

Role of biological markers and CT severity score in predicting mortality in patients with COVID-19: An observational retrospective study

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Abstract. COVID-19 pandemic is a continuing ongoing emergency of public concern. Early identification of markers associated with disease severity and mortality can lead to a prompter therapeutic approach. The present study conducted a multivariate analysis of different markers associated with mortality in order to establish their predictive role. Confirmed cases of 697 patients were examined. Demographic data, clinical symptoms and comorbidities were evaluated. Laboratory and imaging severity scores were reviewed. A total of 133 (19.1%) out of 697 patients succumbed during hospitalization. Obesity was the most common comorbidity, followed by hypertension, diabetes, coronary heart disease and chronic kidney disease. Compared with the survivor patients, non-survivors had a higher prevalence of diabetes, chronic kidney disease and coronary heart disease, as well as higher values of laboratory markers such as neutrophil-lymphocyte ratio (NLR), D-dimer, procalcitonin, IL-6 and C Reactive protein (CRP) and respectively high values of imaging severity scores. Multivariate regression analysis showed that high values of the proposed markers and chest computerized tomography (CT) severity imaging score were predictive for in hospital death: NLR [hazard ratio (HR): 3.127 confidence interval (CI) 95: 2.137-4.576]; D-dimer [HR: 6.223 (CI 95:3.809-10.167)]; procalcitonin [HR: 4.414 (CI 95:2.804-6.948)]; IL-6 [HR: 3.344 (CI 95:1.423-7.855)]; CRP [HR:2.997 (CI 95:1.940-4.630)]; and CT severity score

[HR: 3.068 (CI 95:1.777-5.299)]. Laboratory markers and imaging severity scores could be used to stratify mortality risk in COVID-19 patients.

Introduction

Coronavirus disease 2019 (COVID-19) has spread rapidly since the outbreak in January 2020, with >220 million confirmed cases and >4.3 million mortalities (1). Most confirmed cases were initially diagnosed as interstitial pneumonia of unknown origin related to a history of exposure to seafood markets (2). Renal dysfunction, gastrointestinal complications, liver dysfunction, cardio-vascular manifestations, neurological and psychiatric abnormalities as well as hematological manifestations were also reported (3,4). Though the majority of symptomatic patients have mild flu-like symptoms, a significant minority develop severe lung injury with acute respiratory distress syndrome (ARDS) (5). A number of risk factors have been associated with its evolution towards a severe or critical disease, including advanced age, male sex, diabetes, hypertension, obesity and underlying heart, kidney and liver disease (6). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to the angiotensin-converting enzyme 2 receptor (ACE2) that physiologically counters the activation of the renin-angiotensin-aldosterone system (7). ACE2 is expressed broadly, including the lung alveolar pneumocytes, enterocytes, bladder urothelial cells, endothelial cells, the heart and the kidneys (8,9). SARS-COV-2 can cause activation of the inflammatory response involving the alveolar epithelium leading to cytokine storm in most severe cases (10). Extensive inflammation within the COVID-19 patient lungs can lead to pulmonary vessels injury that can trigger clot formation (11). High values of inflammatory biomarkers such as IL-6, C Reactive protein (CRP) and procalcitonin are hallmarks for severe and critical patients (12). In addition, levels of fibrin related markers (D-dimer) are moderately or significantly elevated, suggesting coagulation activation, especially in dead patients (13). Lymphopenia and neutrophilia, as well as elevated NLR values, are the main hematological changes in patients with severe COVID-19 (14). Regarding the imagistic

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findings in patients with COVID-19, studies have shown a positive correlation between the severity of COVID-19 and the extent of lung damage expressed by the increased value of the computerized tomography (CT) imaging score (15,16). What the present study observed, based on the studies conducted so far, was that there were imagistic and laboratory differences between patients according to their illness course and that raised the question of whether patients can be stratified into groups of risk using independent predictive variables.

Materials and methods

The present study was a retrospective, single-center, observational study among patients with moderate and severe COVID-19 (including critical ill patients), who were admitted to the Sibiu Emergency County Clinical Hospital during the third wave of the pandemic between 1 November 2020 and 31 January 2021. Patients with complete data ($n=697$) including 564 survivors and 133 non-survivors were randomly selected. All confirmed cases presented the criteria of the interim guidance proposed by the WHO (17), the most important being a positive ARN reverse transcription PCR (RT-PCR) test. Classification of the COVID-19 clinical types was based on the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia, published by the National Health Commission and National Administration of Traditional Chinese Medicine of China (18). Patients were classified as severe COVID-19 (including critical ill patients) if they met any of the following criteria: i) Respiratory rate ≥ 30 breaths/min; ii) oxygen saturation $\leq 93\%$ at rest and iii) $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg. The present study excluded patients who did not have a positive RT-PCR test ($n=15$). The ethics committee of the Sibiu Emergency County Clinical Hospital approved the present study (approval no. 23619/Sept. 28. 2021). Informed consent of the patient was waived due to the retrospective nature of the study. Clinical records and laboratory data were collected from electronic medical database. A group of experienced clinicians reviewed and refined the data. Demographic features, comorbidities, clinical symptoms, signs and main outcome (mortality or survival), as well as hospital stay length were extracted from the electronic medical records. Laboratory assessment consisted of full blood count, coagulation parameters, inflammatory biomarkers and CT severity score. Pulmonary involvement was assessed using a quantitative CT score calculated based on the extent of lobar involvement (0, 0%; 1, <5%; 2, 5-25%; 3, 26-50%; 4, 51-75%; 5, >75%; range 0-5; global score 0-25) (15). A transversal analysis of the laboratory data was conducted by selecting the maximum values for each laboratory marker, including the CT severity score.

Categorical variables were presented as number (percentages %) and compared using the chi-square test. For continuous variables, we established the normality using Shapiro-Wilk test. All the data were skewed so Spearman's correlation coefficient (r_s) was used. Continuous variables were presented as median [interquartile range (IQR)] and compared with Mann-Whitney U test. Optimal cut-off values were determined using receivers operating

characteristics (ROC) curve by calculating the Youden index (sensitivity + specificity-1). Kaplan Meyer curve and log rank test was applied to observe differences in survival on groups of patients. Independent variables with predictive role for mortality were determined using an enter-method univariate and multivariate Cox regression. For hazard ratio (HR), confidence interval (CI) of 95% was also presented. $P < 0.05$ was considered to indicate a statistically significant difference. IBM-SPSS version 20.0 (IBM Corp.) was used to conduct the statistical analysis.

Results

In the final analysis, the present study included 697 patients, based on the aforementioned criteria. The baseline characteristics of the COVID-19 patients are summarized in Table I. During hospitalization 133 patients succumbed and 564 were discharged. The median age of the 697 patients was 64 (52-73), and 361 (51.8%) were men. Obesity was the most common comorbidity followed by hypertension, diabetes, coronary disease and chronic kidney disease. Compared with the survivor group, the non-survivors had a higher prevalence of diabetes, coronary heart disease and chronic kidney disease. The median age of the non-survival group was higher than the survivor group (Table I). Compared with the survival group, the non-survival group had greater disease severity, as evidenced by CT severity score and more frequent complications like disseminated intravascular coagulation and acute respiratory failure, accompanied by higher values of WBC, neutrophils, procalcitonin, CRP, IL-6, D-dimers and NLR and lower lymphocyte and thrombocyte count (Table II).

A correlation analysis was performed on the laboratory markers and severity scores. The most powerful correlated with mortality variables were NLR, CRP, IL-6, CT severity score, procalcitonin and D-dimers ($r_s=0.398$, $P < 0.001$; $r_s=0.370$, $P < 0.001$; $r_s=0.356$, $P < 0.001$; $r_s=0.347$, $P < 0.001$; $r_s=0.558$, $P < 0.001$ and respectively $r_s=0.474$, $P < 0.001$), so they were included in the final analysis. D-dimer values were positively correlated with creatinine levels and liver enzymes. Correlation analysis also showed that CRP, NLR and D-dimers are positively correlated with the extension of pulmonary lesions evaluated through CT imaging score ($r_s=0.453$, $P < 0.001$; $r_s=0.426$, $P < 0.001$ respectively $r_s=0.412$, $P < 0.001$). A multilinear regression showed that increased values of CRP are predictive for a higher CT score value, meaning extensive pulmonary lesions (B: 0.027, CI 95%: 0.020-0.034, $P < 0.001$). There was no significant difference between male and females regarding the CT score value ($P=0.996$).

In order to evaluate the prognostic value and cut-off points for the highly correlated variables with mortality in COVID-19 patients, ROC curves were evaluated. The areas under the curve (AUCs) for NLR, CRP, procalcitonin, D-dimer, IL-6 and CT severity scores were: 0.792 (CI 95%: 0.747-0.837); 0.770 (CI 95%: 0.725-0.814); 0.852 (CI 95%: 0.808-0.896); 0.856 (CI 95%: 0.821-0.891); 0.758 (CI 95%: 0.725-0.814); respectively 0.739 (CI 95%: 0.670-0.809; Table III). The best cut-off values for the presented markers were: 9.9 (sensitivity 65.6% and specificity 81.3%) for

Table I. General characteristics of COVID-19 patients.

Variable	Total (n=697)	Survivor (n=564; 80.91%)	Non-survivor (n=133; 19.08%)	P-value
Demographic characteristics				
Age, median (IQR)	64 (52-73)	62 (50-71)	70 (64.5-80)	<0.001
Sex				0.170
Female	336 (48.20%)	279 (49.5%)	57 (42.9%)	
Male	361 (51.80%)	285 (50.5%)	76 (57.1%)	
Symptoms				
Fever	382 (54.8%)	329 (58.3%)	53 (39.8%)	<0.001
Malaise	547 (78.5%)	428 (75.9%)	119 (89.5%)	0.001
Comorbidities				
Diabetes	168 (24.1%)	127 (22.5%)	41 (30.8%)	0.044
Hypertension	340 (48.8%)	266 (47.2%)	74 (55.6%)	0.079
CKD	83 (11.9%)	52 (9.2%)	31 (23.3%)	<0.001
Obesity	431 (61.8%)	349 (61.9%)	82 (61.7%)	0.962
Coronary Disease	136 (19.5%)	93 (16.5%)	43 (32.3%)	<0.001
Complications				
DIC	93 (13.3%)	56 (9.9%)	37 (27.8%)	<0.001
Acute Respiratory Failure	365 (52.4%)	244 (43.3%)	121 (91.0%)	<0.001

Variables are presented as count (%) and compared with chi-square test. Age was presented as median (IQR) and compared with Mann-Whitney U test. P<0.05. IQR, interquartile range; CKD, chronic kidney disease; DIC, disseminated intravascular coagulation. Other characteristics that were not presented had no statistical significance or low incidence.

NLR; 91.4 mg/l (sensitivity 78.6% and specificity 66.5%) for CRP; 1.45 µg/l (sensitivity 81.1% and specificity 77.1%) for D-dimer; 32.8 pg/ml (sensitivity 71.9% and specificity 72.3%) for IL-6; 0.28 ng/ml (sensitivity 70.5% and specificity 86.9%) for procalcitonin and 18.5 (sensitivity 70.1% and specificity 73.5%) for CT severity score. Then a high value for each parameter was defined, greater than the optimal cut-off points. In addition, Kaplan Meyer curves and log rank test showed significant difference of survival between patients based on the cut-off points of each individual variable included in the final analysis (data not shown).

The present study performed a Cox proportional hazards model in univariate and multivariate analysis to explore the predictive role of high values of the proposed markers. Univariate and multivariate analysis showed that high values of NLR [HR: 3.127 (CI 95%: 2.137-4.576)]; D-dimer [HR: 6.223 (CI 95: 3.809-10.167)]; procalcitonin [HR: 4.414 (CI 95:2.804-6.948)]; IL-6 [HR: 3,344 (CI 95:1.423-7.855)]; CRP [HR:2.997 (CI 95:1.940-4.630)]; and CT severity score [HR: 3.068 (CI 95:1.777-5.299)] (Table IV) are predictive for mortality in COVID-19 patients. Multivariate analysis included age, sex and comorbidities such as diabetes, coronary heart disease, hypertension and obesity (BMI >30 kg/m²).

Discussion

The present retrospective study included 697 patients and in-hospital mortality was 19.08%. Non-survivors presented

more frequently with comorbidities and increased values of the laboratory markers, as well as advanced age. There was no significant difference in survival among the sexes.

The most dominant characteristic regarding the hematological changes in COVID-19 patient are increased NLR due to neutrophilia and lymphopenia. Increased neutrophil number follows inflammatory response and release of pro-inflammatory cytokines like IL-6 and TNF-α by lymphocytes and endothelial cells (19). Neutrophils can also produce VEGF, which could contribute to angiogenesis and disseminated organ damage (20). On the other hand, lymphopenia may be a consequence of inflammatory response or direct leukocyte infection (21). Lymphopenia is also correlated with mortality and COVID-19 severity (22,23). Autopsy studies reveal that the virus can infect the leukocytes, especially lymphocytes. Secondary lymphoid organ sequestration hypothesis has been excluded as autopsies show low lymphocyte cells, especially T helper and regulatory cells in lymph nodes (24).

Hemoglobin levels are significantly different between males and females, as well as between survivors and non-survivors, but when survival rates are compared between males and females the difference is not statistically significant, even if there is a trend in prolonged survival in females (data not shown), proving that hemoglobin levels are correlated with mortality without any significant influence of sex.

Several studies assessed the predictive role of hematological markers in COVID-19 patients. Mo *et al* (25) in a study involving 155 patients with COVID-19 found that

Table II. Laboratory findings in COVID-19 patients (n=697).

Laboratory findings	Normal range	Median (IQR)	Survivor (n=564)	Non-survivor (n=133)	P-value
Hematological markers					
WBC count, x10 ⁹ /l	4-10	7.9 (5.6-12.3)	7.31 (5.4-10.3)	14.5 (7.7-21.8)	<0.001
Neutr. count, x10 ⁹ /l	2-7.5	5.96 (3.9-9.9)	5.38 (3.7-8.5)	12.1 (6.7-19.5)	<0.001
NLR		5.4 (3.1-11.2)	4.8 (2.8-8.4)	15.5 (6.5-30.1)	<0.001
Hemoglobin. g/dl	12-15	13.6 (12.3-14.7)	13.8 (12.7-15)	12.5 (11.3-13.9)	<0.001
Tr. count.x10 ⁹ /l	150-400	207 (163-278)	209 (166-280)	192 (141-271)	0.025
Acute phase reactants					
Procalcitonin. ng/ml	0-0.5	0.1 (0.05-0.39)	0.06 (0.05-0.15)	0.79 (0.2-3.4)	<0.001
IL-6. pg/ml	0-7	19.9 (6.2-58.3)	15.2 (5.3-35.2)	59.1 (20.2-158.7)	<0.001
C Reactive Protein, mg/l	0-5	77 (31.1-153.6)	63.4 (23.4-125.4)	166.9 (94.3-267.2)	<0.001
ESR. mm/h	0-20	48 (28-72)	46 (27-69)	62 (34-81)	0.016
Ferritin, ng/ml	13-150	592 (306-1194)	560 (296-1133)	852 (520-1456)	0.005
Blood biochemistry					
Glucose. mg/dl	80-115	123 (100-177)	118 (97-163)	165 (118-249)	<0.001
Creatinine. mg/dl	0.6-1.3	0.97 (0.8-1.3)	0.92 (0.8-1.2)	1.41 (1.0-3.1)	<0.001
AST. U/L	9-39	38 (27-60)	35 (26-56)	54 (39-88)	<0.001
ALT. U/L	3-43	39 (24-65)	38 (24-62)	44 (26-81)	0.029
Coagulation parameters					
D-dimers. µg/l	0.045-0.5	0.97 (0.5-1.98)	0.79 (0.5-1.4)	3.5 (1.7-9.8)	<0.001
Fibrinogen. mg/dl	170-420	542 (421-707)	525 (415-676)	663 (478-813)	<0.001
Severity scores					
CT severity score	0	15 (10-20)	14 (9-19)	20 (16-22.5)	<0.001

Parameters are presented as medians (IQR). P-values were calculated with Mann-Whitney U test. P<0.05 shows significant differences between survivors and non-survivors. IQR, interquartile range; WBC-, white blood cells; Lym, lymphocyte; Neut, neutrophil; NLR, neutrophils-lymphocyte ratio; Tr, thrombocyte; ESR, erythrocyte sedimentation rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table III. AUC of the proposed variables.

Variable	AUC	P-value	95% CI
CPR	0.770	<0.001	0.725-0.814
IL-6	0.758	<0.001	0.664-0.852
PCT	0.852	<0.001	0.808-0.896
D-dimer	0.856	<0.001	0.821-0.891
NLR	0.792	<0.001	0.747-0.837
CT score	0.739	<0.001	0.670-0.809

AUC, areas under the curve; CI, confidence interval; CRP, C reactive protein; NLR, neutrophil-lymphocyte ratio; PCT, procalcitonin, P<0.05 shows a significant AUC.

refractory patients had higher level of neutrophils compared with general patients. In another retrospective study, NLR was an independent marker for COVID-19 severity together with albumin levels, CRP and serum amyloid A (26). A meta-analysis conducted by Simadibrata *et al* (27) showed that NLR could predict both mortality and severity in COVID-19 patients. The present study showed that mortality

in patients with higher values of NLR is nearly threefold higher (Table IV). The clinical implication of this analysis is important because NLR can be easily calculated. The value of NLR depends on various factors such as hematological disorders and drugs like glucocorticoids (28), which were not assessed in the present study.

Coagulation abnormalities are very common in COVID-19 patients. In the present study, D-dimer values were predictive for mortality (Table IV). In a pooled analysis conducted by Lippi and Falavero (29), higher values of D-dimer were associated with mortality, but median values of the survival were also above normal range. A study proves the same; for example, a case-control study by Pan *et al* (30) showed that median values of D-dimer in survivors exceeded 1 µg/l. In the present study, median values of survivors were also above normal range (0.97 µg/l; Table II). There is evidence that high levels of D-dimers are associated with disease progression and may be the expression of fibrinolysis secondary to disseminated intravascular coagulation (DIC) favored by infection and sepsis (31). Another study shows that D-dimers might reflect coagulation activation due to viremia and inflammation as well as superinfection (11), which begs the question if survivor patients present coagulation disorders as well as non-survivors.

Table IV. Univariate/multivariate Cox regression.

Variable	Cox Univariate analysis		Cox multivariate analysis	
	p-sig	HR (95.0% CI)	p-sig	HR (95.0% CI)
NLR	<0.001	4.825	<0.001	3.127 (2.137-4.576)
D-dimer	<0.001	8.093	<0.001	6.223 (3.809-10.167)
Procalcitonin	<0.001	5.239	<0.001	4.414 (2.804-6.948)
IL-6	0.004	3.167	0.006	3.344 (1.423-7.855)
CRP	<0.001	4.617	<0.001	2.997 (1.940-4.630)
CT severity score	<0.001	3.678	<0.001	3.068 (1.777-5.299)

All presented variables are statistically significant. HR, hazard ratio; CI, confidence interval; NLR, neutrophil-lymphocyte ratio; CRP, C reactive protein. P<0.05 shows predictive value for high levels of each parameter.

Coagulation disorders that lead to disseminated thrombi can determine multiple organ failure in severe patients (32) and the present study showed that D-dimer values are positively correlated with increased creatinine and liver enzymes. The results also showed that patients with higher values of D-dimer have an ~6-fold higher chance of death (Table IV).

The presence of coagulation disorders in non-survivors as well as in survivor patients is very common, which can lead to the hypothesis that there may be different source of D-dimers, because some of the DIC criteria do not fit as there is low consumption of fibrinogen (fibrinogen levels are indeed elevated in both survival and non-survivor patients; Table II) (33). Another path that generates fibrin degradation products is linked to the degradation of fibrin mediated by cathepsin D produced by the alveolar macrophages (34). This could be taken in account as the present study showed positive correlation of D-dimers with extension of pulmonary infiltrates shown by the CT severity score. In a study by Yilmaz *et al* (35), higher D-dimer values correlated with CT severity score along with elevated ferritin serum levels.

In the present study, there was an association between high values of the inflammatory markers and mortality. CRP values have been correlated with the magnitude of lung lesions. In a study by Tordjman *et al* (36), the extension of lung implications in COVID-19 has been highly correlated with lactate dehydrogenase values, lymphocyte count and CRP. In another study, high values of CRP have been correlated with mortality, critical illness and acute kidney injury (37). CRP is a cost-efficient investigation and can predict lung lesion extension in the absence of a CT imaging score (36).

IL-6 is secreted by a wide range of cell type as a response to systemic inflammation (38). Circulating levels of IL-6 are elevated in COVID-19 patients and evaluating the plasma levels can determine whether or not a patient should receive anti-inflammatory therapies or monoclonal antibodies anti-IL-6 such as tocilizumab (38,39). However, in a study by McElvaney *et al* (40) a linear prognostic score based on the difference in IL-6/IL-10 ratio from day 4 to admission (Dublin-Boston score) outperforms the predictive role of IL-6 alone.

High procalcitonin levels could be the gold standard inflammatory biomarker in evaluating mortality in

COVID-19 patients, as the present study showed a nearly fourfold higher incidence of mortality in patients with values of procalcitonin >0.28 ng/ml during the hospital stay. Usually the release of procalcitonin from extra thyroid sources is the effect of bacterial infection by proinflammatory mediators such as IL-6, IL-1 and TNF- α , while INF- γ suppresses its synthesis (41). In survivors, the median values of procalcitonin remained low while in the mortality group median values were nearly 13-fold higher, meaning an exponential increase of procalcitonin levels as the evolution shifts towards mortality (Table II). In COVID-19 patients increase of procalcitonin levels may act as a bacterial superinfection, as were the majority of cases included in the final analysis (data not shown), or as a direct marker of a more severe or widespread viral infection (42). One of the main problems for the present study was that the cut-off value for procalcitonin (0.28 ng/ml) was within a normal range (0-0.5 ng/ml). This corresponds with other studies as Wan *et al* (43) obtained an optimal cut-off value for procalcitonin of 0.25 ng/ml while Cao *et al* (44) obtained an even smaller value of 0.1 ng/ml. Furthermore, in order to exclude systemic inflammation a value of <0.2 ng/ml is necessary, as >0.5 ng/ml values indicate the presence of sepsis, as an analysis shows (45).

In Francone *et al* (15), CT severity scores were correlated with D-dimer and CRP and predicted mortality for CT score values >18. The present study showed CT severity score \geq 19 can lead up to a threefold higher mortality. However, the CT severity score used in the present study to approach pulmonary involvement did not assess qualitative aspects associated with disease progression such as consolidation and crazy paving pattern (46). Scores that approach qualitative aspects of pulmonary involvement, such as the one evaluated by Yuan *et al* (47), have a higher ability in predicting mortality than the present study (AUC 0.901 vs. 0.739).

Compared to other studies that assess the predictive role of markers through the values on admission, the present study considered that the maximal in-hospital values of markers were more reliable in predicting mortality. That would be explained by the fact that the inflammatory phase of COVID-19 usually commences after 7 days (48). For example, in one study the age of patients and NLR measured at admission was associated with mortality with HR of

1.03 (49) compared with the HR of 4.82 the present study, showing increasing chance of mortality as the values change during the hospital stay. A study by Zhou *et al* (50) showed that IL-6 and procalcitonin levels on admission showed no predictive role in multivariate analysis. This proves that the method of the present study of evaluating prognosis might be more accurate and the level of markers on admission might not be enough (51). A study (52) showed that even for patients admitted in ICU with higher values of D-dimer on admission, showed lower incidence of mortality compared with the present study (HR 2.5 vs. 6.2).

The present study has limitations. It performed a retrospective single-center analysis; thus the results cannot be generalized and future studies that could supplement the present study with additional information are needed. The present study also lacked a longitudinal assessment of the laboratory markers as it performed a transversal analysis of the parameters.

The present study could not exclude other viral strains with different mortality as genomic sequencing could not be performed. They would have been an important factor in multivariate analysis.

Laboratory markers and CT severity scores could be used to stratify the mortality risk in COVID-19 patients. High D-dimer and procalcitonin levels were associated with a higher chance of mortality compared with other markers. Laboratory parameters such as CRP, D-dimer and NLR were highly correlated with CT severity scores which in the absence of possibilities in performing a chest CT could easily evaluate lung involvement.

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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.

Authors' contributions

ST and DT contributed to the conception and design of the work, data acquisition and data analysis, interpretation of data, drafting the manuscript and revised it critically for important intellectual content; RM and VB contributed to the conception and design of the work, interpretation of data and revised the manuscript critically for important intellectual content. ST, DT, RM and VB confirm the authenticity of all the raw data. All the authors read and approved the final manuscript.

Ethics approval and consent to participate

The ethics committee of the Sibiu Emergency County Clinical Hospital approved the study (approval no. 23619/Sept. 28. 2021).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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