A new method in foreseeing late-period neuro-psychosis in carbon monoxide poisoning: COHb/Troponin, COHb/Neutrophil, and COHb/Lymphocyte

Karbon monoksit zehirlenmesinde geç dönem nöropskozun öngörülmesinde yeni bir yöntem: Karboksihemoglobin / Troponin, Karboksihemoglobin / Nötrofil ve Karboksihemoglobin/ Lenfosit

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Received/Accepted: October 04, 2018 / March 19, 2019
Conflict of interest: There is not a conflict of interest.

SUMMARY
Objective: Carbon monoxide(CO) poisoning is one of the most common reasons of poisoning and death in the world. Evaluation for the effects of CO poisoning, carboxyhaemoglobin(COHb), troponin(cTn), neutrophil, lymphocyte and their rates—which are COHb/cTn rate(COTR), COHb/neutrophil rate(CONR), COHb/lymphocyte rate(COLR) in terms of Neuro-Psychosis(NP) and mortality is aimed.
Method: 1229 patients who consulted our hospital’s Emergency Department(ED) from January 2005 to December 2008, due to CO poisoning were included in this sectional cohort study. The patients were divided into two groups, NP positive(NP+) and NP negative(NP-), according to their NP groups. They were compared in terms of COHb, cTn, neutrophil, lymphocyte, COTR, CONR, COLR, age, gender, NP, and mortality rates.
Results: 466(%40,9) members of the group NP(-) were males and the other 673(%59,1) members were females. Therewithal, 22(%24,4) members of the group NP(+) were males and the other 68(%75,6) members were females. Red Cell Distribution Width(RDW), Mean Platelet Volume(MPV), neutrophil, lymphocyte, COHb, troponin, COTR, CONR and COLR levels were high in group NP(+). NP was significant in terms of gender and mortality values. The analysis of gender between NP, mortality and the other variables was statistically significant. COTR, CONR, and COLR were statistically significant in Spearman analysis. Sensitivity and specificity values of COTR, CONR, COLR in NP and mortality ROC curve analysis were also found to be significant.
Conclusions: The high levels of COTR, CONR, and COLR at CO poisoning may be predictive and supportive values in terms of ‘complications during and after poisoning’, NP and mortality.
Keywords: Carbon monoxide poisoning, emergency department, COTR, CONR, COLR, neuro-psychosis

ÖZET
Amaç: Carbonmonoksit zehirlenmesi (CO) dünyadaki en sık zehirleme ve ölüm nedenlerinden biridir. CO zehirlenmesi, karboksihemoglobin (COHb), troponin (cTn), nötrofil ve lenfosit ile bunların oranları olan COHb/ cTn oranı (COTR), COHb/nötrofil oranı (CONR) ve COHb/lenfosit oranı (COLR)’ın nöro-psikoz (NP) ve mortalite açısından etkilerinin değerlendirildirilmesi amaçlanmıştır.
Önem: Bu kesitsel kohort çalışmasına, Ocak 2005- Aralık 2008 tarihleri arasında hastanemiz acil servisine (ED) CO zehirlenmesi nedeniyle başvuran 1229 hasta dahil edildi. Hastalar NP grubu göre; NP pozitif (NP+) ve NP negatif (NP-)
olarak iki gruba ayrıldı. COHb, cTn, nötrofil, lenfosit, COTR, CONR, COLR, yaş, cinsiyet, kan şeker, NP ve mortalite oranları açısından karşılaştırıldı. Bulgular: Hastaların NP(−) grubunda 466 (%40,9) erkek, 673 (%59,1) kadındı ve NP(+) grubunda 22 (%24,4) erkek, 68 (%75,6) kadındı (p<0.05). Red cell distrubition width(RDW), Mean Plateate Volum(MPV), Neutrophil, lymphocyte, COHb, Troponin, COTR, CONR ve COLR düzeyleri NP(+) grubunda yüksekti (p<0.05). NP değişkenler açısından cinsiyet ve mortalite açısından anlamlıydı (p<0.05). Cinsiyetin NP ve mortalite ile diğer değişkenler arasındaki analizi istatistiksel olarak anlamlı tespit edildi (p<0.05). Ayrıca COTR, CONR, COLR’in NP ve mortalite ROC curve analizinde duyarlılık ve özgüllük değerleri anlamlı bulundu. Sonuç: CO zehirlenmesinde COTR, CONR ve COLR düzeylerinin yüksek olması zehirlenme anında ve sonrası gelişen komplikasyonlar, NP ve mortalite açısından prediktif yardımcı bir değer olabilir. Anahtar sözcükler: Carbon monoxide poisoning, emergency department, COTR, CONR, COLR, neuro-psychosis

INTRODUCTION
CO is an odorless, colorless gas resulting from the incomplete combustion of fuels containing hydrocarbons. CO’s density in the atmosphere is negligible. Because affinity of CO to hemoglobin(Hb) is about 250 times higher than that of oxygen to Hb, CO prevents the oxygen in the Hb from connecting to the same site. Therefore CO concentration in blood can reach dangerous levels in a short time. Although real frequency is not known, it is estimated that only 1/3 of the cases exposed to poisoning is realized. The fact that the findings are not specific to CO poisoning can cause cases to be not noticed. CO poisoning prevents oxygen transport to the cells and causes hypoxia secondary tissue damage. CO connects to Hb and causes COHb formation. As a result, oxygen relocates and arterial oxygen saturation reduces. It takes 320 minutes for COHb to be halved. CO connects to heart and skeletal muscle myoglobin as well as Hb. Tissue hypoxia increases respiration effort and causes more CO molecules to pass into the blood⁴. Although CO intoxication supports high COHb levels, it has been reported that relating COHb levels to clinical findings and prognosis do not give reliable results. Exposure time is more important. In CO poisoning, chronic exposures with low COHb may be more severe than acute CO poisoning with high COHb. Correlation between COHb level and symptoms ² (Table 1):

| Symptoms and findings | Percentage of CO in the blood (%) |
|-----------------------|----------------------------------|
| *None,                | 0-10                             |
| *Slight head-ache, enlargement of the skin veins, | 10-20                             |
| *Headache, throbbing pain in frontal, | 20-30                             |
| *Severe headache, weakness, nausea, vomiting, blurred vision, dizziness, collapsing, cherry red skin and lips, | 30-40                             |
| *In addition to others; respiration and pulse increases, %50-60 tachycardia, tachypnea, Cheyne-Stokes respiration, coma, convulsions, | 30-40                             |
| *Coma, convulsions, cardiac and respiration depression, possible death, | 40-50                             |
| *Weak pulse, depressed respiration, lack of respiration and death | 60-70                             |
|                      | 70-80                             |

CO intoxication, which is the reason for many consultations to ED, is one of the major toxic deaths³. NP disorders such as dementia, memory loss, personality changes, learning disability, behavior disorder, attention disorder and concentration disorder, psychosis, parkinsonism, paralysis, chorea, peripheral neuropathy and incontinence can be seen approximately 3-240 days after CO poisoning in 10-30% of the cases⁵. Although the presence of late neurologic disorders is more common in advanced ages, it can rarely occur under 20 years⁶. In CO intoxications, cTns increase according to myocardial damage at certain rates. cTn is a very sensitive and specific indication of myocardial injury. In ACS, increased cTn levels are important for both prognosis and the direction of treatment. For this reason, cTn level measurements are
frequently used for ACS differential diagnosis in ED and intensive care units.\textsuperscript{7-10}

Neutrophils and lymphocytes (NL) are easy, cheap, non-invasive and commonly used laboratory determinants of systemic inflammation.\textsuperscript{11,12} NL are combinations of two independent inflammation markers. Neutrophils are indications of ongoing nonspecific inflammation. Lymphocytes are combinations of these two markers as signs of regulator way. NL has proved to be a powerful simple inflammation marker.\textsuperscript{13,14}

When the literature was reviewed, we did not find any studies evaluating the ratio between cTn I, COHb levels, which are the signs of myocardial injury, and neutrophil, lymphocyte; at the time of consultation to ED due to CO poisoning. In this study, it was aimed to evaluate the effects of COTR, CONR, and COLR—which are the ratios of neutrophil, lymphocyte, cTn I and COHb, which are routinely measured during the consultation to ED because of CO poisoning—on the brain.

**MATERIAL AND METHODS**

**Study design and population**

1229 patients (488 males, 741 females; average age 45.15±14.51 years; range 23-94 years, 60.3 females) older than 20 years who consulted ED from January 2005 to December 2008, due to CO poisoning were included in this study.

During consultation; patients who are outpatients; patients who have cerebrovascular disease, psychiatric diseases, chronic liver diseases; patients who receive dialysis treatment due to chronic renal insufficiency; patients who were previously diagnosed with infectious, inflammatory disease or malignancy; patients who previously took the treatments of severe anaemia or other hematologic disease or anaemia; patients who have received erythrocyte suspension in the last six months; were omitted.

After the patients’ consultation to ED, their annual neurology and psychiatry clinic parameters have been followed by the hospital’s automation system for 10 years. Their diagnoses were recorded at the end of each year. Patients generated NP(+) and NP(-) groups according to their late-period findings. In addition, group NP divided into two groups, neuroses, and psychosis.

The study was made in following the Declaration of Helsinki for Human Research and was approved by the institutional review board. Demographic, clinical, and laboratory data from the date of presenting to the ED due to CO poisoning, including the COTR, CONR and COLR levels, were assessed using review of the hospital’s medical records.

COHb, troponin, hemogram and biochemical blood of the patients were taken during their consultations to ED. The patients’ COHb levels were obtained from arterial blood gas analyses using the Acobas® b221 Blood Gas system (Roche, Basel, Switzerland). Neutrophil and lymphocyte were measured using a Beckman Coulter Automated CBC Analyzer (Beckman Coulter, Inc., Fullerton, CA, USA). Neutrophil and lymphocyte normal reference ranges are; 41-73%; 19-45%.

Troponin I levels, which were evaluated within fifteen minutes after the patients were admitted to ED, were measured with a one-step immunofluorometric assay sandwich method using three monoclonal antibodies (AQ90 Flex, Radiometer Medical ApS, Brønshøj, Denmark). The conventional definition of elevated troponin level is when this value exceeds the 99\textsuperscript{th} percentile value of a healthy reference population and elevated test level, which is >0.05 ng/ml, for our laboratory, was accepted as positive. Additionally, non-elevated test level, which is ≤0.05 ng/ml, was accepted as negative.

A diagnosis of CO poisoning was made according to the medical history and a COHb level >5%. CO exposure time was defined as the approximate duration of CO inhalation. Diabetes mellitus was defined as a fasting blood sugar level ≥126 mg/dl or being on antidiabetic treatment. Hypertension was defined as blood pressure ≥140/90 mmHg on more than two occasions during office measurements, or being on antihypertensive treatment.

**3. Statistical Analysis**

The Kolmogorov-Smirnov test was used to verify the normality of the distribution of continuous variables. Continuous variables were expressed as mean±SD or median (min-max) in the presence of abnormal distribution, and categorical variables as percentages. Receiver operator characteristic ROC curve analysis was performed to determine the optimal cut-off point of COTR, CONR and COLR (sensitivity and specificity were maximal) for predicting mortality and NP. Comparisons between the groups of patients were made by the χ\textsuperscript{2}-test for categorical variables, the independent samples t-test for normally distributed continuous variables, and the Mann-Whitney U-test when the distribution was skewed. The correlation was evaluated by Spearman correlation test. All statistical procedures
were performed using SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA). A p-value of 0.05 was considered statistically significant.

RESULTS
466(%40,9) members of the group NP(-) were males and the other 673(%59,1) members were females. Therewithal, 22(%24,4) members of the group NP(+) were males and the other 68(%75,6) members were females(p<0.05). Patients in the group NP(+) spent a long time to consult ED than patients in the group NP (-), and it was significant. Also, White Blood Cell(WBC), Red Cell Distribution Width(RDW), Mean Platelet Volume(MPV), neutrophil, lymphocyte, COHb, troponin, COTR, CONR and COLR levels were high in group NP(+) and it was statistically significant(p<0.05, Table 2).

Table 2: Baseline characteristics of study patients.

|                          | All patients n:1229 | NP(-) n:90  | NP(+) n:1139 | Z       | p-value |
|--------------------------|---------------------|-------------|-------------|---------|---------|
| Mean age(y)              | 45.14±14.50         | 45.29±14.61 | 43.36±13.08 | -1.069  | 0.285   |
| Female                   | 741(%60,3)          | 673(%59,1)  | 68(%75,6)   | -       | 0.002   |
| Male                     | 488(%39,7)          | 466(%40,9)  | 22(%24,4)   | -       | 0.003   |
| CRP mg/L                 | 3.40±3.83           | 2.84±3.27   | 10.45±3.32  | -8.545  | 0.001   |
| CO ET (h)                | 3.24±2.21           | 3.20±2.21   | 3.78±2.22   | -2.965  | 0.013   |
| WBC(10^3/ul)             | 14.22±1.41          | 14.07±1.31  | 16.10±1.23  | -11.866 | 0.001   |
| RDW (%)                  | 7.99±0.92           | 7.85±0.77   | 9.67±0.88   | -13.736 | 0.001   |
| MCHC g/dL                | 33.39±4.07          | 33.34±3.70  | 34.07±3.17  | -3.11   | 0.190   |
| MCV %                    | 87.56±7.29          | 87.52±7.24  | 88.03±7.93  | -0.912  | 0.362   |
| MCH I/L                  | 29.37±2.36          | 29.37±2.37  | 29.43±2.35  | -0.402  | 0.688   |
| Neu %                    | 5.26±2.28           | 4.81±1.53   | 11.01±2.40  | -14.311 | 0.001   |
| Lymph %                  | 1.21±0.69           | 1.09±0.52   | 2.76±0.73   | -14.362 | 0.001   |
| BS (mg/dl)               | 123.60±43.68        | 123.07±43.62| 130.31±44.12| -1.548  | 0.122   |
| Amylase U/L              | 125.08±69.68        | 89.49±49.69 | 98.65±55.29 | -1.518  | 0.129   |
| COTR                     | 5.52±6.80           | 5.62±7.05   | 4.22±1.31   | -2.344  | 0.019   |
| CONR                     | 0.33±0.29           | 0.29±0.27   | 0.72±0.30   | -12.175 | 0.001   |
| COLR                     | 1856.09±60817.89    | 2000.47±63174.78 | 28.88±200.65 | -5.930  | 0.001   |
| COHb (%)                 | 32.62±10.67         | 31.85±10.29 | 42.31±10.67 | -5.854  | 0.001   |
| Tn (mg/dL)               | 0.30±0.95           | 0.27±0.93   | 0.71±1.10   | -8.559  | 0.001   |

NP(+) : Neuro-psychosis Positive; NP(-) : Neuro-psychosis Negative; CRP: C reactive protein; CO ET: Carbon monoxide exposure time; WBC: White blood cell; RDW: Red cell distruibution width; MPV:Mean Platelet Volum; MCHC:Mean Corpuscular Hemoglobin Concentration; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin; Neu:Neutrophil; Lymph: lymphocyte; BS: Blood suger, COHb: Carboxyhemoglobin; Tn:Troponin, COTR: Carboxyhemoglobin/Troponin Rate, CONR: Carboxyhemoglobin/ Neutrophil Rate, COLR: Carboxyhemoglobin /Lymphocyte Rate

NP was not statistically significant in terms of hypertension, diabetes and tobacco product usage in chi-square analysis in terms of variables (p>0.05). However, it was significant in terms of gender and mortality (p<0.05, Table 3A).

The chi-square analysis of gender between NP, mortality and the other variables was statistically significant (p<0.05, Table 3B).
Table 3A. Chi-Square Test Results Relating to the Difference Between Variables of Neuro-Psychosis

| Variable          | Male | Female | χ²     | p-value |
|-------------------|------|--------|--------|---------|
| Gender            | 466(95.5) | 673(90.8) | 9.44 | <0.002 |
| Mortality         | 1103(93.6) | 76(6.4) | 32.83 | <0.001 |
| HT                | 766(92.7) | 60(7.3) | 0.909 | >0.497 |
| DM                | 740(92.5) | 60(7.5) | 0.106 | >0.745 |
| Tobacco           | 697(93.1) | 47(6.3) | 2.81 | >0.094 |

HT: Hypertension, DM: Diabetes Mellitus

Table 3B: Chi-Square Test Results Regarding the Difference Between Gender Variables

| Variable          | Male | Female | χ²     | p-value |
|-------------------|------|--------|--------|---------|
| Neuro-Psychosis   | 466(95.5) | 673(90.8) | 9.44 | <0.002 |
| Mortality         | 476(40.4) | 703(59.6) | 5.71 | <0.020 |
| HT                | 352(42.6) | 474(57.4) | 8.897 | <0.003 |
| DM                | 341(42.6) | 459(57.4) | 8.151 | <0.004 |
| Tobacco           | 232(31.2) | 512(68.8) | 57.22 | <0.001 |

NP occurred in 90 of 1229(7.32%) patients. It has been seen that 56 of them (62.2%) have neurological disorders and 34 of them (37.8%) have psychosis findings. 39(69.6%) of the neurotic patients were females and 17(30.4%) were males. Of the psychotic group, 23(67.6%) patients were females and 11(32.4%) patients were males (χ²=37.65, p=0.001, p<0.05).

The Spearman correlation between the variables and COTR, CONR, COLR is shown in Table 4.
Table 4: Spearman correlation coefficients for COTR, CONR, and COLR

|       | COTR r | p-value | CONR r | p-value | COLR r | p-value |
|-------|--------|---------|--------|---------|--------|---------|
| Nöro-Psikoz | -0.067 | <0.019 | 0.347  | <0.001 | -0.272 | <0.001 |
| CO exposure time | -0.058 | <0.042 | 0.093  | <0.001 | -0.086 | <0.003 |
| Tn    | -0.050 | >0.077 | 0.127  | <0.001 | -0.106 | <0.001 |
| COHb  | -0.047 | >0.098 | 0.117  | <0.001 | -0.100 | <0.001 |
| RDW   | 0.022  | >0.441 | 0.080  | <0.005 | -0.051 | >0.072 |
| MPV   | -0.091 | <0.001 | 0.158  | <0.001 | -0.143 | <0.001 |
| Neu   | 0.185  | <0.001 | 0.268  | <0.001 | -0.112 | <0.001 |
| Lymp  | -0.611 | <0.001 | 0.915  | <0.001 | -0.828 | <0.001 |
| COTR  | -0.858 | <0.001 | -0.858 | <0.001 | 0.935  | <0.001 |
| CONR  | -0.858 | <0.001 | -0.858 | <0.001 | 0.935  | <0.001 |
| COLR  | 0.935  | <0.001 | 0.935  | <0.001 | -       | -       |

According to the ROC curve analysis, the optimal cut-off values of COTR, CONR and COLR to determine NP(+) were COTR; AUC:0.426; >3.46; sensitivity was 77.8% and specificity was 72.7% (p=0.019, p<0.05); CONR: AUC:0.885; >0.3959; sensitivity was 97.8% and specificity was 89.7% (p=0.001, p<0.05), COLR; AUC:0.199; >3.073; sensitivity was 96.2% and specificity was 87.8% (p=0.001, p<0.05 (Figure 1).

Figure 1: ROC curve analysis according to COTR, CONR, and COLR Neuro-Psycosis positivity

According to the ROC curve analysis, the optimal cut-off values of COTR, CONR and COLR to determine mortality positivity were COTR; AUC:0.428; >3.70; sensitivity was 67.9% and specificity was 58.1% (p=0.086, p>0.05); CONR; AUC:0.630; >0.1399; sensitivity was 86.0% and specificity was 72.9% (p=0.002, p<0.05), COLR; AUC:0.382; >5.6117; sensitivity was 85.2% and specificity was 74.1% (p=0.004, p<0.05 (Figure 2).
DISCUSSION

In today’s world, there are few and controversial data on late-period NP in CO poisoning. When the literature was reviewed, we could not find any studies about the correlation between COHb levels and cTn, neutrophil, lymphocyte. Also, we could not detect any studies about NP and mortality according to the rate between COHb levels and cTn, neutrophil, lymphocyte. For this reason, we made our study in order to determine these correlations.

CO intoxication, which is the reason for many consultations to ED, is one of the major toxic deaths. The variations of acute CO poisoning, are firstly seen in organs such as brain and heart where the oxygen need is high\(^{15}\). It is stated that lipid peroxidation is responsible for the neurological disorders in the late period of CO poisoning. It is stated that CO connects to cytochrome oxidase in the cell, causes nitric oxide release from thrombocytes and endothelial cells, causes mitochondrial dysfunction by deactivating mitochondrial enzymes, generates oxidative stress in the cell. In this way; CO causes damage to the vascular endothelium and lipid peroxidation occurs. With brain reperfusion, leukocyte adhesion, subsequent excitatory amino acid, and destructive enzyme release exacerbate the initial oxidative damage. The result of this pathophysiological process is movement disorders, which do not occur on days following the initial poisoning but occur as late complications and defects in cognitive functions such as learning and memory\(^{16}\). In the period between the anoxic phase and the onset of late neurological findings, it is claimed that remyelination, oxidation reactions, central synaptic reorganization, transsynaptic neuronal degeneration and subsequent physiopathologic events such as denervation supersensitivity and diaschisis, which is the mediator of collateral sprouting, were happened; respectively\(^{17-19}\).

Various neurological conditions can occur in 2-40% of the patients immediately after CO poisoning or after a certain latent period. Findings of these late neurological conditions are; amnestic syndromes, vegetative condition, agnosia, aphasia, apraxia, visual disorders, other focal cortical deficits, dementia, akinetic mutism, spasticity, parkinsonism, chorea, Gilles de la Tourette’s syndrome, seizures, organic affective and personality disorders, psychosis. Late neurological findings may occur after the latent period, which may extend from a few days to three weeks, as in the acute phase of poisoning\(^{20}\).

In our study, the value of COHb in NP(+) group averaged 42 points and the negative group was 31. Totally following the 1229 patients, NP developed in 90(7.32%). In 56(62.2%) of this positive group, neurological patients and in 34(37.8%) development of psychosis findings were observed. 39(69.6%) of the neurotic patients were female and 17(30.4%) were male. In the neurosis group, the most frequent Parkinson's disease and late-term neurological findings and dementia were detected. However, personality changes in the psychosis group were in the foreground. Negative for COTR and COLR, positive for CONR

Figure 2: ROC curve analysis according to COTR, CONR, and COLR mortality positivity
Spearman correlation was detected in this group of NP.

Gender and age show differences in many studies in the literature. The average of males was 61.62%, and 37.73 years, Azmak et al. 22 the average of 76.60 males and 32.60 females was determined in the study. Whereas Hosseinejad et al 23 were in the study of meta-analysis; the 4620 was male (40.12%) and 3057 was female (59.88%) and the average age 31.64 was included in the study. In our study, 741(60.3%) women were present and the average was 45.15 years. It was higher than the average age stated in the literature. One reason for this is the family and society structure, and the other may be due to the overall rise in the society's age average.

The pathophysiological mechanisms of late-term NP of CO intoxication are still not fully understood. There is no study in the literature screening that directly exploring NP syndromes. Only a few cases are present in the form of presentations. Two mechanisms are proposed for pathophysiology. One of them, CO poisoning nitric oxide and other oxygen-free radicals activation24. It is suggested that oxidative damage is largely a mediator to leukocytes. When leukopenic is done in rats, lipid peroxidation is inhibited after CO poisoning. Leukocyte sequestration is significantly increased in brain microvasculature after exposure to CO. Neutrophils have shown to play a role in brain injury in co poisoning25,26. A second mechanism has been reported to increase the thrombotic tendency. Acute CO poisoning has shown to cause intravascular neutrophil activation due to interactivity with platelets27. Oxygen free radicals may affect thrombocyte aggregation and blood flow28. Free radicals can increase platelet adhesion and may cause changes in fibrinolytic isolates29. In addition, hypoxia can cause a direct increase in MPV30,31.

In our study, the number of white spheres in circulation, neutrophil and lymphocyte count was significantly higher in the NP and mortality group. The height in this acute period, short-term increase in mortality, the correlation with np was determined in the late period. In patients with CO poisoning, the height of the RDW and MPV levels were positive for cardiac enzymes and the MPV and RDW in the NP(+) group were significantly higher. While RDW did not show correlation with COTR and COLR, it showed a weak correlation with CONR. However, it was detected MPV negative with COTR and COLR, positive with CONR. According to these finding, CO poisoning caused an increase in MPV, an indication of thrombocyte activation. In patients with CO poisoning, complications may be due to increased thrombocyte activation in addition to hypoxia. This may be reasonable in the use of antiplatelet drugs in acute CO poisoning.

Neutrophil-lymphocyte ratio(NLR) is a widely used laboratory marker of easy, inexpensive, non-invasive and systemic inflammation. Recently, many uncontrolled inflammatory disease cases have increased their relevance as an independent prognostic factor(11,12). While high neutrophil counts reflect inflammation, low lymphocytes reflect poor general health and physiological stress32. NLR combines these two independent markers of inflammation33. NLR has been shown to be an indicator of systemic inflammation34. The important role in the pathophysiology of fatal complications related to CO poisoning of leukocytes was demonstrated in previous studies25,35. Karabacak et al. 36 in his study, systemic inflammation in the etiopathogenesis of CO poisoning could play a role, and in these patients, they found that WBC, MPV, neutrophil count and NLR were significantly higher and that they were also positively or handled. In his studies, while the number of neutrophils in circulation was significantly higher in the group of CO poisoning, the number of lymphocytes was similar in both groups with control and CO poisoning. Systemic inflammation may be effective in the development of complications caused by CO poisoning, therefore, the use of anti-inflammatory drugs in acute CO poisoning may be reasonable.

In our study, the incidence of neutrophil and lymphocyte values detected in the mortality and NP group were determined by the value of the COHb and the relationship between NP and mortality was observed. Neutrophil was positive with COTR and CONR and negative for COLR. Whereas lymphocytes COTR and COLR strong negative, CONR with strong positive correlation was detected. CONR is an indication of ongoing non-specific inflammation and COLR has shown that the regulatory path is a strong simple inflammatory marker as a marker. Determination of NP(+) CONR sensitivity 97.8% and specificity 89.7%, COLR sensitivity 96.2% and specificity 87.8% were determined. To determine mortality positivity, CONR’s sensitivity was found 86.0% and specificity 72.9%, COLR sensitivity 85.2% and specificity 74.1%.

In conjunction with these findings, early mortality after CONR and COLR CO poisoning can be a
predictive marker with the late-term troponin and COHb. cTns are constituents of the contractor's apparatus of cardiomyocytes and released during myocardial necrosis. Serum cTn height is a specific and well-established myocardial necrosis biomarker.\textsuperscript{37,38} The cardiac effects of COHb extend from simple arrhythmias to myocardial infarction.\textsuperscript{39-40} In the study of Satran et al.,\textsuperscript{30} the cardiac biomarker positivity rate, defined as CK-MB and/or troponin elevation, was 44%. Aslan et al. (31), in CO poisoning, there was a significant increase in cTn T levels due to microscopic myocardial necrosis at COHb levels of up to 60%. We found that COHb levels and CO exposure times in troponin-positive patients, mortality and late-term NP patients were also significantly higher. In the NP(+) group, cTn was 0.71mg/dl, and the NP(-) group was cTn 0.27mg/dl. These values were re-evaluated by COHb and cTn. COTR was lower in the positive group and higher in the negative group. Also, COTR with neutrophil and COLR a strong positive correlation was found with the duration of exposure to CO poisoning. MPV, negative with lymphocytes and CONR, neutrophil and COLR. Mortality was 36(72%) in NP(+) group and 14(28%) in NP(-) group. To determine NP(+), COTR, sensitivity 77.8% and specificity 72.7% and to determine mortality positivity. COTR, sensitivity 67.9% and specificity 58.1% were determined. In addition to these data, COTR, CO exposure time and age, cTn positivity and NP may be independent predictive parameters.

For patients with COHb levels between 10% and 20% in the ED, the most common symptom was the headache, which usually develops when COHb levels are around 25%. This suggests that these patients may have had initial COHb levels of between 20% and 30%.\textsuperscript{31} In the group with a COHb value of 20 and below, the early and late period NP symptoms were minimal and mortality was absent, while the COHb value was higher than 20 and both the NP and mortality were high. In addition, in our study, cTn height was seen in all patients in the group with COHb value 40 and above, and the mortality rate increased significantly. In females, NP 68(5.5%) and mortality were 38(3.1%), while NP 22(1.7%) and mortality 12(0.9%) were detected in males. It was seen that COHb value and cTn were high but COTR was low in NP(+). In addition to these findings, it was found that mortality and late np cases were increased in COTR low group.

6. Study limitations

In this study, no history of use of neuro-psychotropic drugs could be found that could affect the prognosis of NP. In addition, we were unable to reach the blood gas parameters and troponin levels, which could be beneficial for evaluating hypoxia and poisoning, except for the first arrival of the emergency room. There was no information on the length of CO exposure and the timing of the blood COHb levels in relation to the CO exposures. Further studies are necessary in this regard. Another limitation was the retrospective nature of the study. The data were reviewed by one researcher who avoided the selection bias; however, misclassification may still exist, which cannot be verified or validated.

CONCLUSION

In CO poisoning, asymptomatic cases of neuropsychological disorders that may develop in the future can easily be overlooked. Consideration of COHb, cTn, COTR, CONR, and COLR levels by physicians may be a predictive value in the prevention of future NP and leading to early diagnosis. If these results can be supported by multicenter and prospective studies, they can be very useful for all patients with CO poisoning due to health Economics policies where the evaluation of the parameters cannot be performed, instead of the parameters that cannot be looked at in ED.

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