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The Effect of Laboratory Parameters and Prognostic Scores on Cardiopulmonary Resuscitation in Coronavirus Disease-19 Patients in Intensive Care Unit

Laboratuvar Parametreleri ve Prognostik Skorların Yoğun Bakım Ünitesinde Coronavirüs Hastalığı-19 Hastalarına Yapılan Kardiyopulmoner Resüsitasyonda Etkisi

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ÖZET

Amaç: COVID-19 hastalarının yaklaşık üçte biri kritik hastalığa yakalanmaktadır. Modifiye Glasgow prognostik skoru(mGPS) ve modifiye sistemik inflamasyon skoru(mSIS), sistemik inflamasyonu gösterir. Bu çalışmanın amacı, COVID-19 olan ve kardiyopulmoner resüsitasyon(CPR) girişiminde bulunan hastalarda kan değerlerinin karşılaştırılmasıyla mGPS, mSIS ve CPR sonucu(spontan dolaşımın geri dönüşü ya da ölüm) arasındaki ilişkiyi değerlendirmektir.
Gereç ve Yöntem: COVID-19 nedeniyle yoğun bakımda yatışı gereken ve CPR uygulanan 65 hasta geriye dönük olarak tarandı. Hastalar CPR sonrası ölen hastaları kapsayan GroupEX (n=45) ve spontan dolaşımın geri dönüşü sağlanan hastaları kapsayan GroupROSC (ROSC) (n=20) olarak iki gruba ayrıldı. Hastaların mGPS ve mSIS değerleri hesaplandı.
Bulgular: GrupROSC' da nötrofil yüzdesi, INR ve bilirubin anlamlı düşük; monosit yüzdesi ve albumin anlamlı yüksek olarak saptandı (p< 0.001, p=0.01, p=0.04, p= 0.01, p=0.004 , p<0.001 sırasıyla). Ek olarak, iki grup arasında mGPS' de anlamlı bir fark vardı (p=0,032). ROC analizinde mSIS ve mGPS, GroupEX'te daha yüksek puanlar gösterdi. mSIS duyarlılığı ve özgüllüğü sırasıyla %83,7 ve %68,4 (p=0,34) ve mGPS duyarlılığı ve özgüllüğü sırasıyla %95,3 ve %68,4 (p=0,09) olarak saptandı.
Sonuç: Sonuçlarımıza göre mGPS ve mSIS, CPR sonuç tahminine katkıda bulunabilir.

Anahtar Kelimeler: COVID-19, mGPS, mSIS, serum biyokimyası, resüsitasyon

ABSTRACT

Aim: COVID-19 causes critical illness in nearly one-third of patients. Modified Glasgow prognostic score (mGPS), and modified systemic inflammation score (mSIS) indicate systemic inflammation. The aim of this study was to assess the association between mGPS, mSIS and cardiopulmonary resuscitation(CPR) result(return of spontaneous circulation or death), through the comparison of blood test results among patients with COVID-19 and attempted CPR.
Material and Methods: Sixty-five patients who required hospitalization in an ICU due to COVID-19, and attempted CPR were screened retrospectively. Patients were separated into two groups; GroupEX covering deceased patients(n=45), and GroupROSC covering patients who attained return of spontaneous circulation(ROSC) (n=20). mGPS and mSIS of patients are calculated.
Results: In GroupROSC, neutrophil percentage, INR, and bilirubin values were found to be significantly low; monocyte percentage and albumin values were found to be significantly higher (p< 0.001, p=0.01, p=0.04, p= 0.01, p=0.004 , p<0.001 respectively). Additionally, there was a significant difference in mGPS between the groups(p=0.032). In the ROC analysis, mSIS and mGPS showed higher scores in GroupEX. mSIS sensitivity and specificity were detected at 83.7% and 68.4%, respectively (p=0.34), and mGPS sensitivity and specificity were detected at 95.3% and 68.4%, respectively (p=0.09).
Conclusion: To our results, mGPS and mSIS can contribute to CPR result prediction.

Key words: COVID-19, mGPS, mSIS, serum biochemistry, resuscitation

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INTRODUCTION

The disease (COVID-19) caused by SARS Cov-2 was declared as pandemic by World Health Organization on February 11, 2020. (1) There is still limited information on the clinical and post characteristics of the disease, particularly in critically ill patients diagnosed with COVID-19. The disease causes critical illness in nearly 1/3 of the patients. These patients need intensive care unit (ICU) admission which has been reported as 5 - 32% in patients hospitalized for COVID-19. (2, 3)

The impact of COVID-19 on cardiac arrest (CA) cases is reported at least 10% of all out of hospital CA(OHCA) and 16% of in hospital CA (IHCA). Also it is reported that, 30-day mortality in COVID-19 cases was increased 3.4 fold in OHCA and 2.3 fold in IHCA. (4) Hypoxemia caused by acute respiratory distress syndrome, viral myocarditis-related cardiogenic shock, sepsis-related vasoplegic shock, thrombotic complications and arrhythmias caused by drug interactions should be considered among cardiac arrest mechanisms of COVID-19 patients (5-7). Once the hemodynamic condition collapses and cardiac arrest occurs, the requirement of cardiopulmonary resuscitation (CPR) arises.

Modified Glasgow Prognostic Score (mGPS) calculated by serum albumin and C-reactive protein (CRP) levels indicating systemic inflammation has related to many cancer types and heart failure so far (8,9). As COVID-19 was related to an infectious process activating systemic inflammation process, it was considered in our study that mGPS could be indicating on the result of CPR in critically ill COVID-19 patients.

Modified systemic inflammation score (mSIS) is an index which is calculated by serum albumin and lymphocyte-to-monocyte ratio (LMR) and is presented to have a prognostic value in different clinical conditions ranging between tumors and inflammatory processes (10,11).

In the literature, we did not encountered studies conducted on mGPS and mSIS to predict the outcomes of the CPR in patients with COVID-19 to fasten the desicion making. The aim of this study was to assess the effects of mGPS and mSIS on CPR outcome, through the comparison of biochemical, hematological and inflammatory markers among patients who were hospitalized and followed-up with COVID-19 and resulted with ROSC and/ or death.

METHODS

Institutional ethics board approval was obtained for all aspects of this study in accordance with institutional policies (approval number: 2021/3067). The study protocol is in accordance with the World Medical Association Declaration of Helsinki.

900 patients who were admitted to the hospital with typical complaints and were hospitalized due to COVID-19 between 11.03.2020 and 08.03.2021 scanned; data of the patients who were admitted to ICU and required CPR were included in the study(n=65). A minimum of 45 minutes of CPR was attempted in accordance with ERC and/or AHA guidelines.

Exclusion criteria: Patients who were pregnant; age under 18; COVID- 19 negative and not CA emerged (so were not performed CPR) were excluded.

Patients who were performed CPR were separated into two groups as GroupEX covering died patients (n=45) and GroupROSC covering ROSC emerged patients (n=20).

Methods: Demographic data, complete blood count, biochemical and coagulation parameters' levels on the ICU admission day of the patients were retrospectively collected. Demographical data were recorded as age and gender. Among complete blood count parameters; white blood cell (WBC), neutrophil, neutrophil%, lymphocyte, lymphocyte%, monocyte, monocyte%, eosinophil, eosinophil%, basophil, basophil%, red blood cell, hemoglobin, platelet, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and LMR values were recorded. Among biochemical parameters; eGFR, urea, creatinine, uric acid, sodium, potassium, calcium, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), albumin, CRP, CRP/ albumin ratio, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gama glutamyl transferase (GGT), total bilirubin and direct bilirubin values were recorded. Among coagulation parameters; fibrinogen, D- Dimer and INR values were recorded. Among prognostic scores; mGPS, was calculated as 2, in patients with CRP > 19 mg/L and hypoalbuminemia (<35 g/L); as 1 in patients with increased CRP or hypoalbuminemia; and 0 in patients with no CRP increase or hypoalbuminemia (12). And mSIS, was calculated using serum albumin and LMR. Values of albumin ≥ 40 g/L and LMR ≥ 3.4 were evaluated as mSIS 0, values of albumin < 40 g/L and LMR ≥ 3.4 were evaluated as mSIS 1 and values of albumin < 40 g/L and LMR < 3.4 were evaluated as mSIS 2 (13).

Statistical analysis

Statistical analysis was performed with SPSS, v.23.0 statistical software (SPSS, Inc., Chicago, IL, USA). The categorical variables were described as frequencies and percentages. Continuous variables were presented as mean and standard deviations. Chi-square ($\chi 2$) tests were used to evaluate the relationship between categorical variables of study subgroups. Independent T test and Mann Whitney U test for the comparison of two groups were the tests used in continuous variables. The area under the curve was calculated by receiver operating characteristic (ROC) regression analyses. We calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) (95% confidence intervals (CIs)) of mGPS and mSIS to assess

tests performance and p values below 0.05 were considered statistically significant.

RESULTS

Mean age in groupEX and groupROSC was found as 70.6(±13.1) and 73.4(±13.0), respectively and there was no significant difference between the groups(p=0.41, p= 0.43, respectively). Among hematological parameters; neutrophil percentage was found 86.17(±9.82) in groupEX and 71.13(±23.27) in groupROSC, monocyte percentage was found 4.08 (±3.90) in groupEX and 9.08(±9.42) in groupROSC and these differences were significant (p< 0.001, p=0.004, respectively). There was no significant difference in hematological parameters (p>0.05). INR among coagulation

Table 1. Details on demographic. hematological. biochemical and coagulation parameters

	GroupEX(n=45)	GroupROSC(n=20)	P
Demographics			
Age (mean±SD)	70.6(±13.1)	73.4(±13.0)	0.43
Gender (%)			
Male	62.2%(28)	50.0%(50)	0.41
Hematological Parameters (mean±SD)			
WBC	12.80(±7.51)	16.66(±24.7)	0.34
NEU#	11.26(±6.65)	8.7(±5.71)	0.129
NEU%	86.17(±9.82)	71.13(±23.27)	< 0.001
LYM#	1.01(±1.17)	1.62(±1.73)	0.10
LYM%	8.63(±7.24)	15.8 (±15.1)	0.12
MO#	0.60(±0.59)	0.98(±0.98)	0.06
MO%	4.08(±3.90)	9.08(±9.42)	0.004
EO#	0.05(±0.08)	0.06(±0.08)	0.81
EO%	0.67(±1.16)	0.49(±0.62)	0.51
BA#	0.01(±0.01)	0.01(±0.02)	0.18
BA%	0.13(±0.22)	0.14(±0.12)	0.89
RBC	3.37(±0.81)	3.64(1.01)	0.27
HGB	9.60(±2.08)	10.64(±2.92)	0.10
PLT	148.77(±120.26)	203.75(149.10)	0.12
NLR	53.75(±227.16)	8.52(±6.17)	0.39
PLR	388.20(±886.34)	221.78(±185.08)	0.42
Coagulation Parameters (mean±SD)			
Fibrinogen	481.18(±293.24)	409.6(±203.8)	0.38
D- Dimer	3609.18(±7453.01)	3493.73(±2540.88)	0.95
INR	2.00(±1.02)	1.41(±0.43)	0.01
Biochemical Parameters (mean±SD)			
eGFR	58.52(±43.52)	51.12(±56.22)	0.56
BUN	130.16(±84.67)	113.87(±74.94)	0.46
Creatinin	10.74(±60.42)	2.48(±1.69)	0.54
Uric Acid	9.32(±20.97)	6.24(±2.17)	0.55
Na	135.43(±21.20)	136.9(±6.65)	0.76
K	7.48(±19.32)	4.67(±0.95)	0.52
Ca	8.13(±1.31)	8.09(±0.96)	0.88
LDH	639.95(±603.10)	802.8(±899.7)	0.4
CPK	325.58(±487.5)	136.80(±94.7)	0.4
Albumin	25.8(±5.8)	31.7(±5.6)	<0.001
CRP	162.15(±150.10)	138.41(±11.-6)	0.53
CRP/Albumin	5.96(±3.80)	4.83(±4.47)	0.30
AST	334.47(±982.72)	341.33(±860.77)	0.97
ALT	100.18(±234.8)	66.64(±161.14)	0.56
ALP	188.04(±179.69)	122.2(±75.5)	0.04
GGT	142.15(±276.93)	97.75(±106.36)	0.50
Total Bilirubin	2.14(±2.35)	1.24(±1.07)	0.04
Direct Bilirubin	1.62(±2.05)	0.75(±0.74)	0.01

Abbreviations: WBC: white blood cell. NEU: neutrophil. LYM: lymphocyte. MO: monocyte. EO: eosinophil. BA: basophil. RBC: red blood cell. HGB: haemoglobin. PLT: platelet. NLR: neutrophil lymphocyte ratio. PLT: platelet lymphocyte ratio. INR: international normalized ratio. eGFR: estimated glomerular filtration rate. BUN: blood urea nitrogen. Na: sodium. K: potassium. Ca: calcium. LDH: lactate dehydrogenase. CPK: creatine phosphokinase. CRP: C- reactive protein. AST: aspartate amino transferase. ALT: alanine amino transferase. ALP: alkaline phosphatase. GGT: gamma glutamyl transferase

parameters was found as 2.00(±1.02) in groupEX and 1.41(±0.43) in groupROSC and this difference was statistically significant (p=0.01). There were significant difference in albumin, total and direct bilirubin levels among biochemical parameters between groupEX and groupROSC. The results in groupEX and groupROSC were 25.8(±5.8) and 31.7(±5.6) for albumin, 2.14(±2.35) and 1.24(±1.07) for total bilirubin and 1.62(±2.05) and 0.75(±0.74) for direct bilirubin, respectively (p<0.001; p=0.04; p= 0.01, respectively). There was no difference of the remained parameters regarding coagulation and biochemical. Details on demographic, hematological, biochemical and coagulation parameters are shown in Table 1.

For mGPS; in GroupEX 6.7%(n=3) of the patients had a score of 1 and 93.3%(n=42) had a score of 2. In GroupROSC; 30%(n=6) of the patients had a mGPS score of 1 and 70% (n=14) had a mPGS score of 2. It was detected that GroupEX had higher mGPS scores and mGPS values presented a significant difference among the two groups(p=0.032). As for mSIS; in groupEX 17.8%(n=8) of the patients had a mSIS score of 1 and 82.2%(n=37) of the patients had a mSIS score of 2. In groupROSC; 30% (n=6) of the patients had a score of 1 and 70% (n=14) of the patients had a score of 2. Although GroupEX has higher mSIS results, this difference was not significant among the groups (p= 0.26) (Table 2).

The correlation analysis showed that albumin levels presented a negative correlation with LMR, CRP, ALP, INR, total bilirubin and potassium levels and a positive correlation with calcium, RBC and HGB. CRP/ albumin rate and creatinine level showed a positive correlation. It was found that LMR value had a negative correlation with albumin and a positive correlation with WBC, neutrophil, PLR, monocyte count, fibrinogen, INR, total bilirubin and direct bilirubin (all parameters p<0.05). In the ROC analysis performed to determine the prognostic value of mSIS and mGPS showed higher score on death result (Figure 1); while mSIS sensitivity was 83.7% and specificity was 68.4% (p=0.34), mGPS sensitivity was 95.3% and specificity was 68.4% (p=0.09). Details for prognostic values of mSIS and mGPS scores are shown in Table 3.

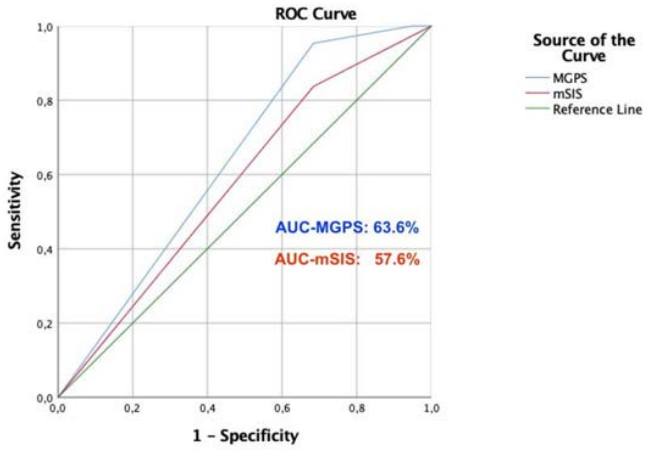

Figure 1. ROC analysis of mGPS(red line) and mSIS(blue line)

DISCUSSION

COVID-19 is a serious disease with high ICU admission rates. Based on a meta-analysis, 1/3 of the patients are

Table 2. Details on mGPS and mSIS

mGPS n(%)	Group EX	Group ROSC	p
0	0	0	
1	3(6,7)	6 (30,0)	0.032
2	42 (93,3)	14(70,0)	
mSIS n(%)			
0	0	0	
1	8 (17,8)	6 (30)	0.26
2	37 (82,2)	14 (70)	

Abbreviations: mGPS: modified Glasgow prognostic score; mSIS: modified systemic inflammation score

Table 3. Details of prognostic values of mSIS and mGPS scores

	Sensitivity(%)	Specificity(%)	Positive Predictivity(%)	Negative Predictivity(%)	AUC %	p
mGPS	95.3	68.4	75	66.6	63.6	0.09
mSIS	83.7	68.4	72.5	42.8	57.6	0.34

Abbreviations: mSIS: modified systemic inflammation score; mGPS: modifies Glasgow prognostic score

hospitalized in intensive care unit and more than 1/3 of the patients hospitalized in intensive care unit are died (14). In the study of Graselli et al. ICU mortality rates were reported as 26% (15). These high rates reported, drived us to focus our study on mGPS and mSIS - prognostic scores using hematological parameters- which can possibly contribute to predict and determine CPR outcomes and duration in cardiac arrest emerged COVID-19 patients.

Many studies are focused on neutrophil and lymphocyte count related to COVID- 19 in the literature and especially increased neutrophil and decreased lymphocyte counts and NLR were found to be related to severe disease (16). In our study, the overall population had a serious disease, thus it was considered that a significant difference did not form among neutrophil count, lymphocyte count and NLR. In a study evaluating monocyte percentage in COVID-19 patients, it was found lower in severe disease group (17). Similar to this study, it was also found to be significantly low in the death group following CPR (groupEX) in our study. A similar significant difference is also available in neutrophil percentage. Thus we think that neutrophil and monocyte percentage among the parameters which may be unnoticable in hemogram, may be considered in ROSC attainability.

In some studies evaluating hematological parameters of COVID-19 patients, LMR levels were found to be significantly lower in critical disease compared to other non-critical disease groups (17,18). A difference was not detected among the relatively more critical (GroupEX) and less critical (GroupROSC) patient groups in our study (p=0.41). The reason of this result may be the fact that all patients in our study population had a severe disease with critical conditions.

COVID-19 brings along bleeding risk together with prothrombotic effects. In COVID-19 patients, INR level was shown to be higher in case of severe disease (19,20). A difference in INR levels among death and survival groups was reported previously(19). In line with literature, INR level was found high in groupEX in our study (2 vs 1.41, p=0.01). Based on our results, high INR levels had a negative relationship with ROSC attainment after CPR.

Albumin and CRP were both related to normal aging but high levels of these parameters were also related to increased morbidity and mortality risk (21,22). CRP/albumin ratio is a parameter with shown predictive value as an early reachable predictor in COVID-19 in addition to many inflammatory and infectious diseases (23). (Hypoalbuminemia and increased CRP were found to be related to severe disease and death in COVID-19, alone (3, 24). CRP/ albumin ratio was shown to be more valid compared to only CRP level in the prediction of 28 day mortality in critical disease compared to non- critical (25). In the present study, CRP/ albumin ratio did not show a difference among the two groups as both of the groups are consisted of critical patients, so it is considered not to be an indicative in terms of CPR result.

The presence of negative correlation between albumin and LMR, CRP, ALP, INR, total bilirubin and potassium in the correlation analysis performed, was associated to albumin's role as one of the main negative acute phase proteins. Liver functions were shown to be indirectly affected through cholangiocytes in COVID-19 (26). Additionally, it is also known that liver dysfunction may develop through hypoxic damage. Paliogiannis and Zinellu stated that bilirubin levels were found higher in COVID-19 (27). Total and direct bilirubin levels were found to be significantly high in groupEX in our study, also (p=0.04; p= 0.01, respectively). When it is considered that our patients are hypoxemic and in a critical condition, needing intensive care and taking multiple drug treatments, high total and direct bilirubin levels can be related to many factors. Still, the presence of this difference in the patients who were performed CPR while being treated under the same conditions in ICU, makes us consider that total and direct bilirubin may be guiding in the prediction of CPR result.

High mortality rates of the disease particularly in patients requiring ICU care, make the identification of prognostic scores which can predict mortality, more considerable. A simple score, mGPS, has been identified as a useful indicator of prognosis in cancer related systemic inflammation and postoperative infectious complications (12). COVID-19 is an infection disease but it has common characteristics with cancer such as systemic inflammatory response, loss of appetite, cachexia and prothrombotic effects. Thus, with its prognostic value shown in many cancer types and systemic inflammation, it was considered that mGPS has the potential of having a significant value on predicting ROSC attainment in COVID-19 patients who had CPR. In COVID-19, which causes an intense systemic inflammatory response formation similar to cancer, the effect of mGPS on CPR results has not been studied before. This study will be the first report on this subject.

Nagasako et al. stated that mGPS had a prognostic value on predicting death in advanced cancer patients in palliative care units (28). Bolat and Biteker reported that mGPS could be used to predict prognosis in heart failure patients with preserved ejection fraction in their study and they excluded patients related with cancer and inflammatory phases (9). Studies in different fields of medicine showed that mGPS is a practical and simple scoring system which is important for prognosis (9,10). In our study, a significant difference was detected in mGPS among the groups and more patients with high mGPS scores were existed at death group (p=0.032). This result has lead us consider that mGPS can be promising in prognosis of COVID-19 patients who had CPR.

COVID-19 is an infectious disease inducing inflammatory processes. Different studies defined mSIS as an important prognostic factor of inflammation (13). According to our results, there was not a significant difference in terms of mSIS between the groups. Advanced level of inflammation due to the presence of severe COVID-19 in the patients in both groups may be the reason for this. In addition, relatively high rates of the sensitivity and specificity of mGPS and mSIS in the ROC analysis are promising for the prediction of CPR outcome performed on COVID-19 patients getting treated in ICUs. The Canadian COVID-19 Emergency Department Rapid Response Network (CCEDRRN) Mortality Score is a valuable mortality predicting system but is mostly designed for level of care discussions with patients for the first referral of the patient for emergency department arrival in case of resource constraints which involves physical examination findings (29). Differently, our study was conducted on mGPS results of ICU patients whose primary treatments had already given and CPR requirement had arised; and has aimed to point out an easily applicapable score with minimal close contact.

Study Limitations

The potential limitations in our study are the single-centered design of the study, limited demographic and monitor data, small sample size and focusing on probability of ROSC achievement which is not assessing long term outcomes.

In conclusion, to sum up, a significant relationship was detected between mGPS and CPR outcome. Additionally, sensitivity and specificity of mGPS and mSIS in CPR of COVID- 19 related death prediction were found high. Based on our results, consideration of especially neutrophil and monocyte percentage, INR, total and direct bilirubin levels in addition to the prognostic scores mentioned above can contribute to CPR outcome prediction. Further, prospective designed studies with larger patient series are required to support our findings.

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Etik Kurul: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Institutional review board (IRB) approval was obtained for all aspects of this study in accordance with institutional policies (approval number: 2021/3067).

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