Archives of Current Medical Research
Arch Curr Med Res 2021;2(2):80-87

Received: 7 December 2020
Revised: 31 December 2020
Acccepted: 10 April 2021
DOI: 10.47482/acmr.2021.19

ORIGINAL ARTICLE

# Carboxyhemoglobin, Methemoglobin and Lactate Levels in Patients with Systemic Inflammatory Response Syndrome

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## Abstract

**Background:** Systemic inflammatory response syndrome (SIRS) is a common, severe inflammatory condition. This condition forms the basis of the definitions of sepsis, severe sepsis, septic shock, and multiple organ failure syndromes. The diagnosis can be made earlier with arterial blood gas analysis, which can provide a lot of information within minutes. This study aimed to determine the value of carboxyhemoglobin (COHb), methemoglobin (metHb), and lactate levels in the prognosis and mortality of patients with SIRS.

**Methods:** Patients who met the SIRS criteria with the first vital signs and laboratory values and who had arterial blood gas analysis according to the clinician's decision were included in the study. The demographic characteristics, prognosis and correlation of 1-month mortality rates of patients with baseline COHb, metHb and lactate levels were investigated.

**Results:** Among non-smoker patients, no significant difference was found between fCOHb values and age, gender, presence of infection, blood pressure, department of hospitalization, and 1-month mortality rates ($p>0.05$). Also, the relationship between fCOHb values and length of stay in the hospital was not statistically significant ($r = -0.013$, $p = 0.883$). Among the patients included in the study; there was no significant difference in metHb values between age groups ($p = 0.9941$), gender ($p = 0.6422$), presence of infection ($p = 0.1311$), blood pressure ($p = 0.7711$), length of stay in hospital ($p = 0.737$), inpatient clinics ($p = 0.6722$) and 1-month mortality ($p = 0.8752$). Lactate values were found to be correlated with the 1-month mortality of the patients ($p = 0.005$). Lactate levels were significantly higher in patients who died within 1-month compared to those who survived.

**Conclusions:** In patients with SIRS, initial COHb and metHb values cannot be considered a predictor for prognosis and mortality. However, lactate values may be useful to predict SIRS mortality even during hospital admission.

**Key words:** SIRS, Carboxyhemoglobin, Methemoglobin, Lactate.

***Cite this article as:*** *Gürü S, Kadı G, Öktem B, Karamercan MA. Carboxyhemoglobin, methemoglobin and lactate levels in patients with systemic inflammatory response syndrome. Arch Curr Med Res. 2021;2(2):80-87*

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## INTRODUCTION

Systemic inflammatory response syndrome (SIRS) is a common disease encountered in the emergency department (ED) (1, 2). Moreover, arterial blood gas analysis, which is frequently used in ED, can provide valuable data for diagnosis and follow-up (3).

Carboxyhemoglobin (COHb) is formed by binding endogenous or exogenous carbon monoxide (CO) to hemoglobin. Proinflammatory cytokines, bacterial toxins, heme protein, hyperoxia, hypoxia and reactive oxygen radicals increase the levels of hemoxygenase and increase endogenous CO production (4). The asymptomatic increase of methemoglobin (metHb) levels as a result of oxidative stress and inadequate mechanisms for elimination of this stress is being investigated as a marker of early diagnosis and long-term prognosis of many inflammatory conditions. It is known that lipopolysaccharides increase the release of nitric oxide (NO) in sepsis conditions, and this increase in the amount of NO results in hypotension. NO, as an oxidative stress factor, enhances the conversion of hemoglobin to metHb (5-7).

Lactate forms as a result of tissue hypoxia (7-9). Under anaerobic conditions, pyruvate is converted into lactate. In critically ill patients, the amount of lactate increases as a result of oxidative stress (9).

The aim of this study was to investigate the clinical value of COHb, metHb and lactate in order to predict prognosis and mortality, obtained by the first arterial blood gas analysis in patients diagnosed with SIRS in ED.

## MATERIALS AND METHOD

At the Gazi University Clinical Research Ethics Committee on 13.04.2015, ethical approval was obtained with the decision number 160.

This study was designed as a prospective clinical study, with patients admitted to ED of a university hospital between April 2015 and June 2015. Patients older than 18 years, who were diagnosed as SIRS with vital signs and laboratory data taken at the time of admission to the ED, whose arterial blood gas samples were taken immediately after admission, were included in the study.

Among patients admitted to ED of Gazi University Faculty of Medicine:

- Patients under the age of 18
- Patients whose informed consent could be obtained from themselves or their legal relatives
- Patients whose blood samples had technical laboratory errors
- Patients who had congenital methemoglobinemia and those exposed to agents causing toxic methemoglobinemia
- Patients with epileptic seizures or previously diagnosed with epilepsy
- Patients who were using biguanides as oral antidiabetic were excluded.

Moreover, patients who were smokers and patients with carbon monoxide intoxication were excluded from the statistics about COHb.

### Data Collection

Data collection started on the date of 01.04.2015 and ended on 30.06.2015. Demographic characteristics of patients, vital signs, laboratory values, diagnoses, source of infection (if present), result of ED visiting, referred clinic (if the patient was admitted), length of stay in hospital and 1-month mortality rates were recorded. Before data collection, written consent was obtained from patients or legal guardians.

### Blood Gas Analysis

Arterial blood gas samples taken from the patients were analyzed with the blood gas analyser (ABL800 BASIC®) within ED.

### Statistical Analysis

Research data were uploaded to the computer using "SPSS (Statistical Package for Social Sciences) for Windows 22.0 (SPSS Inc., Chicago, IL)". The conformity of variables to normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov / Shapiro-Wilk Test). As a statistical method, Mann-Whitney U Test was used for determining the statistical significance of the two independent groups for the variables not normally distributed; Kruskal Wallis Test was used for three independent groups. Bonferroni correction was performed to determine the source of the difference when there was a significant difference between the three independent groups. The relationship between the variables was evaluated by the Spearman's Test. The level of statistical significance was accepted as $p<0.05$.

## RESULTS

One hundred forty-nine patients were evaluated. Three of these patients declined to participate in the study. There were deficits in 4 patients' data. One patient was excluded from the study because he was brought to the ED as cardiopulmonary arrest and the vital signs were unstable.

After the exclusion of eight patients, 141 patients were included in the study. Of the 141 patients, ten patients were active smokers, so they were excluded from COHb evaluations. Analyses on COHb values were performed with the remaining 131 patients. Data of vital signs and laboratory results were recorded for diagnosis of SIRS (Table 1).

**Table 1. Vital signs and laboratory values of patients**

| (n: 141) | Number | % | (n: 141) | Number | % |
|---|---|---|---|---|---|
| **Heart Rate** | | | **Leukocyte** | | |
| Normal | 33 | 23.4 | Leukocytosis (>12000/μL) | 87 | 61.7 |
| Tachycardic (>90) | 105 | 74.5 | Leukopenia (<4000/μL) | 43 | 30.5 |
| Bradycardic (≤60) | 3 | 2.1 | Immature band forms (> 10%) | 0 | 0 |
| | | | Normal | 11 | 7.8 |
| **Temperature** | | | **Blood Pressure** | | |
| Hyperthermic (>38°C) | 30 | 21.3 | Normotensive | 66 | 46.9 |
| Normal (36-38°C) | 111 | 78.7 | Hypotensive (systolic <90 mmHg or systolic blood pressure drops at least 40 mmHg) | 48 | 34.0 |
| Hypothermic (<36°C) | 0 | 0 | Hypertensive (systolic >140 mmHg) | 27 | 19.1 |
| **Tachypnea or Hypocarbia** | | | **pH** | | |
| Normal | 34 | 24.1 | Acidosis (<7.35) | 30 | 21.3 |
| Tachypnea or hypocarbia | 107 | 75.9 | Alkalosis (>7.45) | 41 | 29.1 |
| Tachypnea (>20/min) | 59 | 41.8 | Normal (7.35-7.45) | 70 | 49.6 |
| Hypocarbia (PaCO2<32 mmHg) | 73 | 51.7 | | | |
| Saturation | | | | | |
| Hypoxemic (<95%) | 84 | 59.6 | | | |
| Normal (>95%) | 57 | 40.4 | | | |

The median of COHb fraction (fCOHb) value at the time of admission was 1.1% (min: 0-max: 4.8); the median value of fraction of metHb (fmetHb) was 0.7% (range: 0.1 - 4.0) and the median value of lactate was 1.6 mmol / L (range: 0.3 - 20.0) (Table 2).

**Table 2. Initial arterial blood gas analysis; fCOHb, fmetHb, lactate**

| | Mean±SD | Median (min-max) |
|---|---|---|
| fCOHb (%) | 1.28±0.73 | 1.1 (0-4.8) |
| fmetHb (%) | 0.89±0.66 | 0.7 (0.1-4.0) |
| Lactate (mmol/L) | 2.11±2.15 | 1.6 (0.3-20.0) |
| SD: Standard deviation | | |

Among 141 patients, 64.5% (n:91) have had at least one focal infection, while in 35.5% (n:50) a focal infection could not be found. Among the 91 patients with focal infections; 56% (n:51) had lower respiratory tract infections, 29.6% (n:27) had urinary tract infections, 6.5% (n:6) had gastroenteritis, 4.3% (n:4) had cellulitis, 4.3% (n:4) had intracranial infection, 3.2% (n:3) had infective endocarditis, 1% (n:1) had cryptic tonsillitis.

The mean value of the length of stay in hospital was 9.28 ± 10.69 days and the median value of the length of stay in hospital was 7 days (range: 0.5 - 70). When the 1-month mortality rate of these patients was evaluated, it was determined that 14.9% (n:21) died within one month following their admission to the ED.

A statistically significant relationship was found between fCOHb values and the result of ED visit (p: 0.004). Post-hoc binary comparisons revealed significant differences between "referral to another hospital and left ED", "discharge and left ED" and "death in ED and left ED." Patients who left ED had a higher fCOHb value in comparison to referred patients, discharged patients and patients who died in ED. On the other hand, statistical analyses did not exhibit a significant relationship between fCOHb values and age, gender, the status of infection, blood pressure, place of admission, department of hospitalization, and 1-month mortality rates (p>0.05) (Table 3).

**Table 3. Distribution of COHb values between selected demographic features, vital signs, result of ED visit, place of admission and 1-month mortality**

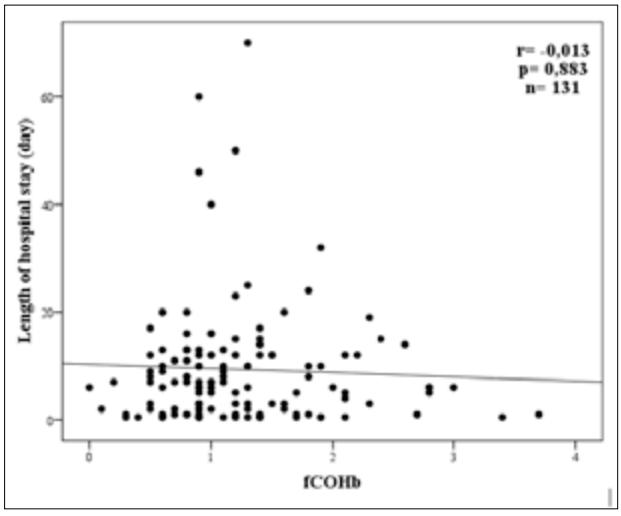
| (n: 131) | fCOHb | | p |
|---|---|---|---|
| | n | Median (min-max) | |
| **Age** | | | |
| <65 | 58 | 1.2 (0.3-3.7) | 0.572[a] |
| 66-80 | 46 | 1.0 (0-3.4) | |
| >80 | 27 | 0.9 (0.2-3.0) | |
| **Gender** | | | |
| Male | 74 | 1.1 (0-3.7) | 0.487[b] |
| Female | 57 | 1.0 (0.1-3.0) | |
| **Status of Infection** | | | |
| Source of infection cannot be found | 47 | 1.0 (0.5-3.7) | 0.802[a] |
| Sepsis | 56 | 1.2 (0-2.8) | |
| Severe Sepsis | 28 | 1.0 (0.3-3.4) | |
| **Blood Pressure** | | | |
| Normotensive | 62 | 1.0 (0.1-3.7) | 0.912[a] |
| Hypotensive (systolic <90 mmHg or systolic blood pressure drops at least 40 mmHg) | 44 | 1.1 (0.3-3.4) | |
| Hypertensive (systolic >140 mmHg) | 25 | 1.0 (0-2.8) | |
| **Result of ED Visit** | | | |
| Discharge | 35 | 0.9 (0.3-3.4) | 0.004[a#] |
| Admitted to hospital | 76 | 1.1 (0-3.0) | |
| Referral to another hospital | 6 | 0.6 (0.5-2.1) | |
| Left ED | 8 | 1.8 (0.9-3.7) | |
| Death in ED | 6 | 0.8 (0.1-1.6) | |
| **Place of Admission (n: 76)** | | | |
| Ward | 42 | 1.0 (0-2.8) | 0.245[b] |
| Intensive care unit | 34 | 1.2 (0.5-3.0) | |
| **Department of Hospitalization (n: 76)** | | | |
| Internal clinics | 71 | 1.1 (0-3.0) | 0.871[b] |
| Surgical clinics | 5 | 1.2 (0.8-2.6) | |
| **1-month Mortality** | | | |
| Exitus | 20 | 1.2 (0.1-2.3) | 0.918[b] |
| Alive | 111 | 1.0 (0-3.7) | |

aKruskal Wallis Test; bMann-Whitney U Test

#Post-hoc binary comparisons showed that the significant difference was between "referral to another hospital and left ED", "discharge to home and left ED" and "death in ED and left ED".

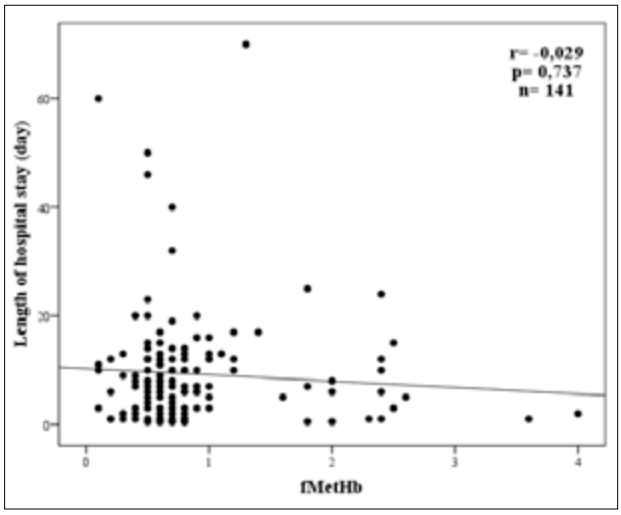
Among 131 non-smoker patients, the relationship between fCOHb values and length of stay in hospital were not found to be statistically significant (r: -0.013, p: 0.883) (Figure 1).

**Figure 1. Relationship between fCOHb values and length of hospital stay**




Among 141 patients included in the study; there was no significant relationship between metHb values and age (p:0.9941), gender (p:0.6422), status of infection (p:0.1311), blood pressure (p:0.7711), length of stay in hospital (p:0.737), place of admission (p:0.6722) and 1-month mortality (p:0.8752) (Table 4, Figure 2).

**Figure 2. Relationship between MetHb values and length of hospital stay**



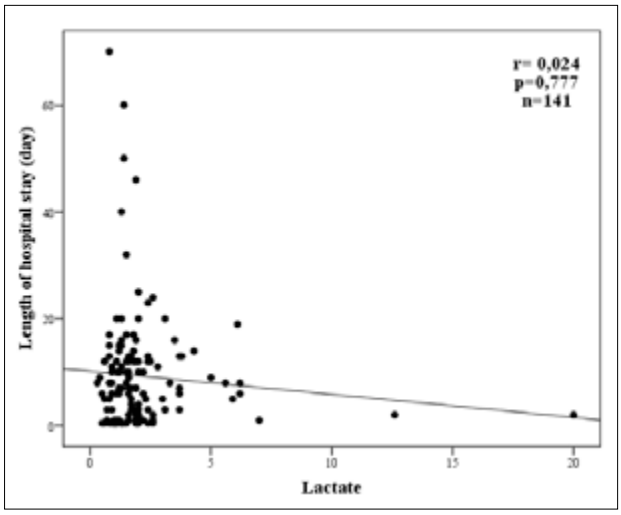

There was a significant relationship between lactate values and 1-month mortality rates of the patients (p:0.005).

Lactate levels were significantly higher in patients who died within 1-month compared to those who survived. However, there were no significant differences between lactate levels and age, genders, the status of infection, blood pressure, the result of ED visit, length of stay in the hospital, and place of admission (p> 0.05) (Table 4, Figure 3).

**Table 4. Distribution of MetHb and lactate values between selected demographic features, vital signs, results of ED visiting, place of admission and 1-month mortality**

| (n: 141) | n | MetHb | p | Lactate | p |
|---|---|---|---|---|---|
| | | Median (min-max) | | Median (min-max) | |
| **Age** | | | | | |
| <65 | 62 | 0.7 (0.1-3.6) | 0.994[a] | 1.6 (0.3-7.0) | 0.799[a] |
| 66-80 | 51 | 0.7 (0.1-4.0) | | 1.6 (0.5-20.0) | |
| >80 | 28 | 0.7 (0.1-2.4) | | 1.6 (0.8-6.1) | |
| **Gender** | | | | | |
| Male | 82 | 0.7 (0.1-4.0) | 0.642[b] | 1.7 (0.3-20.0) | 0.629[b] |
| Female | 59 | 0.7 (0.1-2.5) | | 1.6 (0.5-12.6) | |
| **Status of Infection** | | | | | |
| Source of infection cannot be found | 50 | 0.8 (0.2-3.6) | 0.131[a] | 1.6 (0.6-7.0) | 0.373[a] |
| Sepsis | 62 | 0.7 (0.1-4.0) | | 1.6 (0.3-20.0) | |
| Severe Sepsis | 29 | 0.7 (0.2-2.4) | | 1.9 (0.5-6.1) | |
| **Blood Pressure** | | | | | |
| Normotensive | 66 | 0.7 (0.1-4.0) | 0.771[a] | 1.8 (0.4-20.0) | 0.380[a] |
| Hypotensive (systolic <90 mmHg or systolic blood pressure drops at least 40 mmHg) | 48 | 0.7 (0.2-2.5) | | 1.8 (0.5-6.1) | |
| Hypertensive (systolic >140 mmHg) | 27 | 0.8 (0.4-2.5) | | 1.6 (0.6-3.7) | |
| **Result of ED Visit** | | | | | |
| Discharge | 36 | 0.7 (0.2-2.3) | 0.659[a] | 1.6 (0.5-3.7) | 0.119[a] |
| Admitted to hospital | 84 | 0.7 (0.1-4.0) | | 1.6 (0.3-20.0) | |
| Referral to another hospital | 6 | 0.5 (0.4-1.6) | | 1.6 (1.1-5.0) | |
| Left ED | 9 | 0.8 (0.1-3.6) | | 1.9 (1.1-7.0) | |
| Death in ED | 6 | 0.7 (0.3-2.5) | | 2.8 (1.7-12.6) | |
| **Place of Admission (n=84)** | | | | | |
| Ward | 48 | 0.7 (0.1-4.0) | 0.672[b] | 1.4 (0.3-20.0) | 0.105[b] |
| Intensive care unit | 36 | 0.7 (0.1-2.6) | | 1.7 (0.8-6.2) | |
| **Department of Hospitalization (n=84)** | | | | | |
| Internal clinics | 78 | 0.7 (0.1-4.0) | 0.298[b] | 1.6 (0.3-20.0) | 0.419[b] |
| Surgical clinics | 6 | 0.9 (0.5-1.8) | | 1.9 (1.1-3.5) | |
| **1-month Mortality** | | | | | |
| Exitus | 21 | 0.7 (0.3-4.0) | 0.875[b] | 2.0 (0.9-20.0) | 0.005[b] |
| Alive | 120 | 0.7 (0.1-3.6) | | 1.6 (0.3-7.0) | |
| aKruskal Wallis Test; bMann-Whitney U Test | | | | | |

**Figure 3. Relationship between lactate values and length of hospital stay**




## DISCUSSION

COHb and metHb in this study were not sufficiently correlated to determine prognosis in patients with SIRS. On the other hand, lactate levels in SIRS patients were valuable and significant to predict prognosis.

In a study by De Siqueira et al., which was performed on 200 healthy individuals to determine COHb reference values, COHb average was found as 1.00 ± 0.75% (10). Mean COHb values in 131 non-smoker patients were found similarly in our study. However, it should be taken into account that normal values in the literature are values from healthy control groups. In this study, we only included patients with SIRS who were not active smokers. Our results about mean and median COHb percentages were close to reference values in the literature, but these data for SIRS patients in our study should not be referred to when discussing reference values in healthy individuals.

We evaluated the COHb values of 131 patients to investigate whether COHb could provide a prediction for the clinical course and mortality of patients. Among 131 patients, those who left ED with their own decision were found to have significantly higher COHb values than those discharged from ED, referred to another hospital, and died in ED. This difference could be explained by the fact that patients who left ED had worse clinical conditions than those who were discharged. However, we do not think that this statistically significant difference will be useful in clinical practice.

In Moncure et al.'s study, severe sepsis patients admitted to intensive care units were found to have higher COHb values compared to those who were normotensive (11). However, in the same study, COHb levels did not differ significantly depending on whether there was a focus of infection. Moreover, mortality was not found to be associated with COHb levels (11). In our study, we evaluated COHb values of 131 non-smoker patients and analyzed the difference with regard to sepsis or severe sepsis. However, there were no significant COHb elevations in sepsis or severe sepsis patients compared to patients without infection or between sepsis and severe sepsis patient groups. In the same study by Moncure et al., blood gas samples were taken multiple times from patients during the intensive care unit's follow-up period (11). In our study, the result that COHb values did not express a significant difference may be attributed to the single blood gas sample taken, only at the time of admission. Hunter et al.'s study, performed with blood samples from 32 surgical intensive care unit patients, revealed that COHb values were significantly increased in critically ill patients (12). However, the definition of "critically ill patients" in that study was not distinguished by SIRS but by intensive care scoring (12). There was no significant difference in COHb values of patients hospitalized in intensive care units and non-intensive care units in our study. Also, in our study, COHb values of patients hospitalized in the intensive care unit were not found to be correlated with negative clinical outcomes, unlike the study of Hunter et al. (12). It might also be the result of the fact that our study was designed with a single blood gas sample analysis, which was taken at the time of admission. On the other hand, higher numbers of patients were included in our study, compared to studies of Moncure et al. and Hunter et al. (11, 12). Although a higher number of patients provides more reliable results, only initial COHb values were considered in our study may be a limitation.

Moreover, a group of patients in our study was discharged from ED. This clinical difference between patient groups and the evaluation of the blood gas measurements only at the time of admission might be the reason for the result that COHb values could not be associated with length of stay in hospital and 1-month mortality in SIRS patients. According to our results, COHb levels in blood gas samples taken at admission are not a prognostic marker for length of stay in hospital and 1-month mortality, for patients diagnosed with SIRS with initial vital signs and laboratory values.

MetHb has been associated with the diagnosis and severity of various inflammatory conditions (7, 13). Schuerholz et al. retrospectively evaluated metHb values of 655 internal intensive care patients and revealed that septic patients had higher metHb values at the time of admission to the intensive care unit, which was significantly more prominent compared to non-septic patients and significantly correlated with the changing Sequential Organ Failure Assessment (SOFA) scores (7). Ohashi et al. evaluated 14 septic patients in the intensive care unit and reported that metHb values are higher in those patients compared to 31 non-septic patients hospitalized within the same intensive care unit (14). In this study, we also compared metHb values between patients with and without an infection, but we did not find a significant increase of metHb in the septic group. In the present study, the number of patients who had been discharged from ED in a shorter time period was more than the other studies; therefore, the septic patient group in the study, which had a higher rate, was found to have a better prognosis. This difference may be the reason metHb values were not significantly higher in septic patients in our study. Ohashi et al. had evaluated metHb with the data obtained by serial measurements during the recovery period of sepsis (14). However, when we evaluated metHb values obtained from arterial blood gas analysis at the time of admission, we could not find a significant relationship between the length of stay in hospital and 1-month mortality in patients with SIRS. Our study was the first, investigating the relationship between SIRS and metHb in terms of taking ED patients into consideration and evaluating only blood gas values at the time of admission. Both our literature search and the results of our study showed that metHb was not useful for predicting the prognosis or mortality of patients with SIRS.

It is well-known that many different causes of tissue hypoxia lead to elevated lactate levels over a short period of time (15). SIRS, which is known to be a severe inflammatory process, is an important cause of hypoxic stress. Mikkelsen et al. reported a significant relationship between the 28-day mortality of patients with severe sepsis or septic shock and the first blood gas lactate levels in their study, with 830 patients admitted to the ED in two years (16). Our study was similar to that of Mikkelsen et al., as evaluating initial blood gas values of ED patients. Moreover, in addition to the results of Mikkelsen et al., we found that the lactate levels were also indicative for 1-month mortality in all patients with SIRS and sepsis, not only for patients with severe sepsis and septic shock. Although fewer patients were included, as patients with SIRS who were not hypotensive were included, our study results may be useful for clinicians for a larger patient group than Mikkelsen et al.'s study. Singer et al. performed serial lactate measurements while monitoring 258 sepsis patients followed in the ED, and according to their study, high lactate levels were clearly associated with poor prognosis (8). This study has a smaller number of patients than Singer et al., and we only included those who were fulfilling the SIRS definition and evaluated lactate levels obtained only from initial arterial blood gas analysis. Therefore, our study was able to support the results of Singer et al.'s study in a wider diagnostic spectrum, with less laboratory analysis. In a systematic review by Kruse et al., whether lactate levels at the time of admission were a marker for mortality was investigated. Accordingly, Kruse et al. emphasized that elevated lactate levels at the time of admission were related to patients' mortality. In that review, patients whose lactate values were higher than 2.5 mmol / L in arterial blood gas analysis was reported to have significantly higher mortality rates (19). In our study, higher lactate levels in patients diagnosed as SIRS were significantly associated with 1-month mortality. Higher lactate levels in patients who died within 1 month were significantly higher than those who survived. Thus, lactate levels give the physicians an opinion about mortality in patients with SIRS, even at the time of admission.

In conclusion, it was found that COHb and MetHb values measured in the arterial blood gas samples during admission to the ED were not useful in predicting prognosis or mortality in patients with SIRS. On the other hand, lactate levels were associated with mortality in SIRS, even at admission to ED.

**Declarations**

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

At the Gazi University Clinical Research Ethics Committee on 13.04.2015, ethical approval was obtained with the decision number 160.

## REFERENCES


1. Horeczko T, Green JP, Panacek EA. Epidemiology of the Systemic Inflammatory Response Syndrome (SIRS) in the emergency department. West J Emerg Med. 2014;15(3):329-36.
2. Comstedt P, Storgaard M, Lassen AT. The Systemic Inflammatory Response Syndrome (SIRS) in acutely hospitalised medical patients: a cohort study. Scand J Trauma Resusc Emerg Med. 2009;17:67.
3. Bloom BM, Grundlingh J, Bestwick JP, Harris T. The role of venous blood gas in the emergency department: a systematic review and meta-analysis. Eur J Emerg Med. 2014;21(2):81-8.
4. Slebos DJ, Ryter SW, Choi AM. Heme oxygenase-1 and carbon monoxide in pulmonary medicine. Respir Res. 2003;4(1):7.
5. Wennmalm A, Benthin G, Petersson AS. Dependence of the metabolism of nitric oxide (NO) in healthy human whole blood on the oxygenation of its red cell haemoglobin. Br J Pharmacol. 1992;106(3):507-8.
6. Kosaka H, Uozumi M, Tyuma I. The interaction between nitrogen oxides and hemoglobin and endothelium-derived relaxing factor. Free Radic Biol Med. 1989;7(6):653-8.
7. Schuerholz T, Irmer J, Simon TP, Reinhart K, Marx G. Methemoglobin level as an indicator for disease severity in sepsis. Crit Care. 2008;12(Suppl 2):P448-P.
8. Singer AJ, Taylor M, Domingo A, Ghazipura S, Khorasonchi A, Thode HC, Jr., et al. Diagnostic characteristics of a clinical screening tool in combination with measuring bedside lactate level in emergency department patients with suspected sepsis. Acad Emerg Med. 2014;21(8):853-7.
9. James JH, Luchette FA, McCarter FD, Fischer JE. Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. Lancet. 1999;354(9177):505-8.
10. de Siqueira ME, Martins I, Costa AC, Andrade EL, Esteves MT, Lima SA. [Reference values for carboxyhemoglobin]. Rev Saude Publica. 1997;31(6):618-23.
11. Moncure M, Brathwaite CE, Samaha E, Marburger R, Ross SE. Carboxyhemoglobin elevation in trauma victims. J Trauma. 1999;46(3):424-7.
12. Hunter K, Mascia M, Eudaric P, Simpkins C. Evidence that carbon monoxide is a mediator of critical illness. Cell Mol Biol (Noisy-le-grand). 1994;40(4):507-10.
13. Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management. Ann Emerg Med. 1999;34(5):646-56.
14. Ohashi K, Yukioka H, Hayashi M, Asada A. Elevated methemoglobin in patients with sepsis. Acta Anaesthesiol Scand. 1998;42(6):713-6.
15. Nguyen HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med. 2004;32(8):1637-42.
16. Mikkelsen ME, Miltiades AN, Gaieski DF, Goyal M, Fuchs BD, Shah CV, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. Crit Care Med. 2009;37(5):1670-7.