRP and D-dimer among conventional biomarkers, while DLR, CLR, and the exploratory $TIHLI_3$ index were also associated with adverse outcome and showed useful discriminatory performance. An exploratory combined model including age, CRP, D-dimer, and oxygen saturation also supported the potential prognostic relevance of routinely available admission parameters, but this finding requires external validation. Overall, routine laboratory and clinical variables obtained at admission may support early mortality-oriented risk stratification. However, the proposed cut-off values and exploratory composite indices require validation in larger independent cohorts before broader clinical use.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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