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ANESTHESIA AND INTENSIVE CARE MEDICINE

SEVERITY FACTORS AND PROGNOSTIC SCORES IN CRITICALLY-ILL PATIENTS WITH VIRAL SEPSIS SECONDARY TO COVID-19

Summary of the PhD Thesis

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Introduction

In March 2020, the World Health Organization declares the SARS-CoV-2 pandemic. COVID-19 is an infectious viral disease, manifested mainly through pnuemonia, patients being hospitalized frequently for acute respiratory failure. The association between development of acute organ failure and a SOFA score ≥ 2 points defines viral sepsis secondary to SARS-CoV-2 infection. Although many authors consider COVID-19 primarly a pulmonary disease, scientific evidence supports the hypothesis of a significant or even primary involvement of the hematological and vascular system. Hematological cells have a pivotal role in the initiation and propagation of immunothrombosis and cytokine storm in COVID-19. Identification of clinical correspondents that can mirror the pathophysiological changes precluding acute respiratory failure and subsequently, multiple organ dysfunction, could facilitate: early therapeutic interventions and prevention of disease progression to severe and critical forms, monitoring and hospitalization of patients at risk and reduction of mortality rates.

Moreover, the evolution of the SARS-CoV-2 pandemic represented a challenge for all medical systems, regardless of capacity or performance indices. SARS-CoV-2 is a highly contagious virus, thus the lack of disease prevention through vaccination as well as the absence of specific antiviral drugs, represented factors that favoured a high number of hospitalization and ICU admissions. Furthermore, the need for respiratory support was higher than the available ICU beds and/or mechanical ventilators. Thus, during the pandemic waves, many medical systems adopted crisis management protocols. In these guidelines, risk factors or scores evaluating disease severity or prognosis were used as triage tools for ICU admission. Given the increased number of severe and critical cases, ICU admission based on more or less arbitrary criteria raises concerns about their validity. Thus, it it necessary to introduce these criteria in prospective and retrospective analyses in order to test their discriminative performance.

Taking into account the high scientific interest for these clinical research domains, one of the hypothesis of this PhD thesis is that qualitative and quantitative haematological markers alterations can be useful in the assessment of the severity and prognosis of patients with viral sepsis admitted in intensive care unit. Thus, I studied the predictive value of the dynamic changes of the hematological parameters from the moment of admission and during hospitalization in the intensive care unit. The original and innovative feature of this study

was represented by reporting the predictive power and identifying cut-off values of the derived haematological indices (neutrophils-to-lymphocytes ratio, systemic inflammatory index, derived neutrophils-to-lymphocytes ratio and monocytes-to-lymphocytes ratio) that were assessed in dynamics. Moreover, these cut-off values of the derived haematological indices were independent prognostic factors for mechanical ventilation need and death in multivariate analysis. By reporting these results, I have achieved one of the major objectives of the PhD study.

Another research direction of this PhD thesis was to extend the previous analysis in order to identify independent risk factors for death of any cause at day 28 based on demographic, clinical and paraclinical data at the time of admission to the intensive care unit. Following multivariate Cox proportional hazard analysis, independent factors associated with death of any cause at day 28 were age, neutrophils-to-lymphocytes ratio and SOFA score at the moment of admission. Based on the regression coefficients, I have derived the equation of the new COVID-SOFA score. The model was well calibrated, internally validated and had a predictive power superior to SOFA score for death at day 28. Moreover, I demonstrated that the repetitive use of the score during the intensive care unit stay is associated with a significant improvement in the predictive power for death. By applying the model for the study of all-cause mortality at day 60, I showed the reproducibility and maintenance of the predictive power of the COVID-SOFA score. Finally, I derived the Cox equation to calculate the probability of death at days 28 and 60, respectively. Based on the results obtained, I was able to achieve another major goal of my PhD research.

Taking into account that the differential diagnosis of sepsis secondary to pneumonia is difficult, as the clinical picture can be very similar for bacterial or viral aetiological agents, I decided to carry out within the PhD research a study to assess in an extensive manner the two aforementioned entities. In this study, I included patients with viral sepsis secondary to COVID-19 and patients with bacterial sepsis secondary to bacterial pneumonia. Procalcitonin and the red blood cell distribution width had a very good discriminative power. Moreover, they were strongly correlated with the disease severity. Therefore, the innovative feature of this study is represented by the results obtained for the red cell distribution width. Furthermore, these results support the particular impairment of erythrocytes in bacterial sepsis. Finally, some haematological markers had a good discriminative ability, such as leukocytes, neutrophils and monocytes, whereas other derived haematological parameters and indices had little or no diagnostic ability.

The results presented in this PhD thesis bring a significant contribution to the study of severity and prognostic factors of patients with COVID-19 in the intensive care unit. Also, the development of a prognostic score and an equation to calculate the probability of death provides a valuable new clinical tool that can be used in the management of these patients. Finally, comparative analysis of haematological alterations induced by viral and bacterial sepsis provides new insights into this field and highlights the existence of distinctive pathophysiological mechanisms. Thus, the diagnosis of sepsis and, consequently, the therapeutic approach will be able to be individualized.

I.1. GENERAL PART (current state of knowledge)

1. Viral sepsis secondary to the new coronavirus acute respiratory syndrome (COVID-19)

Sepsis represents a major public health issue worldwide [1], estimated to affect approximately 30 million people annually with up to 5 million deaths [2]. Reported mortality of critically ill patients with COVID-19 had a high variability between 13-86% [3], up to over 90% in some subgroups [4].

Even though it is mainly considered a disease of the respiratory system, based on published data, it has been observed that in COVID-19 the damage is multisystemic and has a polymorphic clinical and biological picture [5]. Severe or critical forms of COVID-19 are considered a form of viral sepsis [6]. Compared to bacterial sepsis, important differences in systemic inflammatory response, organ injury and disease progression are described. Furthermore, viral sepsis secondary to other viral agents exhibits distinct phenotypes [7-9].

The haematological system is a key element in the pathogenesis of SARS-CoV-2 infection. The extent of haematological alterations induced by COVID-19 significantly influences the course of the disease as well as the prognosis of these patients [5, 9-25]. There is a close relationship between quantitative and qualitative alterations of circulating blood cells and endotheliopathy followed by thrombo-inflammation in patients with severe or critical forms of COVID-19 [11, 13-15, 26]. Moreover, distinct phenotypes have been described depending on the magnitude of the hematological system response to SARS-CoV-2 aggression [10, 13].

Neutrophils are involved in the pathophysiology of COVID-19 through: exaggerated recruitment and activation, formation of neutrophil extracellular traps - NETosis, inflammasome activation and release of neutrophilic microparticles [12-14, 27, 28] Lymphocytes play a central role in the immunopathology of viral sepsis secondary to SARS-CoV-2 infection. Both quantitative and qualitative disorders characterize different phenotypes of viral sepsis, play a role in patient triage, predict disease progression as well as severity, risk of superinfection and death [29-32].

Endotheliopathy and immunothrombosis are distinct features of viral sepsis in COVID-19 having specific mechanisms but also common to those in bacterial sepsis [15]. Endotheliitis or capillaritis can occur secondary to direct and indirect injury. Direct injury can be explained by the presence of ACE2 and TMPRSS2 receptors on the endothelial cell

surface [9, 19, 24, 33, 34]. Consequent to endothelial injury, a hypercoagulable state occurs with microthrombosis formation [9]. Indirect injury occurs mainly secondary to proinflammatory status. Eventually, vascular dysfunction and thromboinflammation are sustained by positive feedback loops, the final result being organ failure and/or major thrombotic events [15].

2. Severity and prognostic factors in sepsis secondary to COVID-19

The evolution of the SARS-CoV-2 pandemic has prompted health systems to form the basis of a crisis management. As part of this, it has been necessary to develop diagnostic and triage tools for critically ill patients [35, 36]. Given the high frequency of admission to the intensive care unit (32-40%) and the high mortality (up to 86%) [3], the provision of care based on more or less arbitrarily established criteria raises the question of their validation [35-37].

Socio-demographic data such as gender, age, race, ethnicity or residence were independent risk factors for severe or critical forms of COVID-19, ICU admission and higher mortality [4, 38-51].

Comorbidities and other clinical factors have been reported as independent risk factors for severity or progression of disease to severe and critical forms, ICU admission, need for mechanical ventilation, need for supportive therapies of other organs, long-term sequelae and death [38-42, 44, 46, 49-51].

Laboratory parameters such as ALT, AST, GGT, bilirubin, albumin, LDH, CK, CK-MB, troponin I and T, creatinine, urea or the nitrogen portion of urea (BUN), proteinuria and haematuria are indicators of acute organic injury. They are associated with disease severity and progression, may predict hospitalisation, admission to intensive care, need for organic replacement therapy, and death or long-term complications [3, 4, 18, 19, 24, 26, 38-41, 46, 49, 50, 52-62].

Zinellu et al. [63] conducted a meta-analysis of 71 studies and analyzed hematologic factors associated with disease progression and mortality in patients with COVID-19. Neutrophilia (HR: 1.62, (1.46; 1.80)), lymphopenia (HR: 1.62: (1.27; 2.08)) and thrombocytopenia (HR: 1.74 (1.36; 2.22)) were independently associated with mortality and disease progression in patients with COVID-19 [63]. Furthermore, red blood cell distribution width and monocyte distribution width have predictive value for death and progression to

severe forms in this group of patients [64, 65]. NLR is the most studied hematologic marker, being the variable most frequently associated with severity (96% of studies) and mortality in analyses that included patients with COVID-19 [62]. In a meta-analysis that included 2967 patients, NLR had an AUC for predicting death of 0.90. For a cut-off value ≥ 6.5, the positive odds ratio was 6.3, and the diagnostic odds ratio was 32 [66]. Furthermore, Simadibrata et al. reported a NLR hazard ratio value for death of 2.74 (95% CI, 0.98 - 7.66) in a meta-analysis that included 6033 subjects from 15 studies [67].

The SOFA score is one of the diagnostic criteria for sepsis according to Sepsis-3 [68]. In viral sepsis secondary to severe SARS-CoV-2 infection, the SOFA score had inadequate discriminatory value in terms of prognosis for death or triage for initiation/assignment of mechanical ventilation. Thus, the SOFA score should be used with caution in these situations [37, 69, 70].

Lombardi et al. performed external validation of 32 prognostic scores reported in the literature (30-day in-hospital mortality or ICU admission) in patients with COVID-19 [71]. Of the 32 scores studied, 19 had a significantly lower predictive value at the time of external validation than the discriminative power originally reported. For in-hospital mortality, only 7 scores maintained an AUROC value above 0.75 at external validation [71].

Meijs et al. performed external validation of 8 scores on 551 COVID-19 patients admitted to the ICU from the *Euregio Intensive Care COVID* cohort. Mortality in the whole cohort was 36% [72]. The 4C Mortality Score [73] had the best discriminative power for death (AUC; 0.70, 0.64-0.76) and moderate calibration. The discriminative power observed in this study is lower than that reported by the authors who developed the score as well as Lombardi et al [71]. Finally, the risk of bias of this score was considered unclear by the authors.

Severity and prognostic scores commonly used in critically ill patients, such as CURB-65 [74], APACHE II [75] and SOFA [76] had low predictive ability with AUCs of 0.68 (0.64-0.73), 0.65 (0.60-0.69), and 0.62 (0.56-0.68), respectively.

Buttia et al. [77] recently published a systematic review on prognostic models with predictive power for severity and mortality of patients with COVID-19. This systematic review included 314 studies in which a total of 353 models were reported. Of these, only 37 were performed on ICU patients, and the authors outline that 99.4% of predictive models are at high risk of bias. Furthermore, only 17.5% of studies adhered to the TRIPOD (Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) guidelines for reporting predictive models [78].

II. PERSONAL CONTRIBUTIONS (original)

3. Study I: Dynamic changes of the derived hematologic indices are independent prognostic factors for invasive mechanical ventilation need and death in critically ill patients with COVID-19

3.1. Introduction (aim, hypothesis, and specific objectives)

The haematological system is a key element in the progression to severe and critical forms of COVID-19. Based on pathophysiology and molecular biology data in the literature, qualitative and quantitative disorders precede or are the triggering factor for cytokine storm as well as immune-thrombosis. Thus, early clinical identification may predict progression to critical forms (implicitly, the need for invasive ventilatory support) or death.

The objective of this study was to identify the relationship between the dynamics of alterations in haematological indices (NLR, dNLR, SII, PLR and MLR) and the events studied (need for invasive ventilatory support and death), as well as the predictive power of each haematological index individually.

3.2. Materials and methods

This is a multicenter, observational, retrospective study that included 272 patients with severe and critical forms of COVID-19. Data analysis was performed according to the two events studied: (I) need for invasive mechanical ventilation and (II) death. Patients in the first group were divided into 3 subgroups: (1) patients under invasive mechanical ventilation on ICU admission, (2) patients who required initiation of mechanical ventilation during their ICU stay, and (3) patients who did not require invasive mechanical ventilation during their ICU stay. Patients in the second group were classified as survivors and deceased.

The delta values (Δ) of haematological indices were calculated as: the 48-hour value of a parameter - the value of the same parameter at the time of admission. The discriminative power of the derived haematological parameters was studied using Receiver Operating Characteristics (ROC) analysis. The results were expressed as the area under the ROC curve (AUROC) together with the cut-off values identified based on the Youden index. Sensitivity (Sb.), specificity (Sp.), positive predictive value (PPV) and negative predictive value (NPV) were also reported for the established cut-off values. Finally, the parameters identified to

have discriminative value in the ROC analysis were further studied using multivariate Cox proportional hazard regression.

3.2. Results

In the studied cohort, male subjects had the highest proportion (186/272), with no significant differences between the studied groups (p > 0.05). The mean age of the whole cohort was 62.7 (± 12) years, with a statistically significant difference in the need for invasive mechanical ventilation between subgroups 1 and 3, respectively 2 and 3: 64.9 (±9.9) vs. 65.4 (±11) vs. 58.5 (±12.4), p < 0.0001. I maintained the same observation for the death event, survivors being younger (58.2 (±11.8) vs. 66.8 (±10.5), p < 0.0001). Patients requiring invasive mechanical ventilation at the time of admission (group 1) and those who required invasive mechanical ventilation during their ICU stay (group 2) had significantly higher mortality compared to those who did not require invasive ventilatory support (group 3) (81.7% and 76.1% vs. 13.3%, p < 0.0001).

Haematological indices values at admission had no discriminative power in terms of the need for invasive mechanical ventilation. Areas under the curve for NLR, SII, dNLR, PLR and MLR ranged from 0.521 to 0.573, the models being rejected (p > 0.05).

On the other hand, hematological indices values at admission have low discriminative power for death. Models were accepted for all indicators entered into the analysis with area under the curve values ranging from 0.572 to 0.621 (p < 0.05).

In terms of prediction for invasive mechanical ventilation requirement, the differences between the areas under the ROC curves are significant (p < 0.0001) at 48 h compared to those at admission. Furthermore, the predictive ability of the delta values is marginally or even significantly increased (for NLR) for prediction of invasive mechanical ventilation requirement.

Thus, the discriminative model is very good for ΔNLR, ΔSII and ΔdNLR with area under the curve values between 0.826 and 0.876 (p < 0.0001). For ΔPLR and ΔMLR, the model performance is good with area under the curve values between 0.713 and 0.774 (p < 0.0001) (Figure 3.1., Table III.1).
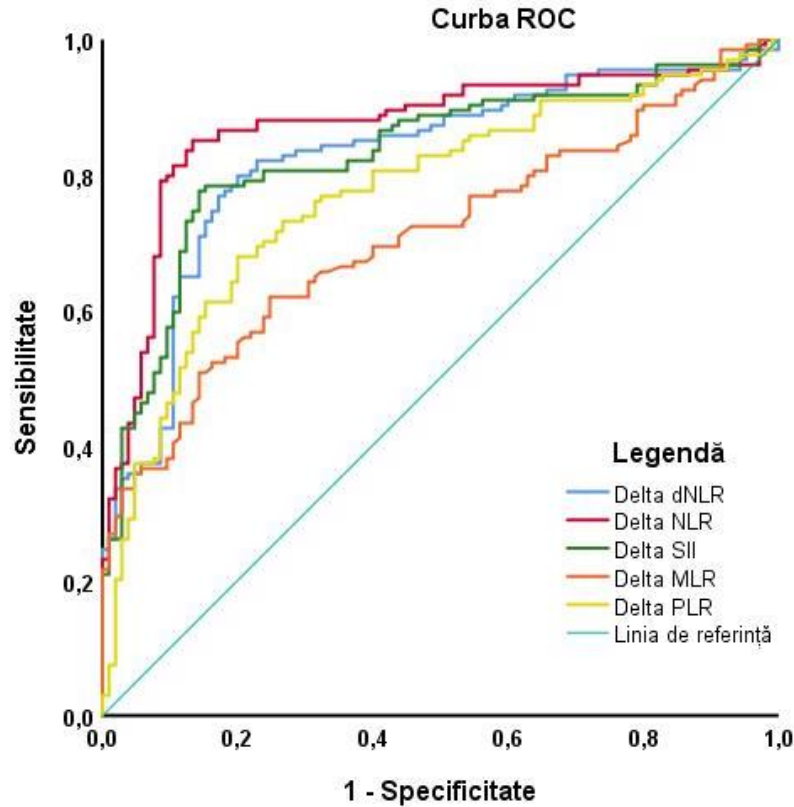
Figure 3.1. Discriminative power for invasive mechanical ventilation requirement
of dynamically measured haematological parameters

Table III.1. Cut-off values of haematological indicators as predictors for invasive
mechanical ventilation

				Prediction of IMV need				
	AUC	**95% CI**	*p*	**Cut-off**	**Sb%**	**Sp%**	**VPP%**	**VPN%**
ΔNLR	0.876	0.824-0.920	< 0.0001	>2	79.5	91.4	92.1	78
ΔSII	0.834	0.781-0.887	< 0.0001	>340	79.5	80	83.3	75.7
ΔdNLR	0.826	0.772-0.880	< 0.0001	>1	70.5	84.8	85.3	69.5
ΔPLR	0.774	0.714-0.834	< 0.0001	>50	68.2	79	80.4	66.4
ΔMLR	0.713	0.648-0.778	< 0.0001	>0.1	53.8	81.9	78.9	58.5

For prediction of death, the differences between the areas under the ROC curves are significant (p < 0.0001) at 48 h compared to those at admission. Moreover, the predictive ability of the 48 h values is marginally or even significantly increased (for NLR and dNLR) compared to the delta values for prediction of death.

Thus, the discriminative model is very good for NLR 48h and dNLR 48h with area under the curve values between 0.831 and 0.867 (p < 0.0001). For SII, PLR and MLR the

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model performance is good with area under the curve values between 0.740 and 0.796 (p < 0.0001) (Figure 3.2., Table III.2).

Concerning prediction of death, the differences between the areas under the ROC curves are significant (p < 0.0001) at 48h compared to those at admission. Moreover, the predictive ability of the 48h values is marginally or even significantly increased (for NLR and dNLR) compared to the delta values for prediction of death.

Thus, the discriminative model is very good for NLR 48h and dNLR 48h with area under the curve values between 0.831 and 0.867 (p < 0.0001). For SII, PLR and MLR the model performance is good with area under the curve values between 0.740 and 0.796 (p < 0.0001) (Figure 3.2., Table III.2).
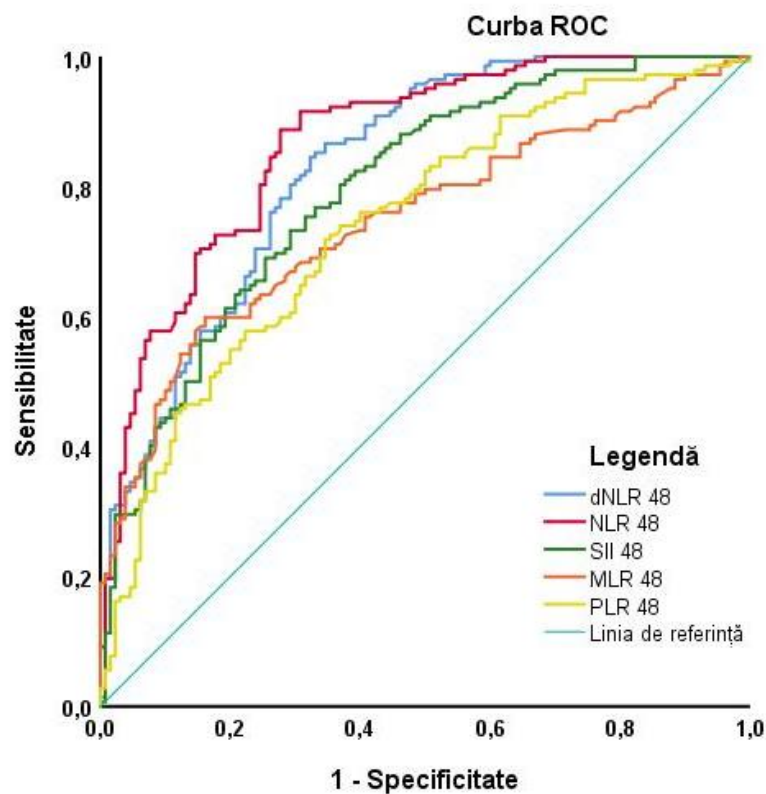
Figure 3.2. Discriminative power for death of dynamically measured haematological parameters

Tabel III.2. Cut-off values of haematological indicators as predictors of death

	AUC	95% CI	p	Cut-off	Sb%	Sp%	VPP%	VPN%
Prediction of death								
NLR 48 h	0.867	0.825-0.909	< 0.0001	>11	86.6	72.3	77.4	83.2
SII 48 h	0.796	0.744-0.848	< 0.0001	>3700	71.8	70.8	72.9	69.7
dNLR 48 h	0.831	0.784-0.879	< 0.0001	>6.93	80.3	70	74.5	76.5

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PLR 48 h	0.740	0.682-0.798	< 0.0001	>300	82.4	49.2	63.9	71.9
MLR 48 h	0.747	0.689-0.805	< 0.0001	>0.64	60	80.8	77.3	64.8

The following factors were entered into the multivariate models according to their association with the event in the univariate analysis:

a. Need for invasive mechanical ventilation. Haematological parameters were adjusted for: age > 60 years, 48-hour CRP value, need for non-invasive mechanical ventilation on admission, severe hypoxaemia at 48 hours (P/F < 100 mmHg), diabetes mellitus and Charlson comorbidity index.

b. Death: Hematological parameters were adjusted for: age > 60 years, Charlson comorbidity index, SOFA score at 48 hours, healthcare-associated infections, CRP value at 48 hours, severe hypoxaemia at 48 hours (P/F < 100 mmHg), tocilizumab therapy and need for mechanical ventilatory support.

In all models for predicting invasive mechanical ventilation requirement, the need for non-invasive mechanical ventilatory support on admission and severe hypoxemia at 48 hours were independent risk factors with hazard ratio values between 1.89 and 2.04 for NIV and 1.52 and 2.17 for severe hypoxemia. Furthermore, in models for ΔSII and ΔMLR, the C-reactive protein value was an independent predictor (HR = 1.003, 95% CI 1.001 - 1.005, p < 0.05)

For haematological indices as predictors for IMV, HR values were as follows: ΔNLR > 2: HR = 5.05 (95% CI, 3.06-8.33, p < 0.0001), ΔSII > 340: HR = 3.56 (95% CI 2. 21 - 5.74, p < 0.0001), ΔdNLR > 1: HR = 2.61 (95% CI 1.7 - 4.01, p < 0.0001), ΔPLR > 50: HR = 1.95 (95% CI 1.29 - 2.93, p = 0.001) and ΔMLR > 0.1: HR = 1.73 (95% CI 1.19 - 2.51, p = 0.004).

For the second studied event (death), the HR values at 48 hours adjusted in the multivariate analysis were: NLR > 11: HR = 2.25 (95% CI: 1.31 - 3.86, p = 0.003), SII > 3700: HR = 1.68 (95% CI: 1.13 - 2.49, p = 0.01), dNLR > 6.93: HR = 1.89 (95% CI: 1. 2 - 2.98, p = 0.005), PLR > 300: HR = 1.66 (95% CI: 1.04 - 2.64, p = 0.025), MLR > 0.64: HR = 1.49 (95% CI 1.003 - 2.2, p = 0.048).

4. Study II: Development and internal validation of a prognostic model that predicts all-cause mortality at day 28 in critically ill patients with COVID-19 - the COVID-SOFA score

4.1. Introduction (aim, hypothesis, and specific objectives)

Clinical and paraclinical factors at the time of admission are correlated with severity, disease progression and mortality in critically ill patients with COVID-19. The SOFA score has lower discriminative power for severity and mortality in patients with viral sepsis secondary to COVID-19. If in the studied cohort the SOFA score will have reduced but significant discriminative power for death at day 28, it is possible to modify the SOFA score in a manner that better reflects the particularities of patients with viral sepsis secondary to COVID-19.

The objective of this study is to replicate the CLIF-ACLF score methodology to improve the predictive value of the SOFA score in patients with COVID-19 by adding parameters identified to be independent prognostic factors.

4.2. Materials and methods

This is an observational, retrospective, cohort study including 425 patients with COVID-19 admitted to the intensive care units (4 independent wards) of two tertiary centers: the Elias University Emergency Hospital and the "Dr. Carol Davila" Central Military Emergency Hospital were included.

Predictive models were constructed using Cox proportional hazards regression. Data were entered into the regression using the forward stepwise method. Variables were retained in the model if p-value < 0.05 and removed if p > 0.1. The following variables were entered into the model: age, neutrophil to lymphocyte ratio (NLR), SOFA score, CRP, D-dimer, ferritin and sex. The COVID-SOFA score equation was calculated based on regression coefficients. The Hosmer-Lemeshow test was used to assess model calibration (goodness-of-fit).

To compare the obtained model with the original SOFA score we used the Akaike information criterion (AIC), the Bayesian information criterion (BIC) and the likelihood ratio test.

Discriminative power was assessed using concordance statistics (Harrell's C-index or Harrell C-index, ROC curve analysis (AUROC), Precision-Recall curve analysis (AUPRC)

and prediction of error rate improvement. The areas under the curve for the SOFA score and the COVID-SOFA score were compared using the method described by DeLong et al. [79]. The areas under the PRC (AUPRC) were compared using bias-corrected accelerated bootstrapping (BC(a) at resampling rate = 1000 iterations). The difference between the two curves was considered significant if both 95% confidence interval limits of BC(a) were positive and > 0. The prediction of error rate improvement was calculated according to the following formula: 100 x (C-Harrell$_{COVID-SOFA}$ − Index - C-Harrell$_{SOFA}$ Index)/(1 - C-Harrell$_{SOFA}$ Index) [80]. Its value was expressed as a percentage.

Finally, the probability of mortality was calculated based on the Cox equation [81]:

Rewritten for the COVID-SOFA score:

$$S(t) = 1 - e^{[-CI(t) \times \exp(\beta(t) \times COVID\text{-}SOFA)]}$$

Where, t = time point for the probability of survival (day 28); CI(t) = baseline cumulative hazard levels for the given time; $\exp(\beta(t) \times COVID\text{-}SOFA)$ = probability index; $\exp\beta(t) = \exp\beta$ for the COVID-SOFA score at the given time multiplied by the calculated value of the COVID-SOFA score.

Internal validation was performed by bias-corrected accelerated bootstrapping (BC(a) at resampling rate = 1000 reiterations) for calibration, Cox regression and PRC. The model was considered significant if both 95% confidence interval bounds of BC(a) were positive and > 0.

4.3. Results

The median age of the entire group was 64 years [55-57] (Figure 4.2.), and 68.2% of patients were male. At ICU admission, 51 (12%) patients were invasively mechanically ventilated (IMV), 225 (52.9%) were non-invasevaly mechanically ventilated (NIV) and 149 (35.1%) required high-flow oxygen therapy (HFOT). The median SOFA score on admission for the whole group was 4 [3-5] points. Statistically significant differences were observed between IMV, NIV and HFOT patients (8 [6-9] vs. 4 [3-5] vs. 3 [2-3] points, p < 0.001).

For the final model, the statistical software kept age (Figure 4.11.), neutrophil to lymphocyte ratio value (Figure 4.12.) and SOFA score (Figure 4.13.) as independent predictors. Based on the regression coefficients, the following equation was calculated:

COVID-SOFA score = 10 x [0.037 x Age + 0.347 x ln(NLR) + 0.16 x SOFA]

The value obtained in brackets is multiplied by 10 and rounded to facilitate the use of the final SOFA score. The final model was well calibrated for mortality at day 28 ($\chi2$ Hosmer-Lemeshow = 5.45, p = 0.7). Table IV.1. summarizes the full Cox regression model for the COVID-SOFA score.

Tabel IV.1. Final Cox regression model and validation by bias corrected accelerated bootstrapping

Event=death on day 28 of admission	Cox proportional hazard regression Method: bottom-up, stepwise				(BC(a)) bootstrapping (resampling = 1000 cases)			
Covariate	β	p	HR	95% CI Exp(b)	β	Bias	p	95% CI for BC(a)
Age	0.037	<0.001	1.038	1.026 – 1.05	0.037	0.001	0.001	0.025 – 0.052
ln(NLR)	0.347	0.001	1.415	1.167 – 1.717	0.347	0.002	0.002	0.181 – 0.597
SOFA at admission	0.16	<0.001	1.176	1.107 – 1.248	0.16	0.001	0.001	0.095 – 0.214

The event was coded as 1 and represented death within 28 days of admission to intensive care ;
BC(a) = bias corrected accelerated; β = regression coefficient; HR = hazard ratio; 95% CI = 95% confidence interval;
ln = natural logarithm; NLR = neutrophil-to-lymphocyte ratio;

Tabelul IV.2. Comparative analysis of the discriminative power of scores COVID-SOFA and SOFA

	Index-C, 95% CI	Dif. Index-C	Error rate prediction	AUROC 95% CI	Dif.* AUROC	P*	AUPRC 95% CI	Dif. AURPC 95% BC(a) CI
All-cause mortality at day 28								
C-SOFA Admission ICU	0.697 0.662–0.731			0.796 0.755–0.833			0.813 0.757–0.858	0.079
		0.058	16.06%		0.097	<0.001		
SOFA Admission ICU	0.639 0.605–0.672			0.699 0.653–0.742			0.734 0.674–0.787	0.066–0.094
C-SOFA 48 h	0.733 0.700–0.765			0.862 0.826–0.893			0.870 0.820–0.907	0.086
		0.045	14.42%		0.074	<0.001		
SOFA 48 h	0.688 0.654–0.723			0.788 0.746–0.826			0.784 0.727–0.832	0.07–0.11

The probability for death according to the chosen time criteria was calculated using the Cox equation [81] rewritten for the COVID-SOFA score:

$$S(t) = 1 - e^{[-CI(t) \times \exp(\beta(t) \times \text{COVID-SOFA})]}$$

Coefficients for COVID-SOFA score on admission to intensive care unit:

$$CI(\text{day } 28) = 0.017; \exp(\beta)(\text{day } 28) = 1.1045$$

Coefficients for COVID-SOFA score on admission to intensive care unit:
$$CI(\text{day } 28) = 0.010; \exp(\beta)(\text{day } 28) = 1.1134$$

5. Study III: Haematological parameters and procalcitonin as discriminants between viral sepsis secondary to COVID-19 and bacterial sepsis secondary to bacterial pneumonia

5.1. Introduction (aim, hypothesis, and specific objectives)

The systemic inflammatory response, and thus immunological changes, have distinct features in the two types of sepsis. Haematological parameters assess the host response to infection. The magnitude of this response can differentiate the two clinical entities based on alterations in haematological parameters and procalcitonin.

The objective of this study is to identify the discriminative value of haematological parameters and procalcitonin between viral and bacterial sepsis.

5.2. Materials and methods

To test the discriminative ability of hematological parameters, I conducted a ROC analysis with calculation of the area under the curve (AUC or AUROC) for each indicator. For each variable, the cut-off value was calculated using the Youden index. Furthermore, sensitivity (Sb%) and specificity (Sp%) were calculated for the identified cut-off value. Finally, discriminative and diagnostic power was reported as positive likelihood ratio (+LR) and negative likelihood ratio (-LR). Bivariate analysis using the Spearman rho coefficient was used to study the correlation of ranks between two independent continuous variables.

5.3. Results

The median age of the whole group was 68 years [58-77], with a significant difference between the two groups. Patients with bacterial sepsis had higher median values for age compared to patients with viral sepsis ($p < 0.001$).

Of the haematological parameters studied, procalcitonin had the best discriminative ability of all parameters measured with an AUROC value of 0.92 (95% CI: 0.87-0.95). Thus, the model had excellent predictive value. RDW% had very good discriminative power with an area under the curve value of 0.87 (95% CI: 0.82-0.91, $p < 0.001$).

Similar to bacterial sepsis, a higher procalcitonin value is associated with higher SOFA scores (Spearman rho coefficient = 0.58 (95% CI: 0.46-0.68), $p < 0.001$) in patients with viral sepsis.

Table V.1. Discriminative analysis of haematological parameters and procalcitonin

	AUROC 95% CI	Youden Index 95% CI	Cut–off 95% CI	Sb% 95% CI	Sp% 95% CI	+LR 95% CI	–LR 95% CI
PCT	0.92	0.71	> 1.49	76.6%	94.2	13.22	0.25
(p<0.001)	0.87–0.95	0.61–0.77	1.28–1.9	68.2–83.7	88.9–97.5	6.7–21.1	0.18–0.35
RDW%	0.87	0.66	> 14.8	80.7%	85.5%	5.56	0.23
(p<0.001)	0.82–0.91	0.57–0.75	14.6–15.2	72.6–87.2	78.5–90.9	3.68–8.42	0.16–0.33
Leucocytes	0.78	0.5	>16	64.5%	85.5%	4.45	0.41
(p<0.001)	0.72–0.83	0.4–0.58	14.4–17.3	55.4–72.9	78.5–90.9	2.91–6.81	0.32–0.53
Monocytes	0.77	0.44	>0.69	63.2%	81.2%	3.35	0.45
(p<0.001)	0.71–0.82	0.32–0.52	0.55–0.9	53.6–72	73.6–87.3	2.31–4.87	0.35–0.58
Neutrophils	0.76	0.49	>14.1	64.5%	84.1%	4.05	0.42
(p<0.001)	0.7–0.82	0.37–0.57	10.9–14.9	55.4–72.9	76.9–89.7	2.7–6.07	0.33–0.54
Eosinophils	0.72	0.43	>0.001	66.1%	76.8%	2.85	0.44
(p<0.001)	0.6–0.7	0.32–0.54	0.00–0.001	57.1–74.4	68.9–83.6	2.1–4	0.34–0.57
PLR	0.71	0.35	≤259	65.3%	69.6%	2.15	0.5
(p<0.001)	0.64–0.76	0.23–0.43	226–392	56.3–73.6	61.2–77.1	1.62–2.85	0.38–0.65
MLR	0.69	0.34	>0.73	61%	72.9%	2.25	0.54
(p<0.001)	0.61–0.75	0.19–0.4	0.59–1.17	51.8–69.6	64.3–80.3	1.64–3.08	0.42–0.68
Basophils	0.68	0.27	>0.01	67.7%	59.4%	1.67	0.54
(p<0.001)	0.6–0.72	0.17–0.39	0.001–0.02	58.8–75.9	50.7–67.7	1.32–2.11	0.41–0.73
Platelets	0.67	0.28	≤189	51.6%	76.8%	2.23	0.63
(p<0.001)	0.6–0.73	0.16–0.36	169–281	42.5–60.7	68.9–83.6	1.57–3.15	0.51–0.77
Limfocite	0.6	0.21	>0.85	58.1%	63%	1.57	0.67
(p=0.005)	0.53–0.7	0.09–0.3	0.33–1.04	48.9–66.9	54.4–71.1	1.21–2.05	0.52–0.85
NLR	0.59	0.18	>27.24	25%	93.5%	3.83	0.8
(p=0.01)	0.52–0.66	0.09–0.25	24.5–38.4	17.7–33.6	88–97	1.9–7.73	0.72–0.9
iGr	0.58	0.17	>0.14	50.8%	66%	1.49	0.75
(p=0.023)	0.52–0.67	0.08–0.24	0.01–0.41	41.7–59.9	57.4–73.8	1.12–1.99	0.6–0.93
SII	0.54	_	_	_	_	_	_
(p<0.32)	0.46–0.6						
dNLR	0.52	_	_	_	_	_	_
(p<0.59)	0.47–0.58						

AUROC = area under the ROC curve, 95% CI = 95% confidence interval, Sb% = sensitivity, Sp% = specificity, +LR = positive likelihood ratio, -LR = negative likelihood ratio, RDW% = red cell distribution width, NLR = neutrophil to lymphocyte ratio, dNLR = derived neutrophil to lymphocyte ratio, MLR = monocyte to lymphocyte ratio, PLR = platelet to lymphocyte ratio, iGr = immature granulocyte, SII = systemic inflammatory index

6. Conclusions and original and innovative contributions of the thesis

6.1. Conclusions

In study I *"Dynamic changes of derived hematologic indices are independent prognostic factors for invasive mechanical ventilation need and death in critically ill patients with COVID-19"* I presented important results regarding the predictive power of derived haematological indices for invasive mechanical ventilation requirement and death. These results support the hypothesis of a key role of hematological cells in the progression of COVID-19 to critical forms and death. The originality of this study is also supported by the methodology based on I was able to identify cut-off values for dynamic measurements of these parameters and to establish independent predictive power by multivariate analysis with confounders. Thus, I believe that the results I have reported have supported the working hypothesis and the objectives proposed at the time of the initiation of this study have been met.

In study II *"Development and internal validation of a prognostic model that predicts all-cause mortality at day 28 in critically ill patients with COVID-19 - the COVID-SOFA score"* I reported results regarding the construction of a new score for predicting death in patients with viral sepsis secondary to COVID-19 admitted to the ICU. In the studied cohort, the SOFA score had modest predictive power for death by any cause at day 28 after ICU admission, confirming one of the working hypotheses. Age and values of NLR and SOFA score at ICU admission were factors independently associated with all-cause mortality at day 28 in multivariate analysis. The COVID-SOFA score was superior to the SOFA score, with significantly higher discriminative power and improved prediction error. Furthermore, the accuracy of this score increased significantly when used in a repeated and dynamic manner, confirming the working hypotheses set at the time of the study's inception as well as some of those stated in study I.

Study III *"Haematological parameters and procalcitonin as discriminants between viral sepsis secondary to COVID-19 and bacterial sepsis secondary to bacterial pneumonia"* outlined the haematological and immunological features of the response to infection in two distinct types of sepsis. The results reported in this study were partially in agreement with the working hypotheses set at the beginning. Procalcitonin had the best discriminative ability between bacterial and viral sepsis, with increased sensitivity and specificity. The hypothesis that a procalcitonin value >0.5 ng/mL differentiates between bacterial sepsis secondary to

bacterial pneumonia and viral sepsis secondary to COVID-19 was disproved by our results. In both types of sepsis procalcitonin value was positively correlated with disease severity, but the correlation was stronger between procalcitonin and viral sepsis. This result may partially explain the cut-off value >1.49 ng/mL for differentiating bacterial from viral sepsis. After procalcitonin, red blood cell distribution width (RDW%) was the haematological parameter with the best discriminative ability, with values >14.8% having a high accuracy for the diagnosis of bacterial sepsis.

6.2. Original and innovative contributions of the thesis

- Neutrophil-to-lymphocyte ratio is the haematological index with the best predictive power for invasive mechanical ventilation need and death

- A ΔNLR > 2 and NLR > 11 at 48 hours after ICU admission is an independent predictor of the need for invasive mechanical ventilation and death (to my knowledge, at the time of publishing these results this was the first study to report the predictive power of NLR dynamics for the two events, Article 1 [26])

- The COVID-SOFA score has superior predictive power compared to the SOFA score for death from any cause at day 28 in critically ill patients with COVID-19

- COVID-SOFA score improved prediction error by up to 16%

- The predictive power of the COVID-SOFA score increases significantly in repeated measurements at 48 hours and maintains its superiority over the SOFA score

- Application of the COVID-SOFA score for all-cause mortality at day 60 has very good reproducibility and maintains its superior accuracy to the SOFA score

- A procalcitonin value >1.49 ng/mL has excellent discriminative power between bacterial sepsis secondary to bacterial pneumonia and viral sepsis secondary to COVID-19 (to my knowledge, at the time of publishing these results, this was the first study to report this cut-off value of procalcitonin for differentiating the two types of sepsis, Article 3 [25])

- A RDW value >14.8% has very good discriminative power between bacterial sepsis secondary to bacterial pneumonia and viral sepsis secondary to COVID-19 (to my knowledge, at the time of publishing these results, this was the first study to report this cut-off value of RDW% for differentiating the two types of sepsis, Article 3 [25])

List of scientific papers published as a result of the doctoral research

1. **Moisa E**, Corneci D, Negoita S, Filimon CR, Serbu A, Negutu MI, Grintescu IM. Dynamic Changes of the Neutrophil-to-Lymphocyte Ratio, Systemic Inflammation Index, and Derived Neutrophil-to-Lymphocyte Ratio Independently Predict Invasive Mechanical Ventilation Need and Death in Critically Ill COVID-19 Patients. Biomedicines. 2021; 9(11):1656.
    https://doi.org/10.3390/biomedicines9111656
    https://www.mdpi.com/2227-9059/9/11/1656
    Journal indexed in PubMed and Web of Science databases (Clarivate Analytics), ISI impact factor = 6.081
    Article I, Chapter 3 (pag. 43-80), Appendix 1 (pag. 165-183)

2. **Moisa E**, Corneci D, Negutu MI, Filimon CR, Serbu A, Popescu M, Negoita S, Grintescu IM. Development and Internal Validation of a New Prognostic Model Powered to Predict 28-Day All-Cause Mortality in ICU COVID-19 Patients—The COVID-SOFA Score. Journal of Clinical Medicine. 2022; 11(14):4160.
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    Journal indexed in PubMed and Web of Science databases (Clarivate Analytics), ISI impact factor = 4,964
    Article II, Chapter 4 (pag. 81-110), Appendix 2 (pag. 184-201)

3. **Moisa E**, Dutu M, Corneci D, Grintescu IM, Negoita S. Hematological Parameters and Procalcitonin as Discriminants between Bacterial Pneumonia-Induced Sepsis and Viral Sepsis Secondary to COVID-19: A Retrospective Single-Center Analysis. International Journal of Molecular Sciences. 2023; 24(6):5146.
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