Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2021;46(2):566-573
DOI: 10.17826/cumj.852885

ARAŞTIRMA / RESEARCH

The effect of thiol/disulfide homeostasis on chronic obstructive pulmonary disease-related mortality

Thiol/disülfid homeostazının kronik obstrüktif akciğer hastalığı ile ilişkili mortalitedeki etkisi

Hacı Mehmet Çalışkan[1], Bilal İlanbey[2], Duygu Zorlu Karayiğit[3], Zamir Kemal Ertürk[4], Burak Çelik[1], Süleyman Ersoy[1]

[1]Kırşehir Ahi Evran Üniversitesi Tıp Fakültesi, Acil Tıp Anabilim Dalı, [2]Tıbbi Biyokimya Anabilim Dalı, [3]Göğüs Hastalıkları Anabilim Dalı, Kırşehir, Turkey
[4]Etimesgut Şehit Sait Ertürk Devlet Hastanesi, Ankara, Turkey

Cukurova Medical Journal 2021;46(2):566-573

Abstract

Purpose: Our study investigates the correlation between thiol/disulfide homeostasis and mortality among chronic obstructive pulmonary disease (COPD) patients with hypercapnic respiratory failure (HRF).

Materials and Methods: This cross-sectional prospective study comprises a total of 104 subjects, including 64 HRF patients admitted to the Emergency service due to respiratory failure and 40 healthy controls. HRF patients were further divided into two subgroups as those in whom mortality occured after 1 month (n=14), and those who survived (n=50). Thiol/disulfide homeostasis was evaluated using a novel and automated assay developed by Erel and Neselioglu.

Results: The total thiol (TT) and native thiol (NT) levels were significantly lower in the HRF group than the control group, whereas the mean disulfide (Ds)/TT and Ds/NT values were significantly higher. The Ds levels were not significantly different between the groups. On the other hand, Ds, Ds/TT, and Ds/NT values of surviving HRF patients were significantly lower than those of the HRF patients who died. In this article we found that Ds may be an indicator of mortality in COPD (sensitivity: 85.7%, specificity: 70%, AUC: 0.793, 95% CI: 0.673-0.884, p<0.001).

Conclusion: Thiol/disulfide parameters may be used in emergency service and hospitals in the diagnosis of HRF, and for the prediction and improvement of prognosis.

Keywords: Emergency service, hypercapnic respiratory failure, oxidative stress, thiol

Öz

Amaç: Bu çalışmada Hiperkapnik solunum yetmezliği (HSY) olan kronik obstrüktif akciğer hastalarındaki mortalite (KOAH) ile thiol/disülfid homeostazisi arasındaki ilişki araştırılmıştır.

Gereç ve Yöntem: Bu kesitsel prospektif çalışma, solunum yetmezliği nedeniyle acil servise başvuran 64 hiperkapnik solunum yetmezliği (HSY) hastası ve 40 sağlıklı kontrol dahil olmak üzere toplam 104 kişiden oluşmaktadır. HRF hastaları ayrıca 1 ay sonra mortalite meydana gelenler (n = 14) ve hayatta kalanlar olarak iki alt gruba ayrıldı. Thiol/Disülfid homeostazı, Erel ve Neselioğlu tarafından geliştirilen yeni ve otomatik bir ölçme yöntemi kullanılarak değerlendirildi**.**

Bulgular: Total thiol (TT) ve native thiol (NT) seviyeleri, HSY grubunda kontrol grubuna göre anlamlı derecede daha düşüktü, oysa ortalama disülfid (Ds)/ TT ve Ds / NT değerleri önemli ölçüde daha. Disülfid seviyelerinde ise guruplar arasında önemli bir fark yoktu. Ayrıca Hayatta kalan HRF hastalarının Ds, Ds / TT ve Ds / NT değerleri, ölen HRF hastalarınınkinden önemli ölçüde daha düşüktü. Biz bu makalede Disülfid'in KOAH'da mortalitenin bir göstergesi olabileceğini bulduk (duyarlılık:% 85.7, özgüllük:% 70, EAA: 0.793,% 95 CI: 0.673-0.884, p <0.001).

Sonuç: Tihiol/Disülfid parametreleri acil servislerde ve hastanelerde hiperkapnik solunum yetmezliği tanısında ve prognozun öngörülmesi ve iyileştirilmesinde kullanılabilir.

Anahtar kelimeler: Acil servis, hiperkapnik solunum yetmezliği, oksidatif stres, thiol

Yazışma Adresi/Address for Correspondence: Dr. Hacı Mehmet Çalışkan, Ahi Evran Üniversitesi Tıp Fakültesi, Acil Tıp Anabilim Dalı, Kırşehir, Turkey E-mail: hmehmet.40@hotmail.com
Geliş tarihi/Received: 09.01.2021 Kabul tarihi/Accepted: 13.04.2021 Çevrimiçi yayın/Published online: 20.05.2021

INTRODUCTION

The third leading cause of death is chronic obstructive pulmonary disease according to estimates of World Health Organization[1]. Global trends in COPD show that incidence rates are rising, with higher incidence rates in regions with higher tobacco consumption[2]. The prevalence of COPD is 0.9% and 0.7% among men and women, respectively[3]. Men are more likely to develop COPD due to higher exposure to risk factors. This gender-related gap is expected to close with increasing rates of smoking prevalence among women.

Respiratory failure is defined as insufficient blood oxygenation and/or carbondioxide elimination caused by defective ventilation, distribution, diffusion, and perfusion coordination[4]. Respiratory failure in COPD is divided into two: type I (hypoxemic), caused by impaired gas exchange, and type II (hypercapnic), caused by hypoventilation[2,5]. Both types of respiratory failure affect hemodynamic balance and lead to cellular and organelle damage.

Recent studies have focused on the impact of oxidative stress on COPD-related damage[6]. Both hypoxia and hypercarbia increase the levels of reactive oxygen species (ROS)[7]. Increased ROS levels will disturb the oxidative balance and increase oxidative stress, which translates into higher COPD morbidity and mortality. Hence, researchers aim to understand the oxidant–antioxidant balance COPD patients.

Homeostasis of Thiol/disulfide is one of the parameters that reflect oxidant balance[8]. Homesostasis of dynamic thiol/disulfide takes a major part in the maintenance of several physiological functions, such as antioxidant defense mechanisms, programmed cell death (or apoptosis), and stabilization of protein structures[9]. Only a few studies have evaluated thiol/disulfide homeostasis parameters in COPD[10]. As COPD is a chronic inflammatory disease that can lead to hypoxia and hypercapnia, we speculated that the thiol/disulfide homeostasis would be shifted towards disulfide formation and might provide a further insight both in diagnostic and prognostic perspective. Recently, attemps have been made to further define the exact prognostic indicators in cases of respiratory failure, However, there is no study to evaluate the prognostic importance of thiol/disulfhide homeostasis in patients with hypercapnic respiratory failure. Hence, in the present study, we aimed to investigate the association between the thiol/disulfide homeostasis and short-term mortality in patients with HRF patients.

MATERIALS AND METHODS

This prospective study includes patients treated in the Emergency Service and The Department of Pulmonary Medicine of the Ahi Evran University Training and Research Hospital between February 2018 and June 2019. Local ethics committee approval was obtained from Ahi Evran University Medical Faculty (Date: 09 January 2018; No: 2018- 01/09) and the study was in accordance with the Helsinki Declaration as revised in 2013.

Initially, 192 patients who had been admitted to the emergency service with hypercapnic respiratory failure (HRF) between the study dates were assessed for eligibility for inclusion to the study. Of these 192 patients, 122 were excluded on the basis on our exclusion criteria, and 6 did not give informed consent. Remaining 64 patients were included in the study. Forty healthy subjects were included in the study to comprise the control group. The HRF patients included were further divided into two subgroups as those in whom mortality occured after 1 month (n=14), and those who survived (n=50). Informed consent was obtained from each of the participants.

The criteria of exclusion were as follows: (a) acute or chronic infection (82 patients), (b) chronic liver or kidney disease (8 patients), (c) history of aortic valve replacement or severe cardiovascular disease (9 patients), (d) a family history of hypercholesterolemia (2 patients), (e) malignancy (2 patients), (f) malnutrition (1 patients), (g) recent medical operation (2 patients), (h) oral antioxidant or vitamin use (2 patients), (i) oral contraceptive use (1 patients) , (j) hormon replacement therapy (1 patients), and (k) active smoking (12 patients).

Patients were diagnosed with HRF by Emergency service or pulmonary medicine specialist physicians if the partial CO2 pressure was >45 mmHg, as per the criteria determined by the Turkish Respiratory Society, European Respiratory Society, and American Thoracic Society. The control group comprised healthy people that presented to the hospital for routine physical examination and did not have a history of disease or medication. Clinical and laboratory examinations confirmed that the healthy controls did not have any pathological conditions.

The following variables were obtained from all subjects: demographic data, age, gender, height, weight, BMI, and medical history. Additionally, the clinic providing treatment at the time of initial hospitalization and mortality rates were recorded for HRF patients.

Laboratory parameters

Blood samples were taken from HRF patients in the first three hours of admission and before administration of any medication. The samples were tested for complete blood count (CBC), liver and kidney functions, and coagulation profile. We centrifuged blood samples at 1500 rpm for 10 minutes. Centrifuged samples were stored in plain tubes at -80 °C until analysis.

Clinical chemistry results (blood glucose, urea, creatinine, alanine amino transferase (ALT), aspartate amino transferase (ASP), and C-reactive protein (CRP)) were measured using standard laboratory methods (Cobas 501; Roche Diagnostics®, Germany). Glomerular filtration rate (GFR) was estimated using the simplified MDRD GFR equation as defined by Levey: GFR = 186 × creatinine-1.154 × age-0.203 × 1.212 (if African American) × 0.742 (if female)[11].

The following methods were used for the measurement of CBC parameters: electrical impedance method for red blood cell (RBC) and platelet counts, optical light scattering measurement for white blood cell (WBC) count, photometric measurement for hemoglobin, and Sysmex XN-1000 (Sysmex Corporation, Kobe, Japan) for the remaining parameters. Lactate levels were measured from arterial blood samples using the Cobas® b221 Blood Gassystem (Roche, Basel, Switzerland).

Thiol/disulfide homeostasis parameters

Thiol/disulfide homeostasis markers [total thiol (TT), native thiol (NT), and disulfide (Ds)] were evaluated using a new and automated assay developed by Erel and Neselioglu (12). Obtained results were used to calculate Ds/TT and Ds/NT ratios.

Statistical analysis

Data were analyzed using IBM SPSS Statistics 21.0 for Windows (IBM Corp. Armonk, NY, USA). The Shapiro–Wilk test was chosen for testing the normal distribution of data. Continuous variables with normal distribution were expressed as mean ± standard deviation and continuous variables without normal distribution were expressed as median (min-max). Numbers and percentages were used for presenting categorical variables. Independent sample t-tests and the Mann–Whitney U Tests were used to compare continuous variables with normal distributions, and they were found appropriate. For the identification of mortality risk determinants, we used Cox regression analysis. Receiver operating characteristic (ROC) curve analysis was performed for determining prediction points of Thiol/disulfide homeostasis markers of HRF present and mortality. The point with the highest sensitivity and specificity and the Youden index was used to identify the predictive value. p\0.05 was considered significant for statistical analyses.

RESULTS

Table 1 shows the demorgraphic characteristics along with laboratory findings of both patient and control group. The mean ages of all subjects, the HRF patients, and the control group were 68.44±8.76, 69.51±10.27, and 66.72±7.26 years, respectively. The two groups were not significantly different in demographic properties (age, gender, height, weight) or hypertension and type II diabetes rates. Baseline laboratory parameters except CRP were similar between the groups. Median CRP level was significantly higher in HRF group compared with the healthy controls (2.3 mg/L vs 1.0 mg/L; p=0.015)

We found lower levels of mean TT and mean NT in the group with HRF comparing to the control group (314.0±65.4 vs. 423.6±56.6, p<0.001; 276.9±61.8 vs. 381.4±57.5; p<0.001, respectively), whereas the mean ratios of Ds/TT and Ds/NT were higher (6.0±1.5 vs. 4.3±0.8; p<0.001; 6.9±2.0 vs. 4.8±1.0; p<0.001, respectively). The Ds levels did not reach significant levels of difference (p=0.522).

It was found that both TT and NT levels were valuable for the diagnosis of HRF (AUC:0.896, 95% CI:0.821-0.947, p<0.05; AUC:0.885, 95% CI:0.807-0.939, p<0.05; respectively). The cut-off value for TT was determined as≤ 371.0 μmol/L, while the sensitivity was 85.9% and specificity was 80.0%. The cut-off value for NT was determined as ≤ 310.0 μmol/L, and the sensitivity and specificity were 73.4% and 90.0%, respectively (Table 2, Figure 1).

Table 1. Clinical demographic and laboratory findings of study population

Variables	HRF Group n=64	Control Group n=40	p
Gender, n(%)			
Female	21 (32.8)	13 (32.5)	0,999
Male	43 (67.2)	27 (67.5)	
Age (years)	69.5±10.3	66.7±7.3	0.108
BMI (kg/m2)	27.6±6.7	26.7±3.8	0.339
Hypertension, n(%)	30 (46.9)	19 (47.5)	0.999
Diabetes Mellitus, n(%)	18 (28.1)	11 (27.5)	0.999
Hemoglobin, (gr/dL)	13.6±2.6	13.2±1.8	0.357
WBC, ($x10^3\mu/L$)	8.8 (2.7-22.3)	9.0 (2.4-18.5)	0.920
Platelets, ($x10^3\mu/L$)	227.0 (72.0-362.0)	222.0 (98.0-408.0)	0.925
FBS, (mg/dL)	124.5 (74.0-412.0)	108.5 (74.0-329.0)	0.115
GFR, ($ml/min/1.73m^2$)	76.0±24.4	79.0±18.1	0.478
Urea, (mg/dL)	49.5 (19.0-126.0)	48.5 (21.0-111.0)	0.635
Creatinine, (mg/dL)	0.9 (0.3-2.8)	0.9 (0.3-2.5)	0.716
ALT, (IU/L)	14.5 (5.0-125.0)	14.5 (5.0-121.0)	0.478
AST, (IU/L)	19.5 (7.0-94.0)	18.5 (7.0-73.0)	0.804
CRP (mg/L)	2.3 (0-106)	1.0 (0.1-22.2)	0.015*
Total thiol (mmol/L)	314.0±65.4	423.6±56.6	<0.001*
Native thiol (mmol/L)	276.9±61.8	381.4±57.5	<0.001*
Disulphide (mmol/L)	18.4±4.3	17.9±3.0	0.522
Native thiol/total thiol (%)	88.0±3.4	89.9±3.4	0.008*
Disulphide/total thiol (%)	6.0±1.5	4.3±0.8	<0.001*
Disulphide/native thiol (%)	6.9±2.0	4.8±1.0	<0.001*

WBC, White blood cells; FBS, Fasting blood sugar; GFR, Glomerular filtration rate; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CRP, C-reactive protein; Numerical variables were shown as mean±standart deviaton or median(min-max).

Table 2. Diagnostic performance assessment of oxidative stress markers for predicting hypercapnic respiratory failure

Variables	AUC±SE	%95 CI	p	Cut-off value	Sensitivity (%)	Specificity (%)	+PV (%)	-PV (%)
Total thiol (mmol/L)	0.896±0.03	0.821-0.947	<0.001*	≤ 371	85.9	80.0	87.3	*78.0*
Native thiol (mmol/L)	0.885±0.03	0.807-0.939	<0.001*	≤ 310	73.4	90.0	92.2	*67.9*
Disulphide (mmol/L)	0.531±0.06	0.430-0.629	0.586	-	-	-	-	-
Native thiol/Total thiol (%)	0.679±0.06	0.581-0.767	0.001*	≤ 90.0	78.1	57.5	74.6	*62.2*
Disulphide/Total thiol (%)	0.873±0.04	0.794-0.931	<0.001*	> 4.93	89.1	85.0	90.5	*82.9*
Disulphide/Native thiol (%)	0.860±0.04	0.778-0.920	<0.001*	> 5.88	78.1	92.5	94.3	72.5

AUC, Area under the curve Hazard ratio; SE, Standart error; CI, Confidence interval, +PV, Positive predictive value; +PV, Negative predictive value

Table 3 shows the risk factors associated with in-hospital mortality in HRF patients. Fourteen HRF patients (21.9%) died in the hospital. Baseline laboratory parameters, CRP, TT and NT values were not found to be the risk factors for in-hospital mortality. However, Ds, Ds/TT, and Ds/NT values were significantly higher in patients who died (21.9±3.6 vs. 17.4±4.0, p<0.05;7.1±1.8 vs. 5.7±1.3, p<0.05; 8.6±2.6 vs. 6.5±1.6, p<0.05, respectively).

The diagnostic value of Ds levels in predicting mortality was assessed with ROC curve analysis. The cut-off value was calculated to be 19.0 μmol/L with 85.7% sensitivity and 70.0% specificity (AUC: 0.793, 95% CI: 0.673-0.884, p<0.001) (Table 4, Figure 1).

Table 3. The risk factors associated with in-hospital mortality in hypercapnic respiratory failure

Variables	In hospital mortality		Univariable Cox Regression	
	Alive n=50	Exitus n=14	HR(95% CI)	*p*
Gender,n (%)				
Female	16 (32.0)	5 (35.7)	ref	
Male	34 (68.0)	9 (64.3)	0.92 (0.30-2.78)	0.879
Age (years)	68.8±9.5	71.9±12.9	1.01 (0.97-1.06)	0.610
BMI (kg/m2)	27.5±6.8	28±6.2	1.03 (0.95-1.11)	0.538
Hypertension, n(%)	24 (48.0)	6 (42.9)	0.89 (0.31-2.59)	0.829
Diabetes Mellitus, n(%)	12 (24.0)	6 (42.9)	3.02 (0.92-9.90)	0.108
CRP (mg/L)	1.4 (0-106)	6.7 (0.7-36.4)	1.01 (0.98-1.04)	0.291
Total thiol (mmol/L)	312.4±59.7	319.6±85.1	1.00 (0.99-1.01)	0.650
Native thiol (mmol/L)	276.9±54.9	277.1±84.3	1.00 (0.99-1.01)	0.950
Disulphide (mmol/L)	17.4±4.0	21.9±3.6	1.23 (1.07-1.40)	0.003*
Native thiol/total thiol (%)	88.6±2.8	85.9±4.3	0.83 (0.72-0.96)	0.010*
Disulphide/total thiol (%)	5.7±1.3	7.1±1.8	1.52 (1.11-2.07)	0.008*
Disulphide/native thiol (%)	6.5±1.6	8.6±2.6	1.37 (1.11-1.69)	0.004*

Numerical variables were shown as mean±standart deviaton or median(min-max). HR, Hazard ratio; CI, Confidence interval; CRP, C-reactive protein

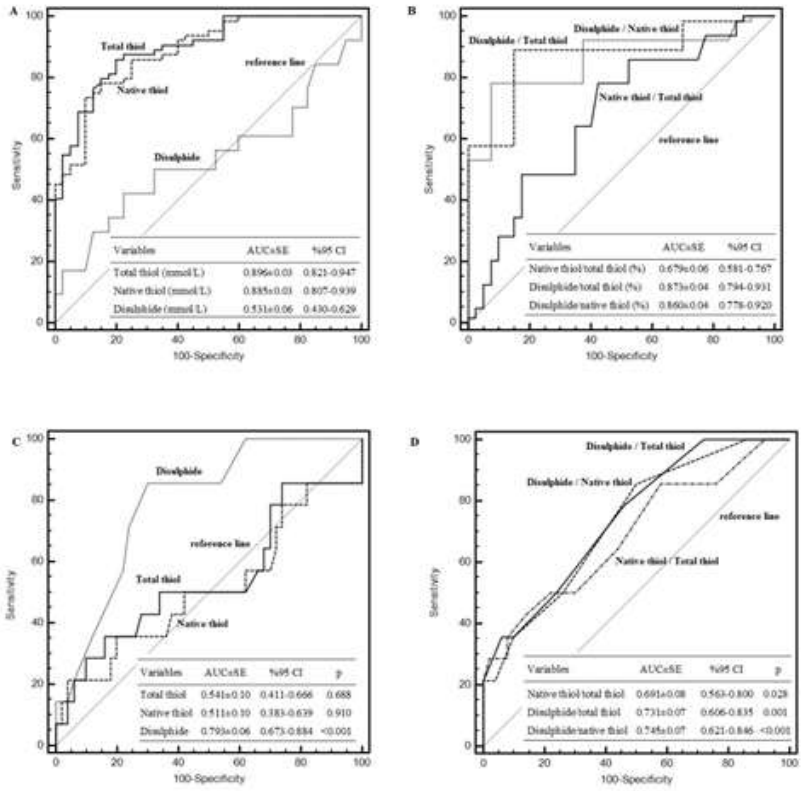

Figure 1. Diagnostic performance evaluation of thiol / disulfide homeostasis markers in predicting HRF and mortality (A-B: predicting HRF; C-D: predicting mortality

Table 4. Diagnostic performance evaluation of oxidative stres markers for predicting in-hospital mortality in hypercapnic respiratory failure

Variables	AUC±SE	%95 CI	p	Cut-off value	Sensitivity (%)	Specificity (%)	+PV (%)	-PV (%)
Total thiol (mmol/L)	0.541±0.10	0.411-0.666	0.688	-	-	-	-	-
Native thiol (mmol/L)	0.511±0.10	0.383-0.639	0.910	-	-	-	-	-
Disulphide (mmol/L)	0.793±0.06	0.673-0.884	<0,001	>19	85.7	70.0	44.4	94.6
Native thiol/Total thiol (%)	0.691±0.08	0.563-0.800	0.028*	≤ 85	42.9	86.0	46.2	84.3
Disulphide/Total thiol (%)	0.731±0.07	0.606-0.835	0.001*	> 5	85.7	50.0	32.4	92.6
Disulphide/Native thiol (%)	0.745±0.07	0.621-0.846	<0,001	>6	75.6	54.0	32.4	90.0

AUC, Area under the curve Hazard ratio; SE, Standart error; CI, Confidence interval, +PV, Positive predictive value; +PV, Negative predictive value

DISCUSSION

Our study is the first to analyze the difference of thiol/disulfide homeostasis between COPD patients and healthy controls and to study its correlation with COPD mortality. We found that HRF patients' NT and TT levels were lower, and their Ds/TT and Ds/NT ratios were higher than those of healthy controls. Additionally, Ds, Ds/TT, and Ds/NT values were significantly higher for HRF patients who died.

Inflammatory cells, such as neutrophils and macrophages, and cigarette smoke are the main sources of oxidant substances in COPD[12,13]. Under physiological conditions, antioxidants such as superoxide dismutase, glutathione, and vitamin C protect the organism against oxidative stress. However, COPD patients' antioxidant levels are significantly low despite increased oxidative stress[14]. It has been shown that COPD patients have increased oxidative stress markers (such as hydrogen peroxide and 8-isoprostane) in peripheral blood, expired air, and induced sputum, which becomes more prominent during exacerbations.

Plasma thiols play a major role in physiological and biological phenomena due to their reversible pro- and antioxidant properties owing to -SH groups[15,16]. The most abundant human plasma thiols are cysteine and homocysteine, respectively. Thiol (R-SH) and disulfide (R-S-S-R) compounds take part in a variety of biochemical functions including protein configuration stabilization, protein and enzyme regulation, carriers and receptors, Na/K transport, and RNA transcription[17]. The pro- or antioxidant effect of thiols will be determined by oxidative stress levels, physiological and biological conditions, and the amount of sulfur-containing amino acids. Thiol groups can inhibit free radicals. The first sign of oxidation caused by ROS is the transformation of thiol groups (-SH) into disulfide groups (-SS-) and oxidized compounds like oxyacids[8].

The lungs are the organs that are most exposed to oxidative stress[18]. Oxidant accumulation in airways leads to defects in genetic material, impairment of the ciliary matrix and functions, and disrupted biological membranes, and it also increases mucus and cytokine production and decreases surfactant activity[19]. Hence, it is important to understand the functions of thiols, which are a part of the antioxidant system, in order to better understand various oxidative stress-related diseases, including COPD.

Babaoglu et al. studied thiol/disulfide homeostasis in the context of asthma, COPD and asthma-COPD overlap syndrome. In all three groups, thiol/disulfide homeostasis was disrupted in favor of disulfide formation[10]. Sengoren et al. reported that patients with obstructive sleep apnea had lower NT and TT levels[20]. Eroğlu et al. and Nar et al. found that Ds levels were not significantly different in COPD and asthma patients, but Ds/TTand Ds/NT ratios were significantly increased[21,22]. We have similarly found that decreased antioxidant activity and increased oxidant levels caused the disruption of thiol/disulfide homeostasis in favor of disulfide formation. We hypothesize that this process is related with increased reactive oxygen radicals in COPD due to chronic inflammation, hypoxia, and hypercarbia[13].

A study by Şahin et al. found a relationship between thiol/disulfide imbalance and bronchial hyperresponsiveness, which was associated with irreversible airway obstruction and damage[23]. Rahman et al. reported insufficient antioxidant response during COPD exacerbation that lasted for 48 hours[13]. They found a dose and time-dependent depletion of intracellular soluble antioxidant, one study showed that oxidative stress products oxidize various molecules, such as thiols and fatty acids, and produce new radical molecules[24]. Thus, lower plasma thiol concentrations might suggest increased oxidative stress and the disruption of thiol/disulfide homeostasis in favor of disulfide formation[25].

In the study of Topuz et al., Ds levels were higher in patients with high-risk scores according to the Pulmonary Embolism Severity Index and they associated this finding with higher mortality[26]. In the study of Şener et al., NT values were found to be lower in a significant level among patients with high-risk scores according to the Pulmonary Severity Index[27]. Similarly, we found that Ds, Ds/TT, and Ds/NT values were significantly higher among the HRF patients who died. A diagnostic Ds cut-off value was determined with ROC curve analysis, showing that high Ds levels are associated with mortality. This finding may suggests a possibility of an index correlating thiol/disulfide homeostasis and the severity of HRF.

These might be considered as the limitations of this study: (a) the monocentric nature of the study, as well as the small sample size; (b) the exclusion of total oxidant and total antioxidant status evaluation; (c) the indeterminate objectivity of thiol/disulfide homeostasis as an indicator of mortality.

As a future perspective, large-scale studies are needed to better delineate the exact relationship of thiol/disulfide homeostasis with short-term as well as long-term mortality in HRF patients. Moreover, future studies assessing the effect of administration of various anti-oxidant therapies especially during the acute phase of HRF in an attempt to decrease short- and long-term mortality can be planned.

We conclude that several factors (Chronic inflammation, hypoxia, hypercarbia, other complications) lead to increased oxidative stress and a subsequent increase in disulfide levels. We have also observed that disturbed thiol/disulfide homeostasis may predict mortality.

Yazar Katkıları: Çalışma konsepti/Tasarımı: HMÇ; Veri toplama: HMÇ, DZK, Bİ; Veri analizi ve yorumlama: HMÇ, ZKE; Yazı taslağı: HMÇ; İçeriğin eleştirel incelenmesi: Bİ, DZK; Son onay ve sorumluluk: HMÇ, Bİ, DZK, ZKE, BÇ, SE; Teknik ve malzeme desteği: Bİ; Süpervizyon: SE, BÇ; Fon sağlama (mevcut ise): yok.
Etik Onay: Bu çalışma için Ahi Evran Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulundan 09.01.2018 tarih ve 2018-01/09 74 sayılı kararı ile etik onay alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.
Yazarın Notu: Dr. Yusuf Dursun'a katkılarından dolayı teşekkür ediyoruz.

Author Contributions: Concept/Design : HMÇ; Data acquisition: HMÇ, DZK, Bİ; Data analysis and interpretation: HMÇ, ZKE; Drafting manuscript: HMÇ; Critical revision of manuscript: Bİ, DZK; Final approval and accountability: HMÇ, Bİ, DZK, ZKE, BÇ, SE; Technical or material support: Bİ; Supervision: SE, BÇ; Securing funding (if available): n/a.
Ethical Approval: Ethical approval was obtained for this study from the Ahi Evran University Faculty of Medicine Clinical Research Ethics Committee with the decision dated 09.01.2018 and numbered 2018-01 / 09 74.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support
Acknowledgement: Dr. We thank Yusuf Dursun for his contributions.

REFERENCES

1. WHO. Global health estimates: Causes of death, 2000–2016; Top 10 global causes of death. Geneva, WHO, 2018.
2. Senior RM. Chronic obstructive pulmonary disease: Epidemiology, pathophysiology, and pathogenesis. Fishman's Pulm disease and disorders (EDs MA Grippi, JA Elias):659. New York, Mc Graw Hill, 1997.
3. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet. 2007;370:765-73.
4. Markou NK, Myrianthefs PM, Baltopoulos GJ. Respiratory failure: an overview. Crit Care Nurs Q. 2004;27:353-79.
5. Rodriguez-Roisin R, MacNee W. Pathophysiology of chronic obstructive pulmonary disease. Eur Resp Mon. 2006;38:177.
6. Domej W, Oettl K, Renner W. Oxidative stress and free radicals in COPD–implications and relevance for treatment. Int J Chron Obstruct Pulmon Dis. 2014;9:1207-24.
7. Douglas RM, Ryu J, Kanaan A, Rivero MC, Dugan LL, Haddad GG et al. Neuronal death during combined intermittent hypoxia/hypercapnia is due to mitochondrial dysfunction. Am J Physiol. 2010;298:1594-602.
8. Kaplan M, Ates I, Yuksel M, Ozin YO, Alisik M, Erel O et al. Thiol/disulphide homeostasis in celiac disease. World J Gastrointest Pharmacol Ther. 2017;8:120-6.
9. Ates I, Ozkayar N, Altay M, Yilmaz FM, Topcuoglu C, Alisik M et al. Is disulphide/thiol ratio related to blood pressure inmasked hypertension? Clin Exp Hypertens. 2016;38:150-4.

10. Babaoglu E, Kilic H, Hezer H, Dag O, Parlak E, Senturk A et al. Comparison of thiol/disulphide homeostasis parameters in patients with COPD, asthma and ACOS. Eur Rev Med Pharmacol Sci. 2016;20:1537-43.
11. Levey AS, Berg RL, Gassman JJ, Hall PM, Walker WG. Creatinine filtration, secretion and excretion during progressive renal disease. Modification of Diet in Renal Disease (MDRD) Study Group. Kidney Int Suppl. 1989;27:73-80.
12. Rodriguez-Roisin R, Rabe KF, Vestbo J, Vogelmeier C, Agustí A. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 20th Anniversary: a brief history of time. Eur Respir J. 2017;50:1700671.
13. Rahman I, MacNee W. Oxidant/antioxidant imbalance in smokers and chronicobstructive pulmonary disease. Thorax. 1996;51:348.
14. Gülbay B. Patogenez AT and İnflamasyon. Güncel Bilgiler Işığında Kronik Obstrüktif Akciğer Hastalığı (EDs SB Saryal, T Acıcan):21-33: Ankara, Bil Tıp Yayınları, 2003.
15. Yuksel M, Ates I, Kaplan M, Alisik M, Erel O, Saygılı F et al. The dynamic thiol/disulphide homeostasis in inflammatory bowel disease and its relationship with disease activity and pathogenesis. Int J Colorectal Dis. 2016;31:1229-31.
16. Kundi H, Ates I, Kiziltunc E, Cetin M, Cicekcioglu H, Neselioglu S et al. A novel oxidative stress marker in acute myocardial infarction; thiol/disulphide homeostasis. Am J Emerg Med. 2015;33:1567-71.
17. Ates I, Altay M, Yilmaz FM, Topcuoglu C, Neselioglu S, Erel O et al. Dynamic thiol/disulfide homeostasis in patientswith autoimmune subclinical hypothyroidism. Endocr Res. 2016;41:343-49.
18. Orhan Z, Köksal N, Gökırmak M, Hacıevliyagil SS, Hasanoğlu HC, Mehmet N et al. KOAH akut alevlenmesinde oksidatif stres ve tedavinin oksidan-antioxidant denge üzerine etkisi. Resp Dis. 2003;14:5-10.
19. Weinberger B, Laskin JD, Sunil VR, Sinko PJ, Heck DE, Laskin DL. Sulfur mustard-induced pulmonary injury: therapeutic approaches to mitigating toxicity. Pulm Pharmacol Ther. 2011;24:92-9.
20. Sengoren Dikis O, Acat M, Casim H, Haskul I, Neselioglu S, Simsek A et al. The relationship of thiol/disulfide homeostasis in the etiology of patients with obstructive sleep apnea: a case-control study. Aging Male. 2020;23:679-86.
21. Eroğlu O, Badem ND, Baccıoğlu A, Comertpay E, Neselioglu S, Erel O. Significance of thiol/disulphide homeostasis and ischemia modified albumin levels in chronic obstructive pulmonary disease. European Research Journal 2019;5:250-7.
22. Nar R, Çalış AG. Assessment of dynamic thiol/disulfide homeostasis in patients with asthma. Med Lab. 2018;42:99-104.
23. Şahin Ü, Ünlü M, Sütçü R, Delibaş N, Akkaya A. Akut KOAH Alevlenmesiyle başvuran hastalarda tedavinin oksidan/antioxidant sistem üzerine olan etkisi. Tüberküloz ve Toraks Dergisi. 2000;48:317-24.
24. Akbas A, Kilinc F, Sener S, Aktas A, Baran P, Ergin M. Investigation of thiol-disulphide balance in patients with acute urticaria and chronic spontaneous urticaria. Cutan Ocul Toxicol. 2017;36:205-10.
25. Özcan O, Erdal H, Çakırca G, Yonden Z. Oxidative stress and its impacts on intracellular lipids, proteins and DNA. J Clin Exp Invest. 2015;6:331-6.
26. Topuz M, Kaplan M, Akkus O, Sen O, Yunsel HD, Allahverdiyev S et al. The prognostic importance of thiol/disulfide homeostasis in patients with acute pulmonary thromboembolism. Am J Emerg Med. 2016;34:2315-9.
27. Şener A, Çelik GK, Özhasenekler A, Gökhan Ş, Tanrıverdi F, Kocaoğlu S et al. Evaluation of dynamic thiol/disulfide homeostasis in adult patients with community-acquired pneumonia. Hong Kong Journal of Emergency Medicine. 2018;26:343-50.