Annals of R.S.C.B., ISSN: 1583-6258, Vol. 25, Issue 5, 2021, Pages. 5616 - 5625
Received 15 May 2021; Accepted 20 May 2021.

Impact of Smoking Status on Biochemical and Haematological Parameters in Non-ST Elevation Acute Coronary Syndromes

Zainab Atiyah Dakhil[1,2*]
[1]Al-Kindy College of Medicine, University of Baghdad, Baghdad, Iraq
[2] Ibn Al-Bitar Cardiac Centre, Baghdad, Iraq

*stethoscope.med@gmail.com

ABSTRACT

Background: Smoking is a leading preventable cause of mortality and has remarkable negative impact on cardiovascular diseases. Despite many studies focused on impact of smoking on prognosis of patients with acute coronary syndrome (ACS) but no prior studies up to our knowledge focused on how smoking can confound the investigational parameters in ACS. So, this study aimed to assess the impact of smoking on biochemical and haematological parameters in patients with Non-ST-Elevation ACS (NSTE-ACS).
Methods: This is a sub study analysis from a cross-sectional study, which recruited admittedpatients who were diagnosed as acute coronary syndrome, the sub study analysis included only NSTE-ACS patients who were admitted to two teaching hospitals, patients' data were collected including laboratory parameters.
Results: Ninety-nine patients were recruited, 22.22% were females, 63.63% were smokers. Smokers were younger age group (54.9±11.4 years versus 61.5±11.8 years, p=0.009), more to be males, and less to have IHD (27.77% versus 53.96%, p=0.01) than non-smoker counterparts. Smokers had higher serum potassium level (4.4±0.6 versus 4.1±0.5, p=0.02) as well as higher haemoglobin level (13.9±1.8 versus 13.1±2.2, p=0.04), while non-smokers had higher urea than smokers (45.8±25.4 versus 36.02±12.8, p=0.03).
Conclusion: In the context of NSTE-ACS, smokers were younger, more to be males and diabetic but less to be hypertensive than non-smokers, they had higher haemoglobin and potassium levels. Further studies needed to validate the prognostic significance of laboratory markers in smokers compared to non-smoker counterparts in order to address if smoking status should impact the risk stratification of this group to guide management strategy.

Keywords
Laboratory; Biomarker; Cost-Effectiveness; Tobacco; Risk

Introduction

Smoking is a leading preventable cause of death worldwide [1], it causes cardiovascular diseases like ischaemic heart disease (IHD), peripheral arterial disease, and stroke [2-5]. Proposed mechanisms of such negative cardiovascular impacts are abnormal blood rheology, infection and inflammation, oxidative stress, and altered antithrombotic and fibrinolysis systems [2].
As it is common for smokers to develop IHD, it is predicted that acute coronary syndrome (ACS) can occur frequently in them, ACS involves inflammatory and hypoxemic processes resulting in changes in erythropoietin, interleukin-3 and interleukin-6 [2,6] which can cause many variations in haematological parameters in this population [1] with prognostic use of such parameters, for example, high white blood cell count (WBC) is considered an indicator of higher death at 1 and 6 months after myocardial infarction [7].
Biochemical parameters are also affected in ACS whether troponin in myocardial injury [8], or renal indices (urea and creatinine) and electrolytes like potassium which were reported to be important markers of prognosis in ACS patients, and even suggested to play a role in the pathogenesis of ACS [9]. It is unknown if patients' comorbidities like smoking can confound the diagnostic or prognostic significance of biochemical and haematological parameters in ACS as there are limited studies discussed the impact of smoking status on these parameters in ACS

Annals of R.S.C.B., ISSN: 1583-6258, Vol. 25, Issue 5, 2021, Pages. 5616 - 5625
Received 15 May 2021; Accepted 20 May 2021.

patients. Accordingly, this study aimed to evaluate the impact of smoking on biochemical and haematological parameters in patients with NSTE-ACS.

Patients and Methods

Design and patients' selection: This is a sub study analysis from a cross-sectional study, which recruited admitted patients who were diagnosed as acute coronary syndrome, the sub study analysis includes only NSTE-ACS patients (Patients with acute chest pain with no persistent ST elevation).
Study excluded: Patients with persistent ST elevation or new/presumed new left bundle branch block (LBBB), malignancy or terminal illness, end stage renal disease or end stage liver disease. Patients were grouped according to their self-reported smoking status into those who were smokers versus non-smokers.

Setting and duration: The study recruited patients from two teaching hospitals (Al-Yarmouk Teaching Hospital and Ibn Al-Bitar Cardiac Centre) during the period from February 2018 to January 2019.

Demographic characteristic: Each patient was interviewed during hospitalization and a pre-set form was filled by the investigator, this form included patient age, gender, comorbidities, symptoms at presentation.

Biochemical and haematological assays: Venous blood sample (10 ml) was collected from each patient at admission as part of the routine work up during hospitalization, blood sample was collected using a disposable needles and plastic syringes. Every sample was divided into two tubes: two ml put into one tube that contained EDTA for haematological assays (haemoglobin, WBC and platelet count) and the remaining 8 ml put into the second tube and left at room temperature for 10-15 minutes for clotting, then centrifuged at 3600 rpm for 10 minutes, the obtained serum will be transferred then into a new tube and frozen at -20℃ to be used for biochemical analysis (Troponin, urea, creatinine and electrolytes). The blood sample collection and analysis were done by the lab workers in the recruited hospitals. The investigator then abstracted results from patient lab records.

Ethical Approval: The study was performed in accordance with the declaration of Helsinki and followed the local ethical and scientific committee guideline. Acceptance consent to be enrolled in the study was obtained from all patients.

Data Analysis

Collected data were coded and input into computer using SPSS version 24. Numerical variables were expressed as mean ± standard deviation, categorical variables were expressed as frequencies and percentages. Numerical variables were compared using t-test, while categorical variables were compared using Chi-Square test.

Annals of R.S.C.B., ISSN: 1583-6258, Vol. 25, Issue 5, 2021, Pages. 5616 - 5625
Received 15 May 2021; Accepted 20 May 2021.

Results

Ninety-nine patients were recruited including 22 (22.22%) females, 63.63% were smokers. Smokers were younger age group (54.9±11.4 years versus 61.5±11.8 years, p=0.009), more to be males, and less to have IHD (27.77% versus 53.96%, p=0.01) than non-smokers counterparts. No significant difference regarding presence of diabetes, hyperlipidaemia or stroke according to smoking status, table 1.

Smokers were less to have chest pain or dyspnoea on presentation when compared to non-smokers, yet, this difference did not reach statistical significance, figure 1.

Current study revealed higher serum potassium level (4.4±0.6 versus 4.1±0.5, p=0.02) as well as higher haemoglobin level (13.9±1.8 versus 13.1±2.2, p=0.04) in smokers compared to non-smoker patients, while non-smokers had higher urea than smokers (45.8±25.4 versus 36.02±12.8, p=0.03), other laboratory parameters including RBS, creatinine, sodium levels, WBC or platelet count did not differ significantly between the two groups same as troponin positivity status, table 2 and figure 2.

Moreover, there was statistically significant negative correlation between left ventricular ejection fraction in recruited patients and RBS, urea and creatinine levels.

Table 1. Baseline Characteristics in NSTE-ACS According to Smoking Status

Variable	Non-smokers		Smokers		P value
	n.	%	n.	%	
Number of patients	63	63.63	36	36.36	
Mean age (years) mean±SD	61.5±11.8	-	54.9±11.4	-	0.009
Female gender	19	30.15	3	83.33	0.01
Hypertension	42	66.66	18	50	0.1
Diabetes	37	58.73	23	63.88	0.61
History of IHD	34	53.96	10	27.77	0.01
Hyperlipidaemia	17	26.98	15	41.66	0.13
Positive family history of IHD	15	23.8	17	47.22	0.01
Stroke	7	11.11	1	2.77	0.14
Ejection fraction (%) mean±SD	50.4±12.7	-	56.4±13.5	-	0.055

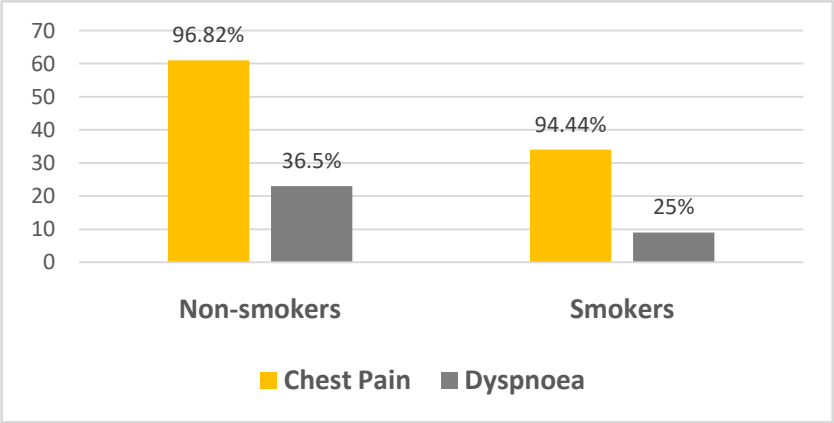

Figure 1. Clinical Presentation in NSTE-ACS patients According to Smoking Status*

Annals of R.S.C.B., ISSN: 1583-6258, Vol. 25, Issue 5, 2021, Pages. 5616 - 5625
Received 15 May 2021; Accepted 20 May 2021.

***Chest pain: p=0.27, dyspnoea: p=0.23**

Table 2. Laboratory Parameters in NSTE-ACS According to Smoking Status

Laboratory Parameter	Mean±SD		p value
	Non-smokers	Smokers	
RBS (mg/dl)	190.6±114.5	166.3±93.8	0.28
Urea (mg/dl)	45.8±25.4	36.02±12.8	0.03
Creatinine (mg/dl)	1.04±0.4	0.92±0.28	0.11
Potassium (mg/dl)	4.1±0.5	4.4±0.6	0.02
Sodium (mg/dl)	136.9±4.2	136.8±4.7	0.9
Haemoglobin gm/L	13.1±2.2	13.9±1.8	0.04
WBC count	(9.03±2.9) $\times 10^3$mcL	(10.2±3.6) $\times 10^3$mcL	0.09
Platelet count	(221.2±67.3)$\times 10^3$mcL	(229.5±64.5) $\times 10^3$mcL	0.55

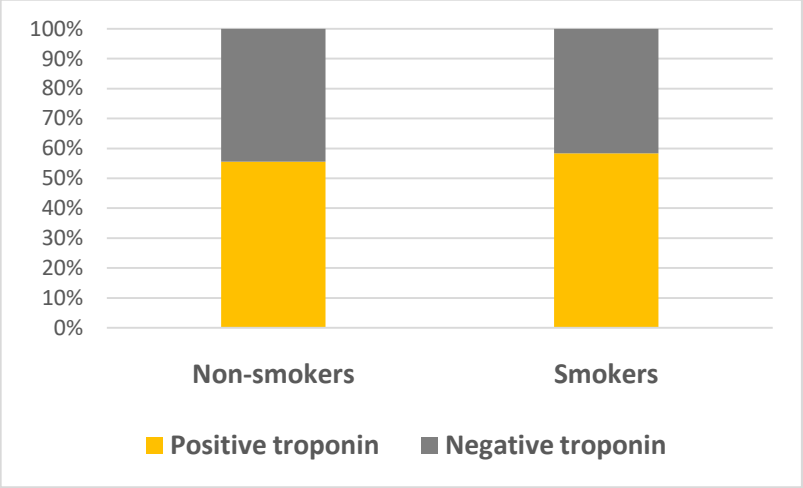

Figure 2. Troponin Status in NSTE-ACS patients According to Smoking Status*
***p=0.78**

Table 3. Correlation of Laboratory Parameters with Left ventricular Ejection Fraction in NSTE-ACS Patients

Laboratory parameter	Pearson correlation with left ventricular ejection fraction (N=76 cases) *	p value
RBS	-0.256	0.026
Urea	-0.23	0.048
Creatinine	-0.33	0.004
Potassium	0.14	0.23
Sodium	-0.14	0.9
Haemoglobin	0.14	0.23
WBC count	-0.01	0.9
Platelet count	-0.07	0.57

* Echocardiography results were available from records in 76 patients.

Annals of R.S.C.B., ISSN: 1583-6258, Vol. 25, Issue 5, 2021, Pages. 5616 - 5625
Received 15 May 2021; Accepted 20 May 2021.

Discussion

Earlier studies assessed the laboratory profile of patients with acute coronary syndromes especially with the low cost of such markers and how they can provide insight for patients' diagnosis and prognosis [6,10,11], yet there is limited data regarding impact of comorbidities and cardiovascular risk factors on laboratory results and subsequent decision making of management in this population. In low-middle income countries, it is crucial to make use of all bedside risk stratification tools and feasible low-cost markers to stratify patients to guide management strategy and it will be helpful to know what clinical variables can confound these laboratory markers. Accordingly, current study highlighted this issue and disclosed no remarkable impact of smoking on myocardial injury parameters (i.e. troponin) nor on inflammatory parameters (like WBC) nor thrombosis parameters (like platelet), however, there was remarkable increase in potassium level as well as haemoglobin level in smokers with NSTE-ACS compared to their non-smoker counterpart. Up to our knowledge, no prior study assessed impact of smoking on laboratory parameters in NSTE-ACS patients in particular.

This study revealed that smokers are younger age, more to be males, with less incidence of hypertension (HT) and IHD but more to have diabetes (not reaching statistical significance) and positive family history of IHD, prior studies suggested higher prevalence of cardiovascular risk factors including older age, HT and diabetes in smokers [12,13]. Diabetes is a well-known risk factor for cardiovascular disease [14], however diabetes and HT were reported higher in non-smokers by other researchers [1].

This study showed that smokers were less to be presented with typical ischaemic chest pain as well as having lower dyspnoea rate than non-smokers, dyspnoea can occur in context of ACS as part of angina equivalent or due to heart failure, however, smokers in this study had higher left ventricular ejection fraction than non-smokers, which may explain more dyspnoea in non-smokers due to more prevalence of heart failure, this was consistent with other studies [1,13,15], however, these studies included STEMI and NSTE-ACS patients unlike our study that focused on NSTE-ACS patients only where data extremely lacking regarding impact of smoking as predictor of heart failure in those patients.

Current study showed higher RBS in non-smokers than smokers, despite higher incidence of diabetes in smoking group as smoking can cause diabetes by producing reactive oxygen species which cause oxidative damage as lipid peroxidation, protein oxidation and DNA damage, also higher cortisol in smokers leading to higher blood glucose levels [16-20], however, the difference between study groups was not statistically significant. Blood urea was higher in non-smokers than smoker counterparts with no significant difference in creatinine level. In the setting of ACS, higher renal indices are important predictors of worse cardiovascular outcomes in ACS [9,21], despite smoking causes reduction in glomerular filtration rate by increased oxidative stress and activation of the renin-angiotensin system [22,23] but having lower renal indices in smokers in this study can be due to older age group with multiple atherosclerotic comorbidities including hypertension in non-smokers. Potassium increased significantly in smokers compared to non-smokers in this study, cigarettes contain many chemicals including nicotine, tar and CO, CO causes tissue hypoxia, increased carboxyhaemoglobin and decreased oxyhaemoglobin which cause respiratory acidosis and electrolyte imbalance including higher potassium, also smoking results in tissue necrosis and skeletal damage causing leak of potassium into serum [24-29].

Smoking results in a procoagulant state with endothelial dysfunction, higher platelet activation and aggregation, along with higher fibrinogen level and thrombin generation, smoking also

causes impairment of fibrin crosslinking resulting in thrombogenic status that contributes to pathogenesis of acute coronary syndromes in this population [30-33]. Carboxyhaemoglobin that results from smoking has no oxygen binding capacity and shifts Hb dissociation curve to the left causing lower ability of oxygen delivery to tissues, accordingly, smokers have higher haemoglobin level as a compensatory mechanism [2,34], moreover, the higher rate of carboxyhaemoglobin, the lower transportation capacity of oxygen by haemoglobin leading to functional anaemia in form of reduced exercise tolerance in smokers [35]. Carbon monoxide increases the capillary permeability which decreases the plasma volume resulting in higher haematocrit in smokers [36,37]. Furthermore, the lower oxyhaemoglobin in smokers causes the higher erythropoietin with subsequent higher haematocrit levels, it had also been suggested that the blood concentration of carboxyhaemoglobin increased in relation to the number of smoked cigarettes [38].This study disclosed more positive troponin in non-smokers than smokers, this was unexpected considering the negative impact of smoking on heart suggesting higher rate of myocardial injury with subsequent positive troponin, yet Lyngbakken et al had found in (THE HUNT) study that lower cardiac troponin I detected in healthy smokers when compared to non-smokers healthy population suggesting that tobacco chemicals may affect myocyte injury and negative cardiovascular effect of smoking is mediated via mechanisms other than subclinical myocardial injury [39].

Conclusion

In context of NSTE-ACS, smokers were younger, more to be males and diabetic but less to be hypertensive and with IHD than non-smokers, they had higher haemoglobin and potassium levels reflecting the effect of carboxyhaemoglobin and tissue hypoxia in smokers. Further studies needed to validate the prognostic significance of these laboratory markers in smokers compared to non-smoker counterparts in order to address if smoking status should impact the risk stratification of this group to guide management strategy especially if we consider the cost-effectiveness of these markers in low-resources countries.

Limitations and Future Studies

We did not assess the correlation between the smoking pack year and laboratory markers, the study also did not assess the prognostic impact of smoking. Additionally, quantitative troponin assays as well as high sensitivity troponin were not available in our facilities due to limited resources, so, qualitative assays used alternatively. Larger population sample is needed in future to further validate the statistical results.

Acknowledgement

The author thanks Mohammed A. Dakhil for his help in data collection in general and blood sample collections and analysis in particular, the author also thanks the medical staff and lab workers at Al-Yarmouk Teaching Hospital and Ibn Al- Bitar Cardiac Centre for their help during data collection process.

References

[1] Cruz MC, Moreira RI, Abreu A, Timóteo AT, Carvalho RS, Ferreira L, Ferreira RC. The smoker's paradox in acute coronary syndrome: Is it real?.*Revista Portuguesa de Cardiologia* (English edition). 2018 Oct 1;37(10):847-55. Available at: https://www.sciencedirect.com/science/article/pii/S2174204918303593

[2] Malenica M, Prnjavorac B, Bego T, Dujic T, Semiz S, Skrbo S, et al. Effect of cigarette smoking on haematological parameters in healthy population. *Medical Archives*. 2017 Apr;71(2):132. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5511531/

[3] Lu JT, Creager MA. The relationship of cigarette smoking to peripheral arterial disease. *Reviews in cardiovascular medicine*. 2004; 5(4):189-93. Available at: https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=3.%09Lu+JT%2C+Creager+MA.+The+relationship+of+cigarette+smoking+to+peripheral+arterial+disease.+Reviews+in+cardiovascular+medicine.+2004%3B+5%284%29%3A189-93.+&btnG=

[4] Law MR, Morris JK, Wald NJ. Environmental tobacco smoke exposure and ischaemic heart disease: an evaluation of the evidence. *Bmj*. 1997; 315(7114): 973-80. Available at: https://www.bmj.com/content/315/7114/973.full.pdf+html

[5] Shah RS, Cole JW. Smoking and stroke: the more you smoke the more you stroke. *Expert review of cardiovascular therapy*. 2010; 8(7): 917-32. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2928253/

[6] Acet H, Ertaş F, Akıl MA, Özyurtlu F, Polat N, BilikMZet al. Relationship between hematologic indices and global registry of acute coronary events risk score in patients with ST-segment elevation myocardial infarction. *Clinical and Applied Thrombosis/Hemostasis*. 2016 Jan;22(1):60-8. Available at: https://journals.sagepub.com/doi/full/10.1177/1076029614533145

[7] Sabatine MS, Morrow DA, Cannon CP, Murphy SA, Demopoulos LA, DiBattise PM, et al. Relationship between baseline white blood cell count and degree of coronary artery disease and mortality in patients with acute coronary syndromes. *J Am Coll Cardiol* 2002 Nov 20; 40(10):1761-8. PMID: 12446059. Available at: https://www.sciencedirect.com/science/article/pii/S0735109702024841

[8] Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD. Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). *Circulation*. 2018 Oct 30;138(20):e618-51. Available at: https://www.onlinejacc.org/content/72/18/2231?_ga=2.30882111.1052258612.1543348926-615127090.1543348926

[9] Adam AM, Nasir SA, Merchant AZ, Rizvi AH, Rehan A, Shaikh AT, et al. Efficacy of serum blood urea nitrogen, creatinine and electrolytes in the diagnosis and mortality risk assessment of patients with acute coronary syndrome. *Indian heart journal*. 2018 May

1;70(3):353-9. Available at: https://www.sciencedirect.com/science/article/pii/S0019483217302833

[10] Budzianowski J, Pieszko K, Burchardt P, Rzeźniczak J, Hiczkiewicz J. The role of hematological indices in patients with acute coronary syndrome. *Disease Markers*. 2017 Jan 1;2017. Available at: https://www.hindawi.com/journals/dm/2017/3041565/

[11] Monteiro Júnior JG, Torres DD, da Silva MC, Martins CM, da Silva IK, do Nascimento ME, et al. Prognostic value of hematological parameters in patients with acute myocardial infarction: Intrahospital outcomes. *PloS one*. 2018 Apr 18;13(4):e0194897. Available at: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0194897

[12] Weisz G, Cox DA, Garcia E, et al. Impact of smoking status on outcomes of primary coronary intervention for acute myocardial infarction: the smoker's paradox revisited. *Am Heart J* 2005 ;150:358---64. Available at: https://www.sciencedirect.com/science/article/abs/pii/S0002870304006234

[13] Venkatason P, Salleh NM, Zubairi Y, Hafidz I, Ahmad WA, et al. The bizzare phenomenon of smokers' paradox in the immediate outcome post acute myocardial infarction: an insight into the Malaysian National Cardiovascular Database-Acute Coronary Syndrome (NCVD-ACS) registry year 2006–2013. *SpringerPlus*. 2016 Dec 1;5(1):534. Available at: https://link.springer.com/article/10.1186/s40064-016-2188-3

[14] Al Zubeidy ZA, Al Qaseer AH, Ridha AF. Assessment of Diastolic Function in Diabetic Patients Using Conventional Echocardiogram & Tissue Doppler Imaging. Mustansiriya Medical Journal. 2017;16(1):34-44. https://www.iasj.net/iasj?func=article&aId=123293

[15] Saleh A. Absence of Smoker's Paradox in Middle Eastern Patients with Acute Coronary Syndrome. *J Vasc Med Surg*. 2016;4(290):2.

[16] Szulinska M, Piorunek T, Suliburska J, Pupek-Musialik D, Kupsz J, Drzymała-Czyz S, et al. Evaluation of insulin resistance, tumor necrosis factor alpha, and total antioxidant status in obese patient smoking cigarette. *Eur Rev Med Pharmacol sci* 2013; 17: 1916–21. Available at: https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=15.%09Szulinska+M%2C+Piorunek+T%2C+Suliburska+J%2C+Pupek-Musialik+D%2C+Kupsz+J%2C+Drzyma%C5%82a-Czyz+S%2C+et+al.+Evaluation+of+insulin+resistance%2C+tumor+necrosis+factor+alpha%2C+and+total+antioxidant+status+in+obese+patient+smoking+cigarette.+Eur+Rev+Med+Pharmacol+sci.+2013%3B+17%3A+1916%E2%80%9321&btnG=

[17] Bhattacharjee A, Prasad SK, Pal S, Maji B, Syamal AK, Mukherjee S. Synergistic protective effect of folic acid and vitamin B 12 against nicotine-induced oxidative stress and apoptosis in pancreatic islets of the rat. *Pharm Biol* 2016; 54(3): 433-444. Available at: https://www.tandfonline.com/doi/full/10.3109/13880209.2015.1043561

[18] Stojkovikj J, Zafirova-Ivanovska B, Kaeva B, Anastasova S, Angelovska I, Jovanovski S, Stojkovikj D. The Prevalence of Diabetes Mellitus in COPD Patients with Severe and Very Severe Stage of the Disease. *Open Access Maced J Med Sci* 2016; 4(2):253-8. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4908741/

[19] Tweed JO, Hsia SH, Lutfy K, Friedman TC. The endocrine effects of nicotine and cigarette smoke. *Trends Endocrinol Metab* 2012; 23(7):334–42. Available at: https://www.sciencedirect.com/science/article/abs/pii/S1043276012000501

[20] Sari MI, Sari N, Darlan DM, Prasetya RJ. Cigarette smoking and hyperglycaemia in diabetic patients. *Open Access Maced J Med Sci* 2018 Apr 15;6(4):634. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5927492/

[21] Saygitov RT, Glezer MG, Semakina SV. Blood urea nitrogen and creatinine levels at admission for mortality risk assessment in patients with acute coronary syndromes. *Emerg Med J*2010;27:105–109. Available at: https://emj.bmj.com/content/27/2/105.short

[22] Leonberg-Yoo AK, Rudnick MR. Tobacco Use: A Chronic Kidney Disease Accelerant. *American Journal of Nephrology*. 2017 Oct 1;46(4):257-60. Available at: https://www.karger.com/Article/FullText/481209

[23] Orth SR, Hallan SI: Smoking: a risk factor for progression of chronic kidney disease and for cardiovascular morbidity and mortality in renal patients – absence of evidence or evidence of absence? *Clin J Am Soc Nephrol*2008;3:226–236. 2 Nagasawa Y, Yamamoto R, Rakugi H, Isaka Y: Cigarette smoking and chronic kidney diseases. Hypertens Res 2012;35:261–265. Available at: https://cjasn.asnjournals.org/content/3/1/226.short

[24] Padmavathi P, Reddy VD, Varadacharyulu N. Influence of chronic cigarette smoking on serum biochemical profile in male human volunteers. *Journal of Health science*. 2009;55(2):265-70. Available at: https://www.jstage.jst.go.jp/article/jhs/55/2/55_2_265/_article/-char/ja/

[25] Bokhoven C, Niessen HJ. Amounts of oxides of nitrogen and carbon monoxide in cigarette smoke, with and without inhalation. *Nature*. 1961 Nov 4;192(4801):458-9. Available at: https://link.springer.com/content/pdf/10.1038/192458a0.pdf

[26] Benowitz NL, Hall SM, Stewart S, Wilson M, Dempsey D, Jacob P. Nicotine and carcinogen exposure with smoking of progressively reduced nicotine content cigarette. *Cancer Epidemiology and Prevention Biomarkers*. 2007 Nov 1;16(11):2479-85. Available at: https://cebp.aacrjournals.org/content/16/11/2479.short

[27] Sagone Jr AL, Lawrence T, Balcerzak SP. Effect of smoking on tissue oxygen supply. Blood. 1973 Jun;41(6):845-51. Available at: https://ashpublications.org/blood/article/41/6/845/40309/Effect-of-Smoking-on-Tissue-Oxygen-Supply

[28] Casasola GG, Alvarez-Sala JL, Marques JA, Sanchez-Alarcos JM, Tashkin DP, Espinos D. Cigarette smoking behavior and respiratory alterations during sleep in a healthy population. *Sleep Breath* 2002; 6: 19-24. Available at: https://link.springer.com/article/10.1007%2Fs11325-002-0019-y

[29] de Oca MM, Loeb E, Torres SH, De Sanctis J, Hernández N, Tálamo C. Peripheral muscle alterations in non-COPD smokers. *Chest*. 2008 Jan 1;133(1):13-8. Available at: https://www.sciencedirect.com/science/article/abs/pii/S0012369215489524

[30] McGill HC Jr. The cardiovascular pathology of smoking. *Am Heart J*1988;115:250–257. Available at: https://www.sciencedirect.com/science/article/abs/pii/000287038890645X

[31] Sambola A, Osende J, Hathcock J, Degen M, Nemerson Y, Fuster V, et al. Role of risk factors in the modulation of tissue factor activity and blood thrombogenicity. *Circulation.*2003;107:973–977. Available at: https://www.ahajournals.org/doi/full/10.1161/01.cir.0000050621.67499.7d

[32] Galanakis DK, Laurent P, Janoff A. Cigarette smoke contains anticoagulants against fibrin aggregation and factor XIIIa in plasma. *Science.*1982;217:642–645. Available at: https://science.sciencemag.org/content/217/4560/642.abstract

[33] Gupta T, Kolte D, Khera S, Harikrishnan P, Mujib M, Aronow WS, et al. Smoker's paradox in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Journal of the American Heart Association*. 2016 Apr 22;5(4):e003370. Available at: https://www.ahajournals.org/doi/full/10.1161/JAHA.116.003370

[34] Aitchison R, Russell N. Smoking - a major cause of polycythaemia. *Journal of the Royal Society of Medicine*. *1988*;81(2):89–91. Available at: https://journals.sagepub.com/doi/abs/10.1177/014107688808100212

[35] McDonough P, Moffatt RJ. Smoking-induced elevations in blood carboxyhaemoglobin levels. Sports Medicine. 1999 May 1;27(5):275-83.doi:10.2165/00007256-199927050-00001

[36] Nadia MM, Shamseldein HA, Sara AS. Effects of Cigarette and Shisha Smoking on Hematological Parameters: An analytic case-control study. *International Multispeciality Journal of Health*. 2015;1(10):44–51. Available at: http://sustech.edu/staff_publications/20170517114643589.pdf

[37] Verma RJ, Patel CS. Effect of smoking on Haematological parameters in Human Beings. *Journal of Cell and Tissue Research*. 2015;5(1):337.

[38] Milman N, Pedersen AN. Blood haemoglobin concentrations are higher in smokers and heavy alcohol consumers than in non-smokers and abstainers—should we adjust the reference range?. Annals of hematology. 2009 Jul 1;88(7):687. Available at: Blood haemoglobin concentrations are higher in smokers and heavy alcohol consumers than in non-smokers and abstainers-should we adjust the reference range? (archives-ouvertes.fr)

[39] Lyngbakken MN, Skranes JB, de Lemos JA, Nygård S, Dalen H, Hveem K, Røsjø H, Omland T. Impact of smoking on circulating cardiac troponin I concentrations and cardiovascular events in the general population: the HUNT Study (Nord-Trøndelag Health Study). *Circulation*. 2016 Dec 13;134(24):1962-72. Available at: https://www.ahajournals.org/doi/full/10.1161/circulationaha.116.023726