Dynamic changes in coagulation, hematological and biochemical parameters as predictors of mortality in critically ill COVID–19 patients:a prospective observational study

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Research Article

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Abstract

Background

This study was created to analyze dynamic alterations in coagulation, hematological and biochemical parameters and their association with mortality of COVID-19 patients.

Methods

The present study was a prospective, one-year-long observational study conducted during the period September 2020/September 2021 on all critically ill, COVID–19 patients with respiratory failure, admitted to the Medical Intensive Care Unit (MICU) of the University Clinical Centre of the Republic of Srpska. The following data were collected: demographic and clinical characteristics of the study population, pre-existing comorbidities (cardiovascular diseases, pulmonary diseases, diabetes mellitus), coagulation, biochemical and hematological parameters. The primary outcome was the proportion of patients who died (non-survivors).

Results

As much as 91 patients with median age 60 (50–67), 76.9% male, met the acute respiratory distress syndrome (ARDS) criteria. It was tested whether dynamic change (delta-Δ) of parameters (C-reactive protein-CRP, interleukin 6-IL-6, absolute lymphocyte count-Ly, fibrinogen, coagulation cascade factors: F II, factor II; F V, factor V, F X, factor X; F XI, factor XI; F XIII, factor XIII) that were found to be predictors of mortality is independently associated with poor outcome in patients. Adjusted (multivariate) analysis was used, where tested parameters were corrected for basic and clinical patients' characteristics. The only inflammatory (biochemical and hematological) parameter which dynamic change had statistically significant odds ratio (OR) was ΔCRP ($p < 0.005$), while among coagulation parameters statistically significant OR was found for Δ fibrinogen ($p < 0.005$) in predicting mortality.

Conclusion

Coagulation, hematological and biochemical parameters' abnormalities are common in critically ill COVID–19 patients. Monitoring of these parameters and their dynamical changes can potentially improve management and predict mortality in critically ill COVID – 19 patients.

Background

Coronavirus disease (COVID–19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS –CoV-2) (1), was reported for the first time in Wuhan, China in December, 2019, and has become an ongoing global pandemic. By April,2022, there have been over 481 million cases and over 6 million

deaths reported globally since the start of the pandemic [2]. COVID-19 is a complex multisystem inflammatory syndrome with multiple organ involvement and with complex pathogenesis including hemostasis, immune system, and hematopoietic system.

The hemostatic pathway abnormalities are very common in critically ill COVID-19 patients and are referred to as COVID-19-associated coagulopathy [3]. Both venous and arterial thrombotic events have been reported as independent mortality risk factors [4]. In the majority of COVID-19 patients,including critically ill,with severe coagulation abnormalities, disseminated intravascular coagulation (DIC) and thrombotic microangiopathy are common complications [5]. D-dimer is the main coagulation biomarker investigated in critically ill COVID-19 patients and itsvalue is significantly enhanced in nearly 50% of COVID-19 patients who are at higher risk of death [6, 7]. In addition, thrombocytopenia, slight prolongation of the prothrombin time (PT), activated partial tromboplastin time (aPTT), increased plasma fibrinogen levels, and reduction in plasma fibrinogen levels in some patients were also found in critically ill COVID-19 patients [3, 7, 8, 9, 10]. Besides, reduced levels of natural anticoagulants (antithrombin and protein C) and decreased factor V activity has been linked to death [7, 11, 12]. Many biomarkers, besides coagulation parameters, has been found to be abnormal in critically ill COVID-19 patients. These include inflammatory markers like elevated CRP, erythrocyte sedimentation rate, white blood cell count, fibrinogen, procalcitonin, as well assigns of tissue injury, such as elevated lactic dehydrogenase (LDH), alanine aminotransferase (AST), cardiac troponins. There are multiple reports that CRP, LDH, creatinine, cardiac troponin I (TnI), ALT, AST, leukocytes, neutrophils, were more elevated in critically ill COVID-19 patients [7, 13, 14, 15]. Some studies have explored the relationship between mortality and laboratory abnormalities. These investigations showed elevated values of CRP, LDH, D-dimer, creatinine, cardiac troponins, leukocytes, ALT, PT and procalcitonin in non-survivors compared to survivors [6, 7, 13, 16, 17]. Additional studies are needed to select the most sensitive biomarkers or combination of biomarkers as predictors of mortality in critically ill COVID-19 patients.

Taking into account the aforementioned, this study was designed to analyze dynamic alterations in coagulation, hematological and biochemical parameters, and their association with mortality of critically ill COVID-19 patients.

Material And Methods

Study design

The present study was a prospective, observational study conducted during an one-year-period (September 1, 2020/August 31, 2021) on selective critically ill COVID–19 patients with respiratory failure, admitted to the MICU of the University Clinical Centre of the Republic of Srpska (UCC-RS). The MICU serves as a referral centre of the Republic of Srpska, which is currently the most advanced multidisciplinary MICU in Bosnia and Herzegovina. Institutional Ethics Commitee provided approval for the study, and informed consent was signed by all patients or their legal representative. COVID–19 was

confirmed by detection of SARS–CoV–2 RNA in nasopharyngeal or throat swab or broncoalveolar lavage semples, using the real time polymerase chain reaction (RT-PCR) method.

Outcomes and predictor variables

The following data were collected: demographic and clinical characteristics of the study population, pre-existing comorbidities (cardiovascular diseases,pulmonary diseases, diabetes mellitus), coagulation, biochemical and hematological parameters. The primary outcome was the proportion of patients who died (non-survivors).

Sample collection

The venous blood samples were collected on day 1 and day 7 of admission to the medical ICU. The following tests were performed:

1) Coagulation parameters: D-dimer, fibrinogen, aPTT, INR, coagulation factors II, V, VII, VIII, IX, X, XI, XII, XIII, vWF, protein C and S. Fully automated coagulation analyser was used for performing all the coagulation tests.

2) Biochemical parameters: urea, creatinin, bilirubin direct, bilirubin indirect, AST, ALT, LDH, creatine kinase, troponin, albumin, ionized calcium-$Ca^{2+,}$ CRP, procalcitonin, IL-6, ferritine, lactate.

3) Hematological parameters: absolute eritrocyte count, absolute leucocyte counts, absolute lymphocyte counts, platelet count, hemoglobin, iron, UIBC, TIBC.

The samples were analyzed in the biochemical laboratory in the UCC-RS. Fully automated biochemeical analyser was used, according to the manufacturer's recommendations.

Inclusion criteria

All adult, RT-PCR positive patientswith respiratory failure due to COVID-19 pneumonia and with a need for mechanical ventilation were included in the study.

Exclusion criteria

Patients were excluded from the study if they had: sepsis or septic shock, respiratory failure not casued by COVID-19, thromboembolic disorders not related to COVID-19, cancer, liver or kidney disease, hematological disorders, surgeries or trauma, pregnancy.

Statistical analysis

The study data were analyzed using SPSS version 26.0. All continuous variables were expressed as median (interquartile range [IQR]) and categorical variables as numbers and proportions. The Kolmogorov–Smirnov test was used for testing the normality of data distribution and Mann–Whitney U and Kruskal–Wallis tests were used for comparing continuos variables between the groups. The chi–square/Fisher exact test and Pearson’s tests were used for comparing categorical data. To analyze the

efficiency of coagulation, biochemical and hematological parameters in predicting mortality, receiver operation characteristic (ROC) curve was used and the area under the ROC curve (AUC) was designed. For calculated AUC for parameters, non–survivor cases were taken as primary outcome.The multivariate logistic regression analysis was performed and adjusting for age, comorbidity and the coagulation, biochemical and hematological parameters.The odds-ratios (OR) with 95% confidence intervals were calculated. The P 0.05 was considered statistically significant.

Results

There were 91 patients included in this study. The demographic and clinical characteristics of the patients are shown in Table 1. Out of the 91 patients, 46 (50.5%) of them died and 45 (49.5%) recovered. The median age was 60 years (IQR, 50–67) and there was a statistically significant association between their age and mortality. The population in this study consisted mostly of men, (76.9%).A total of 70/91 patients (76.9%) receaved full-dose anticoagulation therapy.

Table 1
The demographic and clinical characteristics of the study population

Parameters	Total	Surviver	Non - surviver	p
n (%)	91 (100%)	45 (49.5%)	46 (50.5%)	
Age (years)	60 (50–67)	56,5 (46–63)	61 (56–69)	**0.027**
Male	70 (76.9%)	33 (73.3%)	37 (80.4%)	0.464
Duration of ICU stay (days)	12 (8–18)	12 (8,5–16)	12.5 (7,75 – 20)	0.466
Illnes before hospitalization (days)	6 (5–8)	7 (4–8)	6 (5-8.25)	0.466
SOFA score, day 1	33 (33–50)	33 (33–45)	33 (33–50)	0.402
SOFA score, day 7	33 (33–50)	33 (33–33)	50 (50–80)	**0.000**
APACHE score	15 (8–15)	10 (8–15)	15 (9.75-25)	0.127
SAPS II score	12 (5,80 – 24)	11,8 (4.2–24)	13,4 (6.1–24)	0.599
FiO_2	NA	70 (60–100)	80 (70–100)	0,141
PEEP	NA	10 (8–10)	10 (9,5–10)	0,320
Respiratory rate,admission	NA	30 (27–32)	29 (26–32)	0,765
Heart rate,admission	NA	90 (80–102)	97,5 (80–110)	0,596
Smoking	33 (36.3%)	25 (54.3%)	8 (17.8%)	**0,000**
Cardiovascular desease	14 (15.4%)	7 (15.6%)	7 (15.2%)	1
Hypertension	44 (48.4%)	20 (44.4%)	24 (52.2%)	0,531
Diabetes	32 (35.2%)	14 (31.1%)	18 (39.1%)	0,512
Chronic pulmonary desease	5 (5.6%)	4 (9.1%)	1 (2.2%)	0,198
Chronic kidney desease	4 (4.4%)	2 (4.4%)	2 (4.3%)	1
Charlson index	90 (53–90)	90 (53–90)	78 (53–90)	0,346
ECMO	6 (6.6%)	1 (2.2%)	5 (10.9%)	0,203
CRRT	15 (16.5%)	2 (13.3%)	13 (86.7%)	**0,004**
AKI	30 (33%)	2 (4.4%)	28 (60.9%)	**0,000**
Thromboembolic events	23/91 (25.3%)	8 (34.8%)	15 (65.2%)	0,148

ICU, intensive care medicine; SOFA, sequential organ failure assessment; APACHE, Acute Physiology, and Chronic Health Evaluation II; SAPS II, simplified acute physiology score II; FiO2, a fraction of inspired oxygen; PEEP, positive end-expiratory pressure; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; AKI, acute kidney injury.

Parameters	Total	Surviver	Non - surviver	p
Invasive mechanical ventilation	62/91 (68.1%)	16 (25.8%)	46 (74.2%)	**0,000**
Non-invasive mechanical ventilation	29/91 (31.8%)	29 (100%)	0	**0,000**
Bleeding events	7/91 (7.7%)	0	7 (100%)	**0,000**
Anticoagulation,therapeutic dose	70/91 (76.9%)	39 (55.7%)	31 (44.3%)	0,072

ICU, intensive care medicine; SOFA, sequential organ failure assessment; APACHE, Acute Physiology, and Chronic Health Evaluation II; SAPS II, simplified acute physiology score II; FiO2, a fraction of inspired oxygen; PEEP, positive end-expiratory pressure; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; AKI, acute kidney injury.

All results are given in median [IQR] or as as numbers and proportions

A receiver-operating characteristics curve analysis was performed since there was a statistically significant difference between the groups of survivors and non-survivors for the parameters years, SOFA score day 7, smoking, AKI, CRRT, and IMV. The area under the ROC curve for SOFA score day 7 was the largest (AUC = 0.874), followed by the area under the ROC curve for IMV (AUC = 0.814), indicating that both parameters are excellent predictors of mortality. The third highest area under the ROC curve for AKI (AUC = 0.774) was considered an acceptable predictor of mortality.

Table 2 shows dynamic changes/delta values for biochemical parameters. The delta (Δ) value represents a dynamic change from biomarker value from day one to day seven. Statistically significant difference between survivors and non-survivors for Dbil Δ (p = 0.030), LDH Δ (p = 0.002), troponin Δ (p = 0.008), CRP Δ (p = 0.004) was found.

Table 2
Dynamic changes/ delta (Δ) values for biochemical parameters

Parameters (Δ)	Total	Surviver	Non - surviver	p
Urea delta	1.20 (4.8)	1.50 (5.73)	0.40 (3.70)	0.273
Creatinin delta	-6 (39)	-6 (79.25)	-6 (25)	0.943
Tbil delta	-0.45 (12.68)	0.15 (11.48)	-0.90 (17.02)	0.578
Dbil delta	2.10 (5.80)	0.70 (5.65)	3 (6.50)	**0.030**
AST delta	-7 (47)	-7.50 (57.25)	-5 (39)	0.784
ALT delta	-5 (63)	-5 (50.75)	-5 (70)	0.625
LDH delta	-204 (376)	-323 (416)	-155 (301)	**0.002**
CK delta	-75 (191.75)	-101.50 (184.75)	-4.75 (200.25)	0.614
Troponin delta	7.10 (37.5)	1.95 (48.55)	13 (120.10)	**0.008**
Alb delta	-2 (4)	-2 (5)	-2 (3.50)	0.589
Ca 2^{+}delta	-0.02 (0.21)	-0.01 (0.19)	-0.02 (0.21)	0.515
CRP delta	-3 (124)	31.05 (136.7)	-20.50 (100.65)	**0.004**
PCT delta	0.16 (1.97)	0.46 (5.90)	0.01 (0.99)	0.213
IL–6 delta	-3.10 (95.1)	-3.07 (129.11)	-7.90 (41.80)	0.536
Ferirtin delta	-82 (693)	-112 (1010)	-46 (533.5)	0.815
Lactate delta	-0.40 (1.22)	-0.50 (1.30)	-0.30 (1.64)	0.185

Tbil, total bilirubin; Dbil, direct bilirubin; AST, aspartate aminitransferase; ALT, alanin aminotransferase; LDH, lactic dehidrogenaase; CK, cretine cinase; Alb, albumin: $Ca2^{+}$, calcium; CRP, C – reactive protein; PCT, procalcitonin; IL-6, interleukin 6

Delta value, dynamic change from biomarker value from day 1 to day 7

All results are given in median [IQR]

Table 3 shows dynamic changes/delta (Δ) values for hematological parameters. The Δ value represents a dynamic change from biomarker value from day one to day seven. Statistically significant difference between survivors and non-survivors for RBC Δ ($p = 0.023$), Ly Δ ($p = 0.018$), Hb Δ ($p = 0.003$) was found.

Table 3
Dynamic changes /delta (Δ) value for hematological parameters

Parameters (Δ)	Total	Surviver	Non - surviver	p
RBC delta	-0.42 (1.07)	-0.60 (0.76)	-0.35 (0.76)	**0.023**
WBC delta	1.80 (4.73)	1.01 (4.08)	2.40 (4.88)	0.427
Ly delta	0.22 (0.70)	0.03 (0.79)	0.35 (0.67)	**0.018**
Plt delta	-18 (172)	-57 (172)	-14 (168)	0.104
Hb delta	-13 (32)	-23.50 (44.75)	-6 (18)	**0.003**
Fe delta	0.85 (7.75)	0.85 (7.62)	0.85 (10.45)	0.488
UIBC delta	-6.20 (13.75)	-8.70 (14.70)	-4.30 (12.82)	0.325
TIBC delta	-1.20 (12.20)	-2.15 (11.47)	0 (11.52)	0.208

RBC, red blood count, ; WBC, white blood count; ; Ly, absolute Lymphocyte count; Plt, platelet count; Hb, hemoglobin; Fe, iron; UIBC, unsaturated iron-binding capacity; TIBC, total iron-binding capacity

Δ value, dynamic change from biomarker value from day 1 to day 7

All results are given in median [IQR]

Table 4 shows dynamic changes/delta (Δ) values for coagulation parameters. The Δ value represents a dynamic change from biomarker value from day one to day seven.There was no statistically significant difference between survivors and non-survivors in Δ values for all measured coagulation parameters (except for fibrinogen).

Table 4
Dynamic changes/delta (Δ) values for coagulation parameters

Parameters (Δ)	Total	Surviver	Non-surviver	p
F II delta	-6 (39)	-2.50 (43.25)	-10 (36)	0.703
F V delta	-15 (62)	-1.50 (57)	-18 (51)	0.144
F VII delta	-3 (41)	-6 (45)	-2 (35.50)	0.565
F VIII delta	0 (0.46)	0 (4.25)	0 (0.23)	0.983
F IX delta	-1 (60)	-3 (69.75)	-1 (65.50)	0.739
F X delta	-12 (46)	-0.5 (61.75)	-15 (36.5)	0.170
F XI delta	-14 (51)	-14.5 (53.25)	-14 (51.5)	0.843
F XII delta	-9 (38)	-13.5 (37)	-1 (39)	0.266
F XIII delta	-46 (49.5)	-40.50 (59.25)	-54 (42)	0.599
vWF delta	0 (0)	0 (0)	0 (0)	0.271
protein C delta	16 (49)	3.50 (50.25)	17 (42.50)	0.086
protein S delta	0 (43)	-8.50 (52.25)	1 (32)	0.074
Antithrombin delta	-3 (34)	-4 (36.50)	-3 (38)	0.584
Apt delta	2.40 (9.40)	3.20 (10.08)	2.30 (9.05)	0.116
INR delta	0.04 (0.30)	0.03 (0.29)	0.04 (0.29)	0.453
D – dimer delta	0.20 (11.17)	-1.60 (24.07)	0.43 (4.11)	0.066
Fibrinogen delta	-1.80 (3)	-1.20 (3.24)	-2.30 (2.70)	**0.048**

Coagulation cascade factors: F II, factor II; F V, factor V, F X, factor X; F XI, factor XI; F XIII, factor XIII; vWF, von Wilebrand factor; aptt, partial thromboplastin time; INR, international normalized ratio;

Delta value, dynamic change from biomarker value from day 1 to day 7

All results are given in median [IQR]

Table 5 shows the association between demographic/clinical and biochemical/inflammatory parameters and survival in the study cohort. In the unadjusted(univariate) analysis, the OR was statistically significant for CRP day 1, CRP day 7, ΔCRP and Ly day 7 in predicting mortality. Moreover, the same parameters kept a significant association with a poor prognosis even in the adjusted (multivariate) analysis.

Table 5
Association of demographic/clinical and biochemical/inflammatory parameters with mortality

	Unadjusted			Adjusted*		
Inflammatory Parameters	**OR**	**CI (95%)**	**p**	**OR**	**CI (95%)**	**p**
CRP day 1	1.006	1-1.012	**0.038**	1.008	1.002–1.015	**0.016**
CRP day 7	1.016	1.009–1.024	**0.000**	1.017	1.009–1.024	**0.000**
CRP Δ	1.006	1.001–1.011	**0.010**	1.006	1.001–1.011	**0.029**
IL-6 day 1	1.004	0.999–1.008	0.086	1.004	0.999–1.008	0.107
IL-6 day 7	1.003	1-1.005	0.078	1.002	1-1.005	0.097
IL-6 Δ	1	0.999–1.001	0.462	1	0.999–1.002	0.477
Ly day 1	0.333	0.097–1.141	0.080	0.366	0.097–1.374	0.136
Ly day 7	0.126	0.041–0.379	**0.000**	0.113	0.034–0.377	**0.000**
Ly Δ	0.656	0.341–1.256	0.204	0.636	0.331–1.222	0.175

OR,odds ratio; CI (95%), 95% confidence interval; CRP, C - reactive protein; IL-6, interleukin 6; Ly, total lymphocyte count.

*Adjusted for sequential organ failure assessment (SOFA) score, age, sex, Charlson comorbidity index.

Table 6 shows the association between demographic/clinical and coagulation parameters and survival in the study cohort. In the unadjusted univariate analysis, the OR was statistically significant for F II day 1, F II day 7, F V day 1 and F XIII day 7 in predicting mortality. In the adjusted multivariate analysis only parameters F II day 1 and F XIII day 7 kept a significant association with a poor prognosis.

Table 6
Association of demographic/clinical and coagulation parameters with mortality

	Unadjusted			Adjusted*		
Coagulation Parameters	OR	CI (95%)	p	OR	CI (95%)	p
F II day 1	0.974	0.956–0.992	**0.005**	0.978	0.960–0.997	**0.025**
F II day 7	0.982	0.965–0.999	**0.040**	0.985	0.967–1.002	0.089
F II Δ	1.004	0.991–1.017	0.536	1.003	0.989–1.016	0.719
F V day 1	0.089	0.977-1	**0.049**	0.991	0.980–1.003	0.132
F V day 7	0.993	0.979–1.007	0.358	0.991	0.976–1.006	0.254
F V Δ	1.005	0.996–1.015	0.265	1.003	0.993–1.013	0.567
F X day 1	1.001	0.996–1.006	0.688	1.001	0.995–1.008	0.653
F X day 7	1.005	0.991–1.005	0.484	1.007	0.991–1.023	0.388
F X Δ	1	0.995–1.004	0.860	0.999	0.994–1.005	0.847
F XI day 1	0.991	0.980–1.002	0.094	0.992	0.981–1.003	0.137
F XI day 7	0.987	0.973–1.001	0.066	0.991	0.977–1.005	0.208
F XI Δ	1.002	0.997–1.008	0.400	1.003	0.994–1.011	0.530
F XIII day 1	0.987	0.973–1.001	0.060	0.989	0.975–1.003	0.134
F XIII day 7	0.975	0.952–0.998	**0.035**	0.975	0.950-1	**0.048**
F XIII Δ	1.004	0.992–1.015	0.545	1.002	0.990–1.014	0.744
Fibrinogen day 1	0.789	0.596–1.043	0.097	0.816	0.612–1.087	0.165
Fibrinogen day 7	1.075	0.797–1.449	0.634	1.080	0.777-1.500	0.647
Fibrinogen Δ	1.193	0.959–1.483	0.111	1.175	0.934–1.478	0.168

OR, odds ratio; CI (95%), 95% confidence interval;Coagulation cascade factors: F II, factor II; F V, factor V, F X, factor X; F XI, factor XI; F XIII, factor XIII;

*Adjusted for sequential organ failure assessment (SOFA) score,age, sex, Charlson comorbidity index.

Dynamic change (Δ)of parameters for which we found to be predictors of mortality was tested in order to identify those which were independently associated with poor outcome in patients. Adjusted (multivariate) analysis was used, in which parameters were corrected by basic and clinical patients' characteristics. The only inflammatory parameter which dynamic change had statistically significant OR was ΔCRP and among coagulation parameters statistically significant OR was found for Δfibrinogen, when lethal outcome is concerned, as shown in Table 7.

Table 7
Association of demographic/clinical parameters and dynamic value (Δ value) of inflammatory/coagulation parameters with mortality

	Adjusted*		
Inflammatory Parameters	**OR**	**CI (95%)**	**p**
CRP Δ	1.015	1.007–1.022	**0.000**
IL-6 Δ	1	0.999–1.002	0.527
Ly Δ	0.549	0.291–1.038	0.065
Coagulation Parameters	OR	CI (95%)	p
F II Δ	0.988	0.970–1.006	0.193
F V Δ	0.998	0.986–1.009	0.679
F X Δ	0.997	0.990–1.005	0.481
F XI Δ	1.002	0.994–1.010	0.661
F XIII Δ	0.993	0.979–1.007	0.317
Fibrinogen Δ	1.371	1.029–1.827	**0.031**
OR,odds ratio; CI (95%), 95% confidence interval; CRP, C - reactive protein; IL-6, interleukin 6; Ly, total lymphocyte count; Coagulation cascade factors: F II, factor II; F V, factor V, F X, factor X; F XI, factor XI; F XIII, factor XIII;			
* Adjusted for SOFA score (sequential organ failure assessment), Age, Sex, CRP-day 1, F II-day 1			

Discussion

This study showed that dynamic change of coagulation, biochemical and hematological biomarkers can have significant predictive value for mortality of critically ill COVID-19 patients. The C-reactive protein and fibrinogen are the only two biochemical and coagulation parameters which dynamic changes in critically ill COVID–19 patients are independent predictors of mortality. Recent studies have reported that CRP level is elevated in patients with COVID-19 and may correlate with the severity of the disease, disease progression and mortality [18, 19, 20]. *Sharifpour* et al. had similar results to the present ones; patients who died had significantly higher CRP levels than those who survived [21]. Meta-analysis of 20 studies including 4,843 COVID–19 patients provided by the *Preeti* et al. reported that there was almost four times greater risk of poor outcome for COVID-19 patients with high CRP [22]. It seems that there are no studies that analyzed the dynamic change of this parameter.

It was found in this study that many of parameters can potentially be important predictors of mortality, such as CRP, LDH, troponin, PCT, ferritin, what is similar with previous studies [6, 10, 13]. However, when

multivariate analysis adjusted for SOFA score, age, gender and Charlson comorbidity index was performed, only the CRP value, static or dynamic, was identified as an independent predictor of mortality.

It was found that total red blood count, total lymphocyte count, and hemoglobin can potentially be predictors of mortality, which was also found in other studies [13, 28]. However, multivariate analysis adjusted for SOFA score, age, gender, and Charlson comorbidity index was performed, only the total lymphocyte counts on day seven was identified as a potential independent predictor of mortality. Several studies have associated lymphopenia with poor prognosis of COVID-19 [14, 15, 17, 28]. In available literature no data on lymphocytes dynamic change in COVID-19 patients could be found.

Fibrinogen is a well-studied biomarker in patients suffering from COVID-19. Some studies have indicated that fibrinogen was associated with the severity of COVID-19 disease, while others indicated that fibrinogen alone was not significant in predicting mortality [7, 25, 26]. It was found in the present that change in fibrinogen dynamics, increased fibrinogen levels, and its evaluation over time is an independent biomarker of mortality in seriously ill COVID-19 patients and may guide physicians in predicting the outcomes. Based on the available information, there are no studies that analyzed the dynamic change of this parameter.

This is the first report that studied all coagulation factors (II, V, VII, VIII, IX, X, XI, XII, XII, vWF, protein C, protein S, antithrombin) together with their dynamic changes, in comparison to many published studies that have focused only on few parameters (such as D-dimer, PT, aPTT, factor V, factor VIII) [7, 9, 11 ,12, 23, 24].

This study clearly showed that coagulation factors were poor predictors of mortality and monitoring during the time could not predict poor outcome. Additionally, clotting factor tests cannot be easily undertaken in many laboratories and these analyses are very expensive. Therefore, it can be concluded that regular monitoring of these parameters is not always rational in critically ill COVID-19 patients. Consistent with the previous studies, we found reduced production, or more likely, increased consumption of clotting proteins, coagulation factors, in critically ill COVID-19 patients [27], with potential importance of factor II, factor V and factor XIII in the prediction of the mortality. A more detailed evaluation is necessary.

There are limitations to this study. First, it is a single-center study and second, there is a limited number of patients, considering the size of the pandemic.

Abbreviations

ICU, intensive care medicine; MICU, Medical Intensive Care Unit; UCC-RS, University Clinical Centre of the Republic of Srpska; ARDS, acute respiratory distress syndrome; SOFA, sequential organ failure assessment; APACHE, Acute Physiology and Chronic Health Evaluation II; SAPS II, simplified acute physiology score II; FiO2, a fraction of inspired oxygen; PEEP, positive end-expiratory pressure; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; AKI, acute kidney

injury; Tbil, total bilirubin; Dbil, direct bilirubin; AST, aspartate aminitransferase; ALT, alanin aminotransferase; LDH, lactic dehidrogenaase; CK, cretine cinase; Alb, albumin: $Ca2^{+}$, calcium; CRP, C – reactive protein; PCT, procalcitonin; IL-6, interleukin 6; RBC, red blood count, ; WBC, white blood count; ; Ly, absolute Lymphocyte count; Plt, platelet count; Hb, hemoglobin; Fe, iron; UIBC, unsaturated iron-binding capacity; TIBC, total iron-binding capacity; coagulation cascade factors: F II, factor II, F V, factor V, F X, factor X, F XI, factor XI, F XIII, factor XIII, vWF, von Wilebrand factor; aptt, partial thromboplasin time; INR, international normalized ratio; OR, odds ratio; CI (95%), 95% confidence interval; IQR, interquartile range ; ROC, receiver operation characteristic curve; AUC, the area under the ROC curve.

Declarations

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Authors contributions

BZ, PK, and TK contributed to the study conception. BZ, PK, VDJ, MS, RS, and MDJ contributed to the study design. MJ, DM, and SD contributed to the conduct of experimental research. PK, TK, BZ, MJ, RS, and SD contributed to the analysis and interpretation of the data. All authors reviewed it, contributed significantly to its critical review, and approved the final version of the manuscript. All authors ensure the accuracy or integrity of the results of this study and will be accountable for any question related to this work.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Institutional Ethics Commitee provided approval for the study (01-19-533-2/20), and informed consent was signed by all patients or their legal representative.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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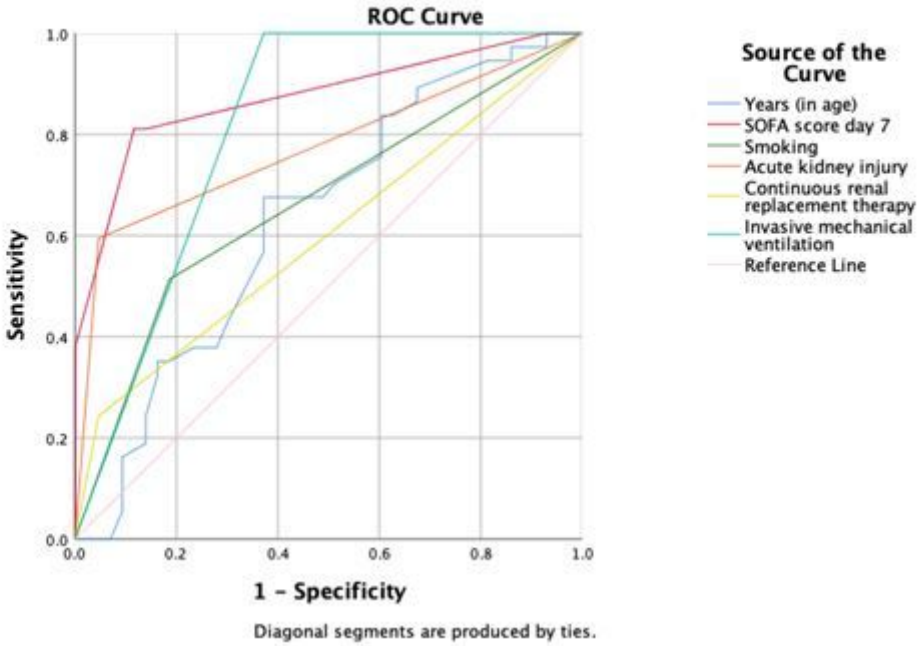
Figures



Parameters	AUC	95% CI	p
Years	0.634	0.512 – 0.756	0.040
SOFA score day 7	0.874	0.792 – 0.955	0.000
Smoking	0.664	0.542 – 0.785	0.012
AKI	0.774	0.665 – 0.883	0.000
CRRT	0.598	0.472 – 0.725	0.131
IMV	0.814	0.717 – 0.910	0.000

Figure 1. Receiver-operating characteristic curves for significant demographical and clinical parameters in the prediction of mortality

Figure 1

See image above for figure legend.

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