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Endocrine-disrupting chemicals and their adverse health effects: A review of current knowledge and the Nigerian situation

Samuel Robsam Ohayi[1]*, Onyinye Hope Chime[2], Ikenna Kingsley Ndu[3]

1 Enugu State University College of Medicine, Department of Histopathology, Nigeria
2 Enugu State University College of Medicine, Department of Community Medicine, Nigeria
3 Enugu State University College of Medicine, Department of Paediatrics, Nigeria

* **Corresponding Author:** Onyinye Hope Chime **E-mail:** dronyichime@gmail.com

ABSTRACT

Objective: Exposure of humans to certain natural or synthetic chemicals known as endocrine-disrupting chemicals (EDCs) can alter different levels of different endocrine functions ranging from synthesis to hormonal actions to metabolism. This disruption may have severe effects on human physiology and health. Some effects may be delayed, only manifesting across generations. The EDCs are ubiquitous in household, pharmaceutical, and industrial products; therefore, humans of all classes, ages, and sexes are readily exposed to several of them over a lifetime. Their harmful effects are believed to occur more in women and children. There is a growing concern among scientists and governments about the adverse effects of EDCs on humans. This has led to a steadily expanding body of research globally on the subject. However, studies investigating possible adverse health effects of EDCs in our country appear negligible. Also, there seems to be no coherent policy thrust from the government for regulating the introduction of EDCs into our environment. This narrative review aimed to provide an overview of the present scientific knowledge about EDCs and the relationships between them and public health and explore the attitude and experience of Nigerian researchers and policymakers about the emerging threat of EDCs and make recommendations for future research and policy direction.

Keywords: Endocrine disruptors, Humans, Hormones, Environmental pollutants, Public health, Nigeria

INTRODUCTION

Endocrine-disrupting chemicals (EDCs) are natural (endogenous or exogenous) or synthetic substances which influence one or more functions of the human endocrine system with consequent harmful health consequences (1). Although the term "endocrine disruptor" was coined in the early 1990s, it was formally introduced by the United States Environmental Protection Agency in 1996 (2, 3). There are over 84,000 such chemicals in various substances used in life and commercial activities, including plastics, fire retardants, pesticides, consumer products, and pharmaceutical agents (4-6). Being ubiquitous, humans of all classes, ages, and sexes are exposed to several of them per lifetime (4). Contact with these chemicals may occur through the soil, air, water, food, dust, fumes, breast milk, physical contact with certain household materials, or in utero through the transplacental spread. These chemicals are also absorbed through the gastrointestinal tract, the skin, etc (7).

Harmful effects of EDCs on human health appear to be related more to the duration (prolonged) of exposure and exposure to a combination of these chemicals than to the dosage exposed (8). These effects also appear to be transgenerational, occurring over two to three generations after exposure, as exemplified by diethylstilbestrol (1,9).

Examples of EDCs and their sources (1,7,10-12).

1.   Persistent organic pollutants (POPs), e.g., polychlorinated biphenyls (PCBs) used in transformer and hydraulic fluids, in paints, oils, and some building materials; organochloride pesticides and polybrominated diethyl ether, also called brominated flame retardants (BFRs) used in furniture, carpet, and electronics

2.   Phthalates are used widely in industrial chemicals and found in plastics, personal care products, food supplements, etc.

3. Bisphenol A (BPA) found in plastics, epoxy resins, and thermal papers
4. Dioxin is a by-product of smelting, chlorine bleaching of paper, and chlorinated herbicide production
5. Parabens found in personal care products, pharmaceutical products, and food preservatives
6. Atrazine found in herbicides
7. Pyrethroids are found in contaminated water, soil and food.

EDCs disrupt the endocrine system by direct and indirect mechanisms that target different levels of the hypothalamic-pituitary-gonadal/thyroid/adrenal pathways. These disruptive effects include acting as hormone receptor agonists or antagonists, alteration of receptor expression, signal transduction, hormone synthesis, transport, storage, metabolism, and elimination of natural hormones from the body and causing epigenetic changes in DNA (2,3,13,14). The disruption of these hormones responsible for maintaining homeostasis, reproduction, development, and behavior may eventually result in harmful effects (1). There is growing concern among scientists, doctors, and governments about potential links between exposure to EDCs and various diseases resulting in different scientific bodies promoting the idea and warning that EDCs can have adverse health impacts (14). However, studies investigating possible adverse health effects of EDCs and the policy thrust about them in our society appear negligible.

This narrative review aimed to provide an overview of the present scientific knowledge about EDCs and the relationships between them and various human diseases and explore the attitude and experience of Nigerian researchers and policymakers about the emerging threat of EDCs and make recommendations for future research and policy direction.

Effects of EDCs on human health

The ability to reproduce and develop is directly related to an individual's endocrine system (1). Human health is under threat with the high prevalence of EDCs in the environment and the surge in the development of many endocrine-related disorders (15). Their resemblance to natural hormones enables them to mimic the actions of these natural substances in the body (16). For instance, while endogenous hormones bind to specific receptors to perform their endocrine functions, these EDCs disturb hormonal balance by activating or inactivating hormone receptors, thereby negatively affecting human development and health (14).

Humans are exposed to a wide array of these chemicals found in everyday products in their daily activities (14). Consequently, it is difficult to determine the total impact exposure to EDCs has on humans. However, scientific reviews and reports have documented impacts on reproduction (infertility, cancers, malformations), thyroid function, body metabolism and obesity, insulin and glucose homeostasis, and neurodevelopment (15). Also, exposure to these substances can occur without producing visible symptoms of any disease or with harmful effects manifesting at later ages and do not manifest in some people (3). The period in life when exposure to these chemicals occurs significantly affects the severity of its effect (3). Research has shown that developing fetuses and neonates are the most vulnerable to endocrine disruption. The EDCs may pose the greatest risk when organs and neural systems develop (3).

Also, exposure during these early formative periods confers the risk of adverse health effects that may last throughout a lifetime (5). Women and children are at the most significant risk of this public and environmental health hazard. These chemicals damage the anatomy and physiology of the female reproductive organs while children are in the rapid growth phase (3).

Over the last few years, some EDCs, otherwise known as obesogens, have had detrimental effects on the action of insulin, promoting weight gain and increasing the risk of type II diabetes.(3) Exposure to several toxicants like PCBs, OCPs, dioxins, BPA, and phthalates has been linked to the development of diabetes and related metabolic disorders (3). A relationship has also been established between the incidence of diabetes mellitus and chronic exposure to moderate and high ($\geq$150μg As/l) inorganic arsenic (17). These exposures result in dysregulation of glucose homeostasis through insulin resistance and impaired glucose uptake (17). Apart from this endocrine toxicity, arsenic has been associated with cardiovascular diseases, skin and bladder cancer, stroke, and neurological effects (19).

In various studies, several exogenous agents were found to have metabolic, oestrogenic, anti-oestrogenic, and androgenic effects (3). Organochlorine pesticides (OCPs), due to their lipophilic nature and bioaccumulation potential, pose the greatest risk as EDCs in the environment (3). Reproductive toxicity resulting from the actions of one of the OCPs, dichlorodiphenyltrichloroethane (DDT), on follicle-stimulating hormone, oestrogen, and androgen receptors includes increased risk of infertility in both sexes, reproductive tract cancer in women, prostate and testicular cancer in men, menstrual disorders in women, low libido, early or delayed puberty in children and congenital disabilities of reproductive organs (3,14).

The EDCs such as BPA, phenols, and phthalates have been associated with premature births, miscarriages, and fetal developmental abnormalities in humans (3). The effects of exposure to diethylstilbestrol have been found to be trans and multigenerational, being seen in the children and grandchildren of exposed mothers (19). These effects include neuro-developmental disorders such as attention-deficit/hyperactivity disorder in children resulting in poor quality of life, low educational capacity, increased risk of obesity, poor morbidity and mortality health indicators, and even premature death in adulthood. This drug has also been linked to vaginal adenocarcinomas in female children of exposed females and hypospadias (abnormal opening of the urethra) in the grandsons and delayed menstrual regularity in their granddaughters (19).

Several EDCs such as propanil, triclosan, phenols, and phthalates impact the formation, function, and longevity of immune cells (4). The immature immune system is more vulnerable to EDCs (4). Maternal exposure to perfluorinated alkylate substances (PFASs) may produce immunotoxic effects in the child during the early developmental period (20). The PFASs are eliminated through breast milk; hence breast milk remains a major source of exposure in childhood. A prospective study among children 18 months to 5 years whose mothers were exposed to PFAS before birth shows an inverse association between prenatal exposure to PFAS and the serum vaccine-induced antibody concentrations against tetanus and diphtheria, resulting in diminished vaccination response (20). Similarly, a study by Dalsager et al. revealed a

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higher incidence of high fever in children whose mothers' serum PFAS concentrations were elevated in early pregnancy (21).

Polychlorinated biphenyls (PCBs), one of the organochlorine pollutants that persist for a long time in the environment, have been reported to have neurotoxic, hepatotoxic, nephrotoxic, immunotoxic, carcinogenic, and cytotoxic effects in various human studies (3). Neuro-developmental deficits have been reported in neonates, infants, and school children exposed to PCBs (22). The PCBs have been shown to produce neurotoxic effects by activating the human thyroid hormone receptor transcription, resulting in the reduction of serum thyroid hormone levels. This interferes with the ability of the thyroid hormone to control neural development in growing children (22)

Lavender oil and tea tree oil, widely used oils, have been reported to potentially act as EDCs in girls and boys (23). These oils demonstrate estrogenic and anti-androgenic properties resulting in prepubertal disorders in adolescents. In boys, cases of abnormal breast development (prepubertal gynecomastia) following the use of these essential oil products have been recorded (24). In girls, premature breast development was observed (23). These abnormal breast growths disappeared with the discontinuation of these hygiene products.

The Nigerian situation

Several researchers have made efforts to study the impact of EDCs in Nigeria and bring attention to their adverse effects on the environment and the human population (25-27). However, a lot more needs to be done because the scope of the problem is not fully appreciated, or worse still, the existence of this public health concern remains unrecognized. Nigeria lacks the structures and policies needed to support the comprehensive studies that could provide the scientific basis to develop strategies for the necessary public health interventions (28).

Currently, Nigeria is making rapid progress in information and communication technology (ICT). Consequently, it has become Africa's most significant electrical and electronic waste (e-waste) dumping ground (26). These e-waste products contain EDCs harmful to humans and pose environmental hazards. (29,30). Nigeria has had an unfortunate history with the transboundary movement of hazardous wastes. Examples include the dumping in June 1988 of over 3,500 tonnes of toxic/harmful wastes originating from Italy in Koko, Delta State, and the massive shipment of container loads of e-waste into Nigeria in 2010 (31). Consequently, the Federal Government enacted the Harmful Waste Act (HWA) in 1988 and the adoption of the National Environmental (Electrical/Electronics Sector) Regulations in 2011.(31,32) However, the effectiveness of these regulatory laws is doubtful, as the importation of e-waste in Nigeria is still thriving (31).

Cosmetic products used by Black women and children have been demonstrated to contain EDCs associated with higher rates of diabetes, obesity, pre-term births, fibroids, early menarche, cancers, and infertility (33-36). In Nigeria, women have greater use of cosmetics and personal care products (PCPs) when compared with men (37). Therefore most of the adverse effects may predominantly affect this population and developing fetuses or infants at lower exposures (37). The government agency responsible for regulating cosmetic products and certifying them safe and of good quality is the National Agency for Food and Drugs Administration and Control (NAFDAC) (38). However, despite all the agency's efforts, illicit trade in these cosmetic products still persists, hence the request that the National Assembly pass the Counterfeit Medical Product Bill to strengthen the war against offenders in the country (39).

There are many methods for waste disposal and management in Nigeria. However, the common waste disposal methods remain primitive and include open dumping, open burning, incineration, unregulated landfills, composting, and dumping into drain channels, streams, and rivers (40). These methods have raised concerns about leaching into the environment and endocrine-disrupting activities in wildlife and humans (41). Unfortunately, Nigeria has not invested adequately in modern waste management technologies such as recycling facilities or plants (40). Most public waste management agencies are poorly funded, understaffed and ill-equipped. However, a significant challenge for protecting and promoting a healthy environment favorable to life in Nigeria is that the constitution has rendered the constitutional provisions impossible to implement (40). In addition, Nigeria has failed to demonstrate the political will needed to amend the constitution in line with international standards flowing from the ratification of the African Charter (40).

Electrical and electronic waste, cosmetic products, and unregulated waste disposal, amongst many others, remain known sources of endocrine-disrupting chemicals (EDCs) and other hazardous substances in Nigeria and other LMICs. It may be argued that there is increased exposure to EDCs in Nigeria based on our records of poor legislation, ineffective regulation, and weak implementation. In 2011, South Africa became the first African country to regulate a substance as an EDC when it prohibited the use of infant feeding bottles containing Bisphenol A (BPA) (28). Unfortunately, the dumping of BPA baby bottles still occurs in Cameroon and Nigeria (42).

An African Conference on Health Effects of EDCs in South Africa recommended actions to reduce exposure to EDCs. These include the following: provision of appropriate training and education programs for individuals who use chemicals and products containing them; adoption of the precautionary principle; establishment of comprehensive biomonitoring programs; funding of additional epidemiology studies, including establishment of African birth cohorts; and increasing research on the impacts of EDCs on Africa's unique wildlife populations (28). These recommendations need serious consideration to help create awareness of the extent and seriousness of the EDCs in our environment and the need for practical, community-based interventions.

CONCLUSION

Since no comprehensive list of EDCs exists worldwide, there is a need for Nigerian researchers to design means of identifying EDCs present in our environment to define strategies to reduce or prevent their exposures and adverse health effects. We recommend further research to determine the scope of the problem of EDCs, especially their prevalence in our country. Infertility is increasing in Nigeria, and there's also an emerging trend of early puberty, especially in girls in our environment.

A link between these emerging trends and EDCs should also be explored in our society. Finally, further research is required to assess the knowledge and perception of the general public about EDCs, as this will guide policy formulation for community intervention.

Conflict of interest: The authors declare no competing interests.

Ethical approval: All procedures performed in this study were in accordance with the ethical standards of the institutional research committee.

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Prognostic importance of platelet/lymphocyte ratio and neutrophil/lymphocyte ratio in proteinuria associated with primary glomerular diseases

Zeki Kemeç[1]*

1 Batman Education and Research Hospital Nephrology Clinic, Batman, TR

* **Corresponding Author:** Zeki Kemeç **E-mail:** zekikemec@gmail.com

ABSTRACT

Objective: Proteinuria is associated with inflammation, endothelial dysfunction, platelet activation, and progression of kidney disease. The biological mechanisms by which platelet/lymphocyte rate (PLR) and neutrophil/lymphocyte rate (NLR) variables play a role in mediating protein excretion are not fully known. Here we aimed to compare NLR and PLR variables between patients with the primary glomerular disease (PPGD) with normal estimated glomerular filtration rate (eGFR) and healthy individuals (HIs). We divided the primary glomerular disease (PGD) participants into three sub-groups according to the level of proteinuria. In addition, a comparison was made between the sub-groups of patients with PGD in terms of these variables.

Methods: This cross-sectional, double arm, single center retrospective study was performed between January 2019 and April 2020. Serum platelet, total, and differential leukocyte analyses were evaluated using an automated cell counter. Biochemical analysis and 24-hour urinalysis in order to measure protein excretion and creatinine (Cr) clearance were performed using a chemistry analyzer. Of 225 participants in the study, 111 were patients with PGD, and 114 were HIs.

Results: A statistically significant difference was found when compared with PPGD and HI participants in terms of red blood cell (RBC), hemoglobin (HGB), white blood cell (WBC), platelet, neutrophil, NLR, and PLR variables. PPGDs revealed higher median C-reactive protein (CRP) and lower median albumin levels compared to HIs. Age, gender, urea, Cr, CRP, WBC, RBC, HGB, platelet, neutrophil, lymphocyte, NLR, and PLR variables between the sub-groups of patients with PGD were not statistically significant. But, there was only a difference between the sub-groups of patients with PGD in terms of albumin levels.

Conclusions: Our data suggested that PLR and NLR can be used as predictors in PPGDs. Higher median CRP and lower median albumin levels were also associated with proteinuria in PPGDs.

Keywords: Proteinuria, neutrophil/lymphocyte rate, platelet/lymphocyte rate, primary glomerular disease, C-reactive protein, serum albumin.

INTRODUCTION

The third cause of end-stage renal disease in the United States is chronic glomerulonephritis, with a 10% portion of dialysis patients [1]. Glomerular diseases are the main cause of proteinuria. Proteinuria, in the general population, increases morbidity and mortality. Glomerulopathies progressing with proteinuria disturb protein processing in the glomerular capillary barrier, and this may worsen the progression of the disease by increasing inflammation. Increased urine protein is associated with increased T lymphocytes mediated tubulointerstitial inflammation, and T-lymphocytes are accepted as a marker for decreased kidney function [2]. Proteinuria is the important sign of renal damage, fibrosis, and glomerulosclerosis in the progression of many kidney diseases [3].

Proteinuria is also associated with platelet activation, inflammation, and endothelial dysfunction [4]. Peripheral leukocyte count is an indicator of systemic immunologic/inflammatory activity. But, information concerning the relations between peripheric leucocyte counts and proteinuria is limited [5-8]. NLR and PLR variables were mostly studied in diabetic patients [9,10]. But in primary glomerulopathies, we did not find any study with these biomarkers. NLR and PLR may be easily evaluated by a simple blood count, and they are novel inflammatory biomarkers.

This study was performed to compare NLR and PLR, as well as serum levels of HGB, RBC, WBC, neutrophil, lymphocyte, platelet, CRP, and albumin between HIs and PPGDs. In addition, sub-groups of PGD patients were compared with these variables according to proteinuria status.

MATERIAL and METHODS

This single center, double arm, cross-sectional retrospective study was performed in accordance with the Declaration of Helsinki, with permission from the local ethics committee. Informed consents were obtained from all participants.

Study groups: We divided all participants into two main groups.

Main group 1: Healthy individuals (HIs); Between January 2019 and April 2020, HIs were selected from healthy volunteers to participate in this study. Demographic characteristics and clinical and biochemical data were recorded on volunteers' admission. Patients with neoplastic diseases, hypertension, cardiovascular diseases, chronic kidney disease (CKD), endocrine diseases, hematologic diseases, inflammatory disorders, and under anticoagulant/ antiaggregant therapy were all excluded from the HIs group.

Main group 2: It consisted of " patients with the primary glomerular disease (PPGD) " participants. Participants with PGD were also recruited between January 2019 and April 2020 from patients admitted to our nephrology clinic. Demographic characteristics and clinical and hematologic-biochemical data were recorded on patients' admission. The inclusion criterion for the patients' group is newly diagnosed PGD with urinary protein excretion >1 g/ day, who had proteinuria for more than six months and did not take any definitive medication. The renal biopsy results of the patients with PGD were as follows: focal segmental glomerulosclerosis (FSGS) (n:22), membranous glomerulonephritis (MNG) (n:45), membranoproliferative glomerulonephritis (MPGN) (n:12), minimal change disease (MCD) (n:5), and immunoglobulin A nephropathy (IgA nephropathy) (n:27).

The eGFR, serum Cr and urea values of the PGD participants were within the normal range. Exclusion criteria were the presence of chronic or systemic disorders [e.g., diabetes mellitus (DM), hypertension], as well as a history of thrombosis or active infection. During patient examination or admission (case note review has been reviewed), none of the participants reported alcohol use, smoking, use of anti-inflammatory drugs, antiaggregant, anticoagulant, antihypertensive, steroids, and immune-suppressive because all drugs may have negative effects on bone marrow and blood cells.

According to the amount of proteinuria, all PGD participants were divided into 3 groups as follows:

Sub-group 1: 45 participants, proteinuria amount 1-1.99 g/ day (mild proteinuria);

Sub-group 2: 27 participants, proteinuria amount 2-3.49 g/ day (moderate proteinuria);

Sub-group 3: 39 participants, proteinuria amount>3.5g / day (nephrotic range proteinuria).

Laboratory tests: Patient data, including routine biochemical parameters, complete blood count, and demographic characteristics, were obtained from medical records. Blood samples were collected after a 12-hour fasting period. RBC, WBC, neutrophil, lymphocyte, and platelet analyses were performed using blood samples that had been collected in tubes with EDTA, using an automatic blood counter (Mindray BC6800 Auto Hematology Analyzer Device [Shenzhen Mindray Bio-Medical Electronics Co.Ltd., Shenzhen, P.R, China]); HGB was quantified spectrophotometrically without cyanide using the same device. Biochemical parameters including serum urea, Cr, albumin, and CRP were analyzed by spectrophotometer using a Beckman Coulter Chemistry Analyzer AU5800 Device (Beckman Coulter Mishima K.K., Tokyo, Japan).

Patients with PGD received an explanation about how to collect a proper 24-hour urine sample. The first morning urine sample of the collection day was excluded, and 24- hour urine was collected, which included the first urine of the following day. Patients were warned to keep urine samples in a cool and dark environment. In the end, the urine containers were transferred to the laboratory within 4 hours. Urinary protein (mg/day) was analyzed by spectrophotometry using a Beckman Coulter Chemistry Analyzer AU480 Device (Beckman Coulter Mishima K.K., Tokyo, Japan).

Definitions: Plasma proteins are important components of blood. The kidneys play an important role in the preservation of these proteins, using kidney tubules to reabsorb the proteins passing through the glomerule filtration barrier. Herewith, the detection of abnormal types or quantities of urinary protein is considered an early indicator of severe renal or systemic disease. Proteinuria is defined as a 24-hour urinary protein excretion of more than 150 mg [11]. PGD has many causes, including MCD, MNG, FSGS, IgA nephropathy, and MPGN [12].

NLR and PLR variables: They are indicated as inflammation markers in the literature. [13,14]. The NLR and PLR were calculated by dividing absolute neutrophil or platelet counts by absolute lymphocyte count [15].

Statistical Analysis

Statistical analysis were done with SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Numerical data were expressed as mean ± median or standard deviation (minimum-maximum), and categorical data expressed as absolute number (%). Chi-Square Test was used for categorical data, T-Test for numerical data or Mann-Whitney U Test were used as the significance test of the difference between the groups.

Kruskal Wallis test was used to compare sub-groups. Tukey test was used for Post Hoc analysis. A ROC curve analysis was performed to identify the sensitivity and specificity of NLR and PLR cutoff values in prediction of proteinuria associated with PGD. Pearson Correlation Analysis was used in the correlation analysis. P <0,05 was considered statistically significant.

RESULTS

As shown in Table 1, of the 225 patients incorporated in the study, 131 (%58.2) were male, and 94 (%41.8) were female; the mean age was 36.49±11.33 years. HIs included 114 participants (75 male, 39 female) aged 18 to 79 years (mean age, 38.25±8.77 years). Patients with PGD included 111 participants (56 male, 55 female) aged 18 to 76 years (mean age, 34.68±13.26 years). Male gender dominant found in the HIs (p=0.020). There was a significant difference in PPGDs compared to HIs in terms of WBC, RBC, HGB, platelet, neutrophil, NLR, and PLR variables. However, there were no statistically significant differences in lymphocytes between groups. The average age of the HIs was significantly higher than the PPGDs (p=0.019). PPGDs revealed higher median CRP and lower albumin levels in comparison with HIs (respectively p<0.001, p<0.001). Average levels of WBC, platelet, neutrophil, CRP, NLR, and PLR variables were higher, but the average levels of RBC and HGB variables were low in PGD participants. ROC analysis was completed to investigate the relationship between NLR-PLR variables and PGD. NLR; AUC: 0.60, P = 0.009; a value of 2.1 for NLR gave 58% sensitivity and 70% specificity.

PLR; AUC: 0.59, P = 0.019; a value of 105.6 for PLR gave 56% sensitivity and 57% specificity and were the effective cutoff points to indicate PPGD with proteinuria (Figure 1).

As shown in Table 2, sub-group 1 participant included 45 participants (26 male, 19 female) aged 18 to 76 years (mean age, 35.6±14.75 years). Sub-group 2 included 27 participants (9 male, 18 female) aged 18 to 61 years (mean age, 33.7±12.45 years). Sub-group 3 included 39 participants (21 male, 18 female) aged 40 to 72 years (mean age, 34.31±12.22 years). There were no significant differences in age, gender, urea, Cr, CRP, WBC, RBC, HGB, platelet, neutrophil, lymphocyte, NLR, and PLR variables between the three sub-groups; There was only a difference between sub-groups in terms of albumin levels (p <0.001). In the post hoc analysis of albumin, while there was no significant difference between sub-group 1 and sub-group 2 (p=0.215), there was a significant difference between sub-group 1 and sub-group 3, and sub-group 2 and sub-group 3 (p<0.001 and p=0.001, respectively).

Table 1: Comparison of demographic and laboratory data of the main groups

Variable	Total (n=225)	Healthy individuals (HIs) (n=114)	Patients with primary glomerular disease (PPGDs) (n=111)	P
Gender (M/F)	131/94	75/39	56/55	0.020
Age (years)	36.49±11.33	38.25±8.77	34.68±13.26	0.019
Albumin (g/dL)	3.94±0.84	4.4±0.23	3.47±0.96	<0.001
WBC ($\times 10^9$/L)	8.18±2.03	7.77±1.47	8.59±2.43	0.002
RBC ($\times 10^{12}$/L)	4.92±0.56	4.99±0.49	4.85±0.61	0.047
HGB (g/dL)	14.22±1.65	14.58±1.32	13.85±1.86	0.001
Platelet ($\times 10^9$/L)	272.76±78.04	251.66±52.28	294.43±93.05	<0.001
Neutrophil ($\times 10^9$/L)	4.6 (1.79-15.8)	4.3 (2.0-8.97)	4.9 (1.79-15.8)	0.009
Lymphocyte ($\times 10^9$/L)	2.48±0.77	2.47±0.66	2.48±0.86	0.886
CRP (mg/L)	2.8 (0.3-11.0)	2.1 (1-5)	5.0 (0.3-11)	<0.001
NLR	1.93 (0.73-17.22)	1.83 (0.73-10.30)	2.14 (0.76-17.22)	0.009
PLR	105.63 (36.73-991.89)	100.41 (51.46-242.72)	110 (36.73-991.89)	0.019

Abbreviations: M: Male, F: Female, WBC: White blood cell, RBC: Red blood cell, HGB: Hemoglobin, CRP: C-reactive protein, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio.
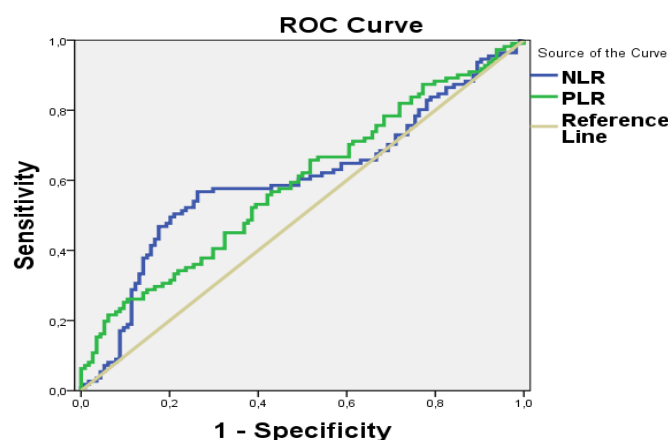
Figure 1: ROC curves for NLR and PLR. Abbreviations: ROC: receiver operator curve; NLR: neutrophil / lymphocyte rate; PLR: platelet / lymphocyte rate

were compared in terms of the same variables among themselves.

Table 2: Comparison of demographic and laboratory data of the subgroups

Variable	Total (n=111)	Sub-group 1 (n=45)	Sub-group 2 (n=27)	Sub-group 3 (n=39)	P
Gender (M/F)	56/55	26/19	9/18	21/18	0.112
Age (years)	34.68±13.26	35.6±14.75	33.7±12.45	34.31±12.22	0.930
Urea (mg/dL)	29 (11-77)	32 (14-77)	24 (11-49)	30 (11-63)	0.196
Cr (mg/dL)	0.70 (0.2-1.38)	0.7 (0.23-1.2)	0.62 (0.2-1.28)	0.70 (0.2-1.38)	0.516
Albumin (g/dL)	3.47±0.96	3.95±0.85	3.61±0.82	2.81±0.81	<0.001
WBC (x10^9/L)	8.59±2.43	8.64±2.23	8.73±3.17	8.45±2.09	0.772
RBC (x10^{12}/L)	4.85±0.61	4.82±0.59	4.88±0.59	4.86±0.66	0.970
HGB (g/dL)	13.85±1.86	13.95±1.91	13.62±1.68	13.88±1.94	0.747
Platelet (x10^9/L)	294.43±93.05	276.98±82.24	312.78±108.71	301.87±92.14	0.402
Neutrophil (x10^9/L)	2.47±1.79	5.38±1.91	5.55±2.40	5.23±1.99	0.722
Lymphocyte (x10^9/L)	2.49±0.87	2.5±0.92	2.49±1.01	2.41±0.69	0.621
CRP (mg/L)	4.99±2.76	5.63±2.66	4.29±2.33	4.73±3.03	0.111
NLR	2.15 (0.76-17.22)	2.09 (0.76-17.22)	2.48 (0.93-4.79)	2.30 (0.92-8.35)	0.722
PLR	110 (36.73-991.89)	102.33 (36.73-991.89)	120.59 (67.09-278.29)	109.31 (75.77-585.0)	0.196

Abbreviations: M: Male, F: Female, Cr: Creatinine, WBC: White blood cell, RBC: Red blood cell, HGB: Hemoglobin, CRP: C-reactive protein, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio.

DISCUSSION

Primary and secondary glomerular diseases cause proteinuria. Glomerulopathy caused by secondary causes such as DM and systemic lupus erythematosus is beyond the scope of this article. The mechanisms explaining the PGD are not yet well elucidated. However, proteinuria and inflammation processes are strongly associated. The causes and mechanisms described in each disease pathology are based on predictions. As the amount of proteinuria increases, the risk of kidney damage increases, and life expectancy decreases. The secret of the mechanisms that make the kidney susceptible to damage in increasing proteinuria is unknown. The pathology of PGDs is generally complicated. Even in diagnostic renal biopsies, these diseases can be associated and/or confused, and these factors may complicate treatment. There are some unknowns that need to be clarified in the pathology of these diseases.

For this reason, the relationship between proteinuria and inflammatory processes in PGDs is the center of the studies [16-22]. Our aim in this study was to examine this mysterious pathology of primary glomerulopathy. Early prognostic predictors of proteinuria have not yet been identified. If a predictor involved in this process is found, it can shed light on the diagnosis and treatment of PGDs.

NLR and PLR variables have not been studied in PPGDs. We wanted to investigate the role of these variables in PGD participants. Significant differences were found when HIs and PPGD groups were compared in terms of WBC, RBC, HGB, platelet, neutrophil, NLR, and PLR variables. CRP variable was significantly higher in PPGDs (p<0.001). Albumin was found significantly lower in PPGDs (p <0.001). No significant difference was found when sub-groups of PGDs

We find a relationship between NLR-PLR inflammation markers and PGDs with proteinuria. In the process of inflammation and proteinuria, with hypoalbuminemia and CRP elevation. ROC analysis showed the sensitivity and specificity of NLR and PLR in PPGD with proteinuria. NLR and PLR can be used as markers in pure glomerulopathies with proteinuria. These new biomarkers can be tried during diagnosis, treatment, and follow-up.

Neutrophils secrete inflammatory mediators, and because of their short life span, neutrophilia is associated with acute inflammation during tissue injury. It was shown that neutrophil activation changes their mobility and increases adherence to the endothelium, all of which lead to capillary occlusion and tissue ischemia [23]. Probably low-grade chronic inflammation, together with other risk factors, lead to increased oxidative stress, vascular damage, endothelial dysfunction, and increased production of cytokines and growth factors, and finally causes renal injury and proteinuria. Where are NLR and PLR involved in the inflammation and proteinuria process? How do changes occur as the amount of proteinuria increases? Due to their similarity to our study, we would like to discuss about previous studies (when we scanned the English literature in detail, we found six studies) on the relationship between these variables and proteinuria.

Afsar B et al. [9], the relationship between proteinuria and NLR in newly diagnosed type-2 DM patients was evaluated, and a significant correlation was determined between proteinuria and neutrophil, lymphocyte, and NLR, and they emphasized NLR as a marker for proteinuria independent of other risk factors in patients with newly diagnosed type-2 DM.

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The relationship between proteinuria and NLR in this study supports our study. The difference of our article from this study is that the compared patient group includes PGD participants, and the studied markers are PLR together with NLR.

Another study by Binnetoğlu E et al. [14] on chronic kidney disease (CKD) patients without DM evaluated the relationship between proteinuria and NLR. It was emphasized that NLR is a prognostic marker for the presence and degree of proteinuria. In this study, unlike the participants in our study, CKD participants were included, and only NLR was studied. Similar to our study, this study also supports the relationship between proteinuria and NLR.

In the study by Emokpae MA et al. [24], the NLR and PLR correlated with the measured traditional inflammatory markers in sickle cell anemia (SCA) patients, with values increasing in SCA patients with macroalbuminuria, and the highest levels were seen in those with impaired renal function. This study highlights the relationship between proteinuria and NLR-PLR markers. The participant group studied is different. Here, similar to our study, the NLR and PLR markers have been studied together. The significance of these markers strongly supports our study.

Yilmaz G et al. [25] investigated the relationship of mean platelet volüme (MPV) and NLR with inflammation and proteinuria in patients with CKD Stage 3-4. Their study showed that the NLR is high in the CKD group and is correlated with uric acid and proteinuria, which are known to be associated with atherosclerosis, in patients with CKD. They thought that NLR might be a determinant of inflammation and atherosclerosis in patients with CKD. The participant group in this study is different. MPV was added to the studied NLR marker. This study is different from our study in these aspects. But the relationship between NLR and proteinuria supports our study. Another difference of our study is that PLR was added to the NLR.

Kutlugun AA et al. [15] evaluated the association between NLR, PLR, and microalbuminuria in patients with normal eGFR. Higher NLR levels were found in microalbuminuric patients with normal eGFR. This study is very similar to our study. The markers studied are the same. The patient group is not PGD but microalbuminuric patients. The fact that there is a relationship between proteinuria and NLR-PLR supports the strength of our study.

Kawamoto R et al. [26] examined the relationship between NLR and eGFR and urinary albumin excretion. Their data showed that NLR might be an important factor for evaluating patients with a higher degree of albuminuria among diabetic outpatients. The relationship between NLR and albuminuria in this study supports our study. Differently, the participant patient group consisted of DM participants. The patient group of our study was different, and NLR and PLR markers were studied together.

There were some unique features in the present study. Unlike the studies mentioned above, NLR and PLR were investigated in PGD participants. Patients in our study had proteinuria; the amount of urine protein was at least >1 g/day. Causative diseases included were PGDs, while secondary or systemic causes (e.g., diabetes, lupus) were excluded. Therefore, the

patients in this study had pure glomerular diseases. Their diagnosis has been proven by renal biopsy.

Our study has some limitations. One limitation of this study was its cross-sectional design, which limited its ability to infer a causal relationship between total and differential blood counts and inflammation and proteinuria. Besides, analyses were based on a single measurement of total and differential blood counts that may not reflect the relation over time. It would be interesting to measure the serial changes of total and differential blood counts to further clarify the role of WBCs-platelets and sub-populations for the development of inflammation and proteinuria. Secondly, when 111 glomerulopathy participants are grouped among themselves, the number of participants in the sub-groups decreases. The roles of NLR and PLR variables are hidden. If the number of participants in this subgroup was high, the roles of these variables could become evident in severe proteinuric glomerulopathies. However, there was a significant difference between PPGD and HIs in terms of both variables. We aimed to examine the study from this aspect. Third, because our study was retrospective, gender and age matching could not be made. We could not analyze the effect of these variables on the results. Fourth the cut-off values for leukocyte, platelet, and lymphocyte ratios, known as inflammatory markers, are unknown. In similar studies, the limit values of the variables mentioned were not determined.

CONCLUSION

Neutrophils, lymphocytes, and platelets, which are simply examined in the blood count, have important roles in the inflammation process. Their subtypes and rates can guide the inflammation process. We found that WBC, RBC, HGB, platelet, neutrophil, NLR, and PLR levels were statistically significant in primary glomerulopathies. If cut-off values were known, NLR and PLR could be used as predictors in glomerulopathies. Higher median CRP and lower median albumin levels were also associated with proteinuria in PPGDs

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Investigating hopelessness and fear among the community during COVID-19 pandemic

Hasan Ergenç[1]*, Zeynep Ergenç[1], Mustafa Usanmaz[2], İbrahim Hakkı Tör[3], Hande Usanmaz[4], Gülsüm Kaya[5]

1 Ayancık Government Hospital, Department of Internal Medicine, Sinop, TR
2 Gazi Government Hospital, Department of Infectious, Samsun, TR
3 University of Health Sciences, Department of Anesthesiology and Reanimation, Erzurum, TR
4 Sinop University, Department of Biochemistry, Sinop, TR
5 Sakarya University Training and Research Hospital, Department of Infection Control Committee, Sakarya, TR

* Corresponding Author: Hasan Ergenc E-mail: dr.hasanergenc@hotmail.com

ABSTRACT

Objective: This study was conducted to determine the levels of hopelessness and fear of COVID-19 in individuals during the COVID-19 pandemic period.

Material and Methods: In this cross-sectional study was concluded Sinop Province, Turkey, from July 2020 to September 2020. The study sample consisted of 1200 individuals living in Sinop who agreed to participate in the study. An interview form was filled by the researcher for the individuals who decided to participate in the study.

Results: Of the 1200 participants, 537 (44.75%) were male, and 663 (55.25%) were female, with a mean age of 38.96. Participants had mild hopelessness (8.42%) and moderate COVID-19 fear (20.74%). There was a direct correlation between the COVID-19 Fear Scale and the Beck Hopelessness Scale. A statistically significant correlation was found between age, education, and fear of COVID-19 (respectively, p=0.001; p=0.010). A statistically significant correlation was found between the number of days the participants went out per week and income and fear of COVID-19 (respectively, p=0.001; p=0.001). There was also a significant difference between work and hopelessness (p=0.033). While there is a weak negative relationship between the fear of COVID-19 and the number of days individuals go out per week; A weak positive correlation was found with age (r=-0.109; r=0.098, respectively).

Conclusion: Due to the rapid spread of the pandemic, it was considered that policymakers and officials should develop effective behavioral strategies to reduce the mental consequences of the pandemic in society.

Keywords: COVID-19, Pandemic, Hopelessness, Fear, Pandemic

INTRODUCTION

There have been several fearsome epidemics of infectious diseases that have affected humanity's history (1). A new type of Coronavirus, named COVID-19, first appeared in Wuhan, China, in 2020 (2,3) It was declared as a COVID-19 pandemic on March 11, 2020 by the World Health Organization (WHO). COVID-19 is a beta virus transmitted to humans through close physical contact (4). The mortality rate of COVID-19 is 2.3% higher than influenza, and it is more contagious than severe acute respiratory syndrome (5,6). The most common clinical features of COVID-19; are cough, fever, shortness of breath, headache, expectoration, nasal discharge, loss of taste and smell, myalgia and diarrhea (7,8).

In addition to the increase in the death rate due to Covid-19, the psychological state of the population has also been adversely affected (9). While the individuals suffer from relatively high mortality and very high infection rate, they naturally got worried about the COVID-19, leading to fear of contacting individuals who might be infected by COVID-19 (10). Unfortunately, the disease itself may be exacerbated due to fear. All individuals worldwide have experienced high anxiety due to the emergence of the COVID-19 resulting in stigma in some cases (10-13).

Fear is one characteristic nature of infectious diseases such as the COVID-19 compared. Researhers indicates to that there is a direct association between fear and its transmission medium and rate and its mortality and morbidity, leading to other psychosocial challenges such as discrimination, stigmatization, and loss of considence (14).

Individuals with high fear levels may not think rationally and clearly in reaction to COVID-19 (15). Another important psychological effect caused by the disease is hopelessness about the future due to the risk of high mortality, the absence of a definitive vaccine and treatment method, and the failure to predict its severity and duration. Hopelessness means the feeling that any effort to make effective change in a patient's disease is ill-fated, even attempting it (16).

Under the outbreaks including the 'Ebola Virus' in the past, the community and individuals at national and international levels were majorly affected by psychosocial disorders because of the sudden outbreak of the disease. People may associate contracting the virus with fear of falling sick, hopelessness, helplessness, stigma, and even death (17).

There is limited research on the psychological effects of the COVID-19 pandemic on society. Therefore, in our study, we aimed to investigate the hopelessness and fear levels caused by COVID-19 in the society during the COVID-19 pandemic and to what extent and due to which factors the society is affected by COVID-19.

MATERIAL and METHODS

This study was carried out in Sinop province between July and September 2020. Ethics committee approval was obtained before starting the research (dated 20.07.2020 and numbered 37732058-514.10). The population of the research consisted of individuals living in Sinop. Convenience sampling technique was used as the sampling method. The data were collected by the researchers as face-to-face interview method. Among the individuals living in Sinop, 1200 individuals participated in the study on a voluntary basis, and the sample of the study consisted of 1108 individuals living in Sinop who agreed to participate in the study. The individuals participating in the study had not received any psychiatric diagnosis before and had not used any medication. Those with mental disorders such as anxiety and depression were excluded from the study. Informed consent was obtained from the individuals participating in the study.

The interview form, which was created by the researcher via scanning the literature, consisted of sociodemographic information and questions about the COVID-19 Fear Scale (FCV-19S) and Beck Hopelessness Scale (BHS). FCV-19S and the BHS were used for the general population to assess their fear and hopelessness about the COVID-19. FCV-19S consists of a five-item Likert type scale from "strongly disagree" to "strongly agree." The minimum possible score for each question is 1, and the maximum is 5. A total score ranged from 7 to 35 (18).

Beck Hopelessness Scale (BHS) which Beck et al. developed in 1974, was used to determine the individual's negative expectations of the future. Seber et al. conducted the Turkish validity and reliability study (19). In BHS consisting of 20 items, each question is scored between 0 and 1. High scores show the hopelessness high level in the individual. The participants were assessed according to their points (0-3 as Minimal, 4-8 as Mild, 9-14 as Moderate, >15 as severe hopelessness level).

Statistical analysis

Statistical analysis of the research was done in SPSS 21 program. The Kolmogorov-Smirnov test was used to test whether the numerical variables fit the normal distribution in the study, and considering that the statistical significance level was above $p<0.05$, the numerical variables were accepted to be suitable for the normal distribution. Pearson correlation coefficient test was used to examine the relationship between Beck Hopelessness Scale and Fear Scale scores. Statistical significance level was taken as $p<0.05$.

RESULTS

Of 1200 individuals participating in the study, 537 (44.75%) were male and 663 (55.25%) were female, and the mean age was 38.96 years. The age, number of individuals living in the family, number of days out per week and FCV-19S and BHS mean scores of the participants are shown in Table-1. The mean score of the Fear of Covid-19 Scale is 20.74±7.03 and the mean score of the Beck Hopelessness Scale is 8.42±4.31. When FCV-19S and BHS scale scores are evaluated; It was determined that the individuals participating in the study had moderate hopelessness and moderate fear of COVID-19.

Information on the participants' gender, education level, marital status, number of children, income level, job level and the presence of any psychiatric illness are presented in Table 2. The participants' 62.9% of them were married, and 91.8% of them had no psychiatric disease. 51.5% had high school degrees, 16.1% had associate's degree, 14.8% had bachelor's degree, 8.6% had primary school degree, 3.8% had master's degree, and .1% was the expert. Six hundred ninety participants (57.5%) had children. 50.4% had middle income, 26.0% had no income, 11.7% received a monthly pension, 9.8% had a good income, 1.4% had bad income, and .8% had minimum income. The 49.7% had a middle job, 29.7% had a low job, 16.1% were unemployed, and 4.4% had a high job (Table-2).

While a significant relationship was found between the age of the individuals and the fear of COVID-19 (p=0.001); There was no significant difference between age and hopelessness level (p=0.066). A significant difference was found between the education level of the participants and both the COVID-19 fear scale score and the hopelessness scale score (respectively, p=0.010; p=0.043). When the number of days out per week and the COVID-19 fear scale score of the individuals were compared, a statistically significant difference was found (p=0.001). In addition, between the income level of individuals and the COVID-19 fear scale score (p=0.001); It was found that there was a significant relationship between the occupation and the level of hopelessness (p=0.033). There was a significant negative correlation between the number of days a week that individuals went out and fear of COVID-19 (p=0.001; r=-0.109). There was a significant positive correlation between age and fear of COVID-19 (p=0.001; r=0.098). There was a negative significant difference between the income level of the participants and the level of hopelessness (p=0.001; r=-220).

Table 1. Participants' age, number of individuals living in the family, number of days out per week, and FCV-19S and BHS mean scores

Variable	X±SS (min-max)
Age	38.96±14.69 (12-92)
Number of individuals living in the family	3.61±1.20 (1-10)
Number of days out per week	4.88±1.43 (0-7)
The Fear of COVID-19 Scale	20.74±7.03 (0-35)
Beck Hopelessness Scale	8.42±4.31 (0-19)

Table 2. Information on the sociodemographic data of the participants

Variables		N (%)
Gender	Male	537 (44.8)
	Female	663 (55.3)
Marital status	Married	755 /62.9)
	Single	445 (37.1)
Presence of psychiatric illness	Yes	98 (8.2)
	No	1102 (91.8)
Educational status	Masters'	45 (3.8)
	High school	618 (51.5)
	Associate's	193 (16.1)
	secondary school	62 (5.2)
	Bachelor's	178 (14.8)
	Primary school	103 (8.6)
	Expert	1 (0.1)
having children	Yes	690 (57.5)
	No	510 (42.5)
Income status	Bad	17 (1.4)
	Lower	9 (0.8)
	Middle	605 (50.4)
	Good	117 (9.8)
	Pension	140 (11.7)
	No	312 (26.0)
Job income levels	Unemployment	193 (16.1)
	Low	357 (29.7)
	Middle	597 (49.7)
	High	53 (4.4)

Table 3. The relationship between the participants' sociodemographic data and The Fear of COVID-19 and The Fear of COVID-19 scores. *Correlation; $p<0.05$, ** 0ne-way ANOVA $p<0.05$,

Variable Age	P value	r
The Fear of COVID-19 Scale	0.001*	0.098
The Fear of COVID-19 Scale	0.066	0.053
Gender		
The Fear of COVID-19 Scale	0.081	
Beck Hopelessness Scale	0.421	
Marital status		
The Fear of COVID-19 Scale	0.472	
Beck Hopelessness Scale	0.877	
Presence of psychiatric illness		
The Fear of COVID-19 Scale	.745	
Beck Hopelessness Scale	.506	
Educational status		
The Fear of COVID-19 Scale	0.010**	
Beck Hopelessness Scale	0.043	
Having children		
The Fear of COVID-19 Scale	0.355	
Beck Hopelessness Scale	0.191	
Number of individuals living in the family		
The Fear of COVID-19 Scale	0.104*	0.047
Beck Hopelessness Scale	0.705*	0.011
Number of days out per week		
The Fear of COVID-19 Scale	0.001*	-0.109
Beck Hopelessness Scale	0.841	-0.006
Income status		
The Fear of COVID-19 Scale	0.001**	
Beck Hopelessness Scale	0.055	
Job income level		
The Fear of COVID-19 Scale	0.058	
Beck Hopelessness Scale	0.033**	

DISCUSSION

In this study, the levels of mental disorders such as fear and hopelessness in individuals during the COVID-19 pandemic were investigated. The present study showed a direct relationship between the fear and hopelessness of the general population. It means that when the fear of COVID-19 increases, the hopelessness about COVID-19 also increases. The participants had mild hopelessness level and medium fear of COVID-19. Age positively affected the fear of COVID-19; when age increases, fear of COVID-19 increases. Education negatively affected the fear of COVID-19 in the studied participants; the higher education, the lower fear of COVID-19. The findings also showed that the number of days the person goes out a week also negatively affected the fear of COVID-19. That is the lower number of days the person goes out a week, related to the higher fear of COVID-19. The income, job, and education also negatively affected the hopelessness of the participants. In other words, the higher the income, job status, and education, the lower the hopelessness about COVID-19.

According to the results obtained from our study; This is in line with some studies showing that people experience feelings of helplessness, increased levels of self-blame, depression, and fear of getting sick or dying (20-22).

Ahorsu et al. found FCV-19S higher overall scores to indicate a more severe fear of COVID-19 and did not find the effect of age and gender on the response pattern of the fear (18), while our study found the relation of age on the fear but found that gender was not associated with the mentality caused by the COVID-19. Our study results are also not in line with the study results by Bitan et al. (23) and Limcaoco et al. (24, 25) who found an association between gender and fear of COVID-19.

Hacimusalar Y et al. (26) found a significant relationship between the income rate and this situation that is the hopelessness of people was affected by the loss of income and that the uncertainty of the pandemic situation affected this situation, and McLaughlin et al. (27) also found that the working parents faced several problems during the pandemic due to vacation of the schools and children staying at home and that the pandemic, leading to loss of income, coincide with the results of our study.

Jeong et al.(28) also found an association between inadequate basic supplies and feelings of uncertainty and frustration during the quarantine period, which are similar to the results of our study.

Harper et al. (29,30) also found a significant relationship between staying at home and fear of the COVID-19, and Galea et al. found the serious effect of physical distancing on the mental health of the population (31), which is consistent with our study results.

The fear of unknown and new infective factors and uncertainty for the future was also affected by the pandemic in the social isolation and staying at home in a study by Khan et al. (32) while our study found that the number of days the person goes out a week negatively affected only the fear of COVID-19.

Our study results also support the study results by Ustun et al. (33) who found that those with fear of infecting others and being infected also had anxiety about the future, sadness, and anxiousness.

Lee et al. (34) showed a significant association between age and education and the mental disorders; that is, those who were more educated and were younger had higher fear about Coronavirus, and extreme hopelessness, are different from our study results.

CONCLUSION

It is concluded that age, education, and the number of days a person goes out a week affected the fear of COVID-19. It means that the older, less educated, and more isolated people experience higher fear of COVID-19. Income, job, and education also affected the hopelessness of the participants. The hopelessness level is reduced by increasing income, job status, and education. The participants had mild hopelessness level and medium fear of COVID-19during the pandemic. When the fear of COVID-19 increased, the hopelessness level also increased. Those who have lower education, job status, and income should be supported more to reduce the psychological distress of pandemic's. Due to the pandemic's rapid spread, the policymakers and authorities should adopt effective behavioral strategies to reduce the mental consequences of this pandemic.

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MSD

Factors associated with the recovery of chemotherapy induced cardiomyopathy in HER2 overexpressing breast cancer

Eser Açıkgöz[1], Sadık Kadri Açıkgöz[2], Ülkü Yalçıntaş Arslan[3], İmran Ceren[1]

1 Ankara Abdurrahman Yurtaslan Oncology Research and Education Hospital, Dept of Cardiology, Ankara, TR
2 Ankara City Hospital, Dept of Cardiology, Ankara, TR
3 Ankara Abdurrahman Yurtaslan Oncology Research and Education Hospital, Dept of Oncology, Ankara, TR

* Corresponding Author: Eser Açıkgöz E-mail: dreacikgoz@gmail.com

ABSTRACT

Objective: Chemotherapy induced cardiomyopathy (CI-CMP) is an important and potentially deadly complication of chemotherapy. However, factors associated with the recovery of CI-CMP have not been studied adequately so far. In this study, determinants of the recovery of CI-CMP in HER2 overexpressing breast cancer patients who received a chemotherapy regimen consisting of Doxorubicin, Trastuzumab, Paclitaxel and Cyclophosphamide and developed CI-CMP were investigated.

Material and Methods: 88 patients with CI-CMP among 1.410 HER2 positive breast cancer patients were enrolled and followed up for a median of 64 months. A multivariate logistic regression analysis model was used to assess the association between recovery of CI-CMP and other variables

Results: The median age of the participants was 52, and similar between groups. CI-CMP was recovered in 52 patients (59.1 %). Hypertension, diabetes mellitus, clinical heart failure, ECG anomaly, visceral metastasis, heart rate and blood glucose were significantly lower in recovered patients. A multivariate logistic regression analysis revealed that diabetes mellitus (OR 0.030, CI 0.010-0.083, p<0.001), heart rate (OR 0.799, CI 0.700-0.913, p<0.001), minimum LVEF during follow-up (OR 1.115, CI 1.015-1.223, p=0.03), development of clinical heart failure (OR 0.238, CI 0.098-0.876, p=0.022) and visceral metastasis (OR 0.022, CI 0.002-0.226, p=0.001) were independent predictors of the recovery of CI-CMP.

Conclusion: According to our results, Diabetes mellitus, heart rate, minimum LVEF during follow-up, development of clinical heart failure, and presence of visceral metastasis were independently associated with the recovery of CI-CMP. Particularly, relationship between diabetes and recovery of CI-CMP is notable and deserves further research.

Keywords: cardiomyopathy, chemotherapy, Anthracycline, Trastuzumab, breast cancer

INTRODUCTION

Breast cancer is the most prevalent cancer type and the second leading cause of cancer mortality among women worldwide (1). Although new oncological therapies allow a prolonged lifespan for patients with breast cancer, one of the chemotherapy complications, chemotherapy induced cardiomyopathy (CI-CMP), may overshadow this benefit to some degree since it is the second cause of death in breast cancer survivors (2).

Anthracyclines and Trastuzumab are two commonly used chemotherapeutic agents in breast cancer despite having well-known cardiotoxic effects (3,4). Anthracyclines are not only one of the most effective anticancer treatments ever developed but also famous for their cardiotoxicity with a 5-fold greater risk than non-anthracycline chemotherapeutics (3). On the other hand, Trastuzumab is an Immunoglobulin G1 monoclonal antibody that targets human epidermal growth factor receptor 2 (HER 2) and is used exclusively in HER2 overexpressing breast cancer (4). While anthracyclines induce a dose-related and potentially irreversible cardiac toxicity, Trastuzumab induced cardiac toxicity is generally reversible and not related to dose. Nowadays, anthracyclines and Trastuzumab are often used sequentially and in combination with other potentially cardiotoxic agents like Paclitaxel and Cyclophosphamide in breast cancer in order to ensure enhanced effectiveness at the expense of cardiac safety which necessitates more attention for CI-CMP (5).

Risk factors for the development of CI-CMP is generally well defined and includes but are not limited to factors such as age, hypertension, diabetes, coronary artery disease, atrial fibrillation, renal failure and type of chemotherapy (6). In order to develop a strategy to reduce the frequency of CI-CMP, determining the factors associated with the recovery of CI-CMP is also crucial but it has not been studied adequately so far. In the present study, we sought to investigate the determinants of recovery of CI-CMP in HER 2 overexpressing breast cancer patients who received a widely used chemotherapy regimen consisting of doxorubicin, Trastuzumab, Paclitaxel and Cyclophosphamide and developed CI-CMP as a result.

MATERIAL and METHODS

Study Population

Among 7.180 consecutive breast cancer patients who were referred to cardiology clinic as part of routine follow up in a tertiary oncology Center between January 2015 and January 2020, 1.410 patients were HER 2 positive. Most commonly used chemotherapy protocol was 4AC (Adriamycin [Doxorubicin]-Cyclophosphamide) -12 P (Paclitaxel) + Trastuzumab in this population and 1.248 patients who received this protocol was selected. Eighty-eight of these patients developed CI-CMP and formed our study population. Thirty-eight patients were excluded from the study due to preexisting heart failure, more than mild valvular heart disease, coronary artery disease and cardiomyopathy (**Figure1**). The study protocol was approved by the Institutional Ethics Committee.

Analysis of Patient Data

Medical history and demographic information of the patients were obtained from hospital records. Venous blood samples were taken from all patients for hematologic and biochemical analysis at the time of CI-CMP diagnosis. A 12 lead ECG was recorded in each patient. Transthoracic echocardiography was performed before initiation of chemotherapy, before starting Trastuzumab and then once 3 months if the ejection fraction is in normal range and once a month if the ejection fraction drops below 55%. All patients underwent a comprehensive examination, including M-mode, two-dimensional and Doppler echocardiography (Ultrasound AS, Horten, Norway). Left ventricular ejection fraction was calculated by using Modified Simpson's method. All examinations were performed by an experienced cardiologist who had no knowledge of the patients' clinical information.

Definitions

Chemotherapy induced cardiomyopathy was defined as a decline in left ventricular ejection fraction (LVEF) of at least 10% to less than 50% (5). CI-CMP recovery was defined as, at least two consecutive LVEF measurements $\geq$ 50%. Hypertension was defined as systolic blood pressure $\geq$140 mmHg or diastolic blood pressure $\geq$ 90 mmHg or current antihypertensive medicine use. Diabetes mellitus was defined as a fasting blood glucose $\geq$ 126 mg/dL, HbA1c $\geq$ 6.5 or current antidiabetic medicine use.

Chemotherapy protocol

The chemotherapy protocol which used in the present study consisted of doxorubicin 60 mg/m^2 and Cyclophosphamide 600 mg/m^2 per each cycle, for four cycles with 3-week intervals, followed by Paclitaxel 80 mg/m^2 and Trastuzumab 4 mg/kg loading dose and 2 mg/kg weekly for 12 weeks. After that, Trastuzumab 6 mg/kg 3 weekly was continued to 1 year for non-metastatic patients and over one year in metastatic patients. If necessary, radiotherapy was started only after completing anthracycline and Cyclophosphamide therapy with a dose of 50 Gray. If CI-CMP develops, chemotherapy was stopped and treatment with an ACE inhibitor and beta blocker was started in the absence of specific counter indications to these drugs. Other heart failure medications were given, if necessary, in accordance with the current heart failure guidelines.

Statistical analysis

SPSS Statistics version 18.0 for Windows (SPSS Inc., Chicago, IL) was used for statistical analysis. Distribution pattern of the continuous variables was determined by using The Kolmogorov-Smirnov method. Continuous data was presented as mean and standard deviation or median and interquartile range according to distribution pattern. The Student's T test was used to compare data with normal distribution and Mann-Whitney U test was applied to compare the data without normal distribution. Categorical data was presented as frequencies and percentages and analysed using chi-square test. A multivariate logistic regression analysis model was used to assess the association between recovery of CI-CMP and other variables. In this model, variables with a p value <0.25 in univariate logistic regression analysis were selected for multivariate model. A two tailed p value <0.05 was considered significant.

RESULTS

Totally 88 patients with chemotherapy induced cardiomyopathy were included to the study. Cardiomyopathy was recovered in 52 (59.1 %) patients and not recovered in 36 (40.9 %). The median follow-up time was 64 months. The median age of the participants was 52 and similar between groups. In patients with recovered CI-CMP, rates of hypertension, diabetes mellitus, clinical heart failure, ECG anomaly and visceral metastasis were significantly lower. Mean heart rate and blood glucose were also significantly lower in recovered CI-CMP group.

Admission LVEF, rate of smoking, median blood pressures, previously used medications and heart failure medications except furosemide started after CI-CMP diagnosis were similar between groups. All patients received the same doses of doxorubicin (240 mg/m^2), Cyclophosphamide (2400 mg/m^2) and Paclitaxel (960 mg/m^2) according to chemotherapy protocol. Median Trastuzumab dose was not different between groups (**Table 1**).

A multivariate logistic regression analysis revealed that diabetes mellitus (OR 0.030, CI 0.010-0.083, p<0.001), heart rate (OR 0.799, CI 0.700-0.913, p<0.001), minimum LVEF during follow-up (OR 1.115, CI 1.015-1.223, p=0.03), development of clinical heart failure (OR 0.238, CI 0.098-0.876, p=0.022) and visceral metastasis (OR 0.022, CI 0.002-0.226, p=0.001) are independent predictors of the recovery of CMP (**Table 2**).
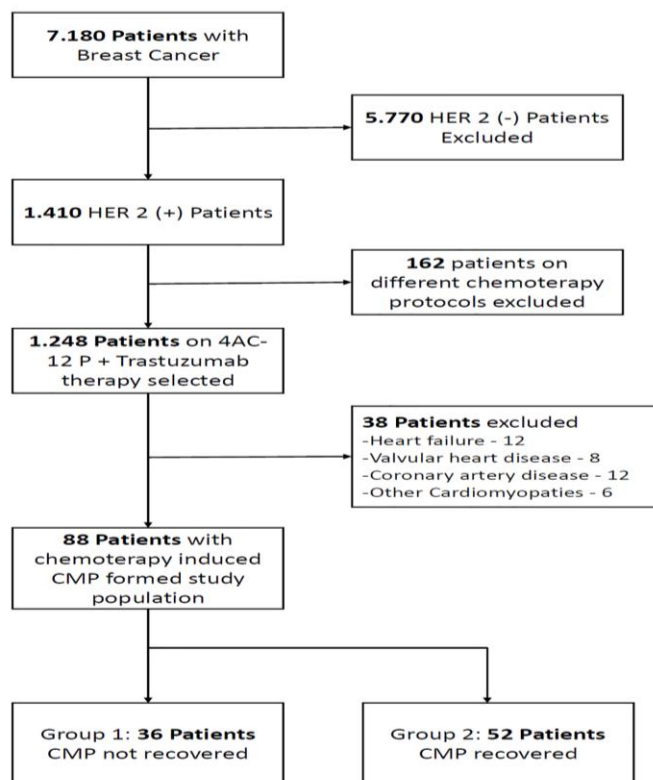
Figure 1. Patient selection algorithm

Table 1. Demographic, clinical, and laboratory characteristics of study participants.

	All CMP n=88	CMP not recovered n=36	CMP recovered, n=52	P value
Age (years)	52 (16)	53 (17)	50 (13)	0.308
Hypertension – n (%)	28 (31.8)	12 (33.3)	16 (30.7)	0.117
Diabetes – n (%)	36 (40.9)	24 (66.7)	12 (23.1)	**<0.001**
Hyperlipidemia – n (%)	41 (46.6)	18 (50)	23 (44.2)	0.384
Smoking – n (%)	19 (21.6)	8 (22.2)	11 (21.2)	0.407
BMI (kg/m^2)	27.6 (8.2)	27.9 (9.3)	27.4 (8.4)	0.434
Heart rate (min^{-1})	84.5 (18.8)	93 (12)	80 (10)	**<0.001**
Systolic BP (mmHg)	122 (26)	126 (22)	123 (25)	0.258
Diastolic BP (mmHg)	72 (20)	76 (18)	72 (16)	0.310
Glucose (mg/dl)	93.5 (18.3)	102 (26)	92 (14)	**0.035**
BUN (mg/dl)	13.0 (4.4)	13.0 (6.0)	13.0 (3.0)	0.115
Creatinine (mg/dl)	0.70 (0.16)	0.70 (0.23)	0.68 (0.13)	0.180
Hemoglobin (g/dl)	12.7 (1.5)	12.6 (2.9)	12.7 (1.5)	0.393
Platelets (x1,000/ml)	271 (96)	280 (106)	271 (97)	0.839
WBC (x1,000/ml)	6.80 (2.35)	7.10 (2.35)	6.7 (2.43)	0.398
Previous Medications				
Beta Blockers-n (%)	8 (9.1)	3 (8.3)	5 (9.6)	0.865
ACE Inhibitors-n (%)	12 (13.6)	5 (13.9)	7 (13.5)	0.988
Spironolactone-n (%)	2 (2.3)	1 (2.8)	1 (1.9)	0.789
Calcium antagonist-n (%)	10 (11.4)	4 (11.1)	6 (11.5)	0.767
Trastuzumab dose	72 (22)	76 (24)	70 (18)	0.594
Radiotherapy-n (%)	38 (43.1)	18 (50)	20 (38.5)	0.282
Visceral metastasis-n (%)	26 (29.5)	18 (50)	8 (15.4)	**<0.001**
Estrogen receptor (+)-n(%)	54 (61.4)	24 (66.7)	30 (57.7)	0.528
Progesterone receptor(+)-n(%)	38 (43.2)	14 (38.9)	24 (46.2)	0.311
Time to CI-CMP (months)	10 (20)	11 (22)	10 (12)	0.544
Clinical heart failure	14 (15.9)	10 (27.8)	4 (7.7)	**0.009**
ECG anomaly – n (%)	31 (35.2)	14 (38.9)	18 (32.7)	0.248
LVEF - Admission (%)	62.0 (4.0)	62.0 (5)	62.0 (4.0)	0.878
LVEF - Minimum (%)	40 (5.0)	38 (10)	43 (5)	**0.027**
LVEF - Last (%)	55.0 (11.5)	45 (5)	58 (5)	**<0.001**
Heart failure medications given				
Beta Blockers – n (%)	80 (90.9)	33 (91.6)	47 (90.4)	0.511
ACE Inhibitors – n (%)	75 (85.2)	31 (86.1)	44 (84.6)	0.457
Spironolactone– n (%)	8 (9.1)	6 (16.6)	2 (3.8)	0.067
Furosemide– n (%)	14 (15.9)	10 (27.8)	4 (7.7)	**0.009**

BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; WBC, white blood cell; ACE, angiotensin converting enzyme; CI-CMP, chemotherapy induced cardiomyopathy; ECG, electrocardiography; LVEF, left ventricular ejection fraction.

Table 2. Multivariate logistic regression analysis demonstrating the association between chemotherapy induced cardiomyopathy recovery and other factors.

Variables	Univariable		Multivariable	
	OR (95 % CI)	p value	OR (95 % CI)	p value
Age	0.976 (0.933-1.020)	0.281	-	-
Hypertension	0.471 (0.186-1.195)	0.113	0.546 (0.235-1.145)	0.108
Diabetes	0.080 (0.017-0.386)	<0.001	0.030 (0.010-0.083)	**0.001**
Heart rate	0.883 (0.834-0.934)	<0.001	0.799 (0.700-0.913)	**0.001**
BUN	0.860 (0.748-0.990)	0.035	0.871 (0.686-1.116)	0.096
Creatinine	0.911 (0.831-1.231)	0.432	-	-
ECG anomaly	0.729 (0.299-1.775)	0.486	-	-
LVEF - Minimum	1.084 (1.012-1.161)	0.021	1.115 (1.015-1.223)	**0.03**
Clinical heart failure	0.217 (0.062-0.759)	0.017	0.238 (0.098-0.876)	**0.022**
Visceral metastasis	0.182 (0.067-0.493)	0.001	0.022 (0.002-0.226)	**0.001**
Radiotherapy	0.625 (0.265-1.476)	0.284	-	-

OR, odds ratio; CI, confidence interval; BUN, blood urea nitrogen; ECG, electrocardiology; LVEF, left ventricular ejection fraction.

DISCUSSION

In the present study, we investigated the factors associated with the recovery of CI-CMP in a group of patients who received an anthracycline and TrastuzumabTrastuzumab based chemotherapy protocol for HER2 positive breast cancer and found out that diabetes mellitus, heart rate at the time of CI-CMP diagnosis, minimum LVEF during follow-up, development of clinical heart failure and presence of visceral metastasis were independently associated with recovery of CI-CMP. The unique aspect of the present study was its homogenous population in terms of both cancer diagnosis and chemotherapy protocol which renders a healthy analysis of independent predictors of the recovery of CI-CMP possible with minimal confounding factors. Despite the advancements in cardio-oncology in recent years, exact mechanism of chemotherapy induced cardiotoxicity remains to be elucidated. Doxorubicin, which classic example of cardiotoxic chemotherapeutics, and Trastuzumab have different mechanisms for cardiotoxicity with proposed common points. Oxidative stress has long been believed to be the major cause of doxorubicin induced cardiotoxicity (7). However, additional mechanism such as DNA damage, mitochondrial dysfunction, defects in apoptosis, iron handling and dysregulation of autophagy which proposed cause of antioxidants were shown to be ineffective in preventing cardiac side effects of doxorubicin (7,8). On the other hand, Trastuzumab suppresses autophagy in cardiomyocytes by suppressing HER2 signalling and trigger accumulation of reactive oxygen species (9). Furthermore, doxorubicin activates HER2 signalling pathway and increases HER2 protein levels in cardiomyocytes and render them dependent to HER2 signalling for survival in stressed conditions. Thus, cardiomyocytes become more sensitive to Trastuzumab after doxorubicin treatment (10). Cyclophosphamide cardiotoxicity is rare and primarily seen in patients receiving high doses before bone marrow transplantation (11). Total bolus dose, older age, mediastinal irradiation and combination therapy with other cardiotoxic drugs are risk factor for Cyclophosphamide cardiotoxicity (12). Taxanes are frequently used together with other cardiotoxic drugs in breast cancer treatment and contribution of individual drugs to cardiotoxicity in such multidrug regimens is difficult to assess.

The absolute cardiotoxic risks of taxans are unknown and some reports suggest that they may be safe alternatives to anthracyclines in patients with preexisting left ventricular dysfunction (13). Factors associated with the recovery of CI-CMP have not been clearly identified so far despite the fact that non-recovery of left ventricular function is associated with worse survival (14). Decreased ejection fraction, enlarged left ventricular size, pulmonary hypertension, introduction of heart failure treatment and older age were associated with recovery in previous studies (14-16). Similarly, the results of the present study demonstrated that minimum LVEF during follow-up, development of clinical heart failure and heart rate at the time of CI-CMP diagnosis which may be an indicator of neurohormonal activation and progression of heart failure are independently associated with CI-CMP recovery. Diabetes mellitus was another predictor of CI-CMP recovery in our study. Diabetes is a well-known risk factor for chemotherapy induced CMP in both patients receiving Trastuzumab and doxorubicin but its predictive value for recovery of CI-CMP was demonstrated for the first time in the present study (5,6). Actually, there is growing evidence about the relationship between doxorubicin cardiotoxicity and cardiac metabolic alterations as a result of imbalanced insulin signaling and cardiac insulin resistance (6,1). Moreover, studies about two antidiabetic agents, metformin and empagliflozin, revealed that these agents have promising protective effect against the development of doxorubicin induced cardiotoxicity (17,18). Thus, relationship of non-recovery of CI-CMP and diabetes is not surprising and diabetic patients who receive cardiotoxic chemotherapy need special attention. Surely, further studies are required in order to elucidate the association of diabetes, antidiabetic medications, and the development and recovery of CI-CMP. Interestingly, advanced cancer may contribute to impairment of cardiac insulin signaling via reduced pancreatic insulin production secretion of insulin-degrading enzymes, which may explain the findings of the present study, which suggested that presence of visceral metastasis is related to recovery of CI-CMP (19). In addition, other cancer related mechanisms such as proteolysis by ubiquitin-proteasome pathway, also mitochondrial dysfunction and release of proinflammatory cytokines may further contribute to heart failure development in advanced cancer (20).

The present study has several limitations. First, it is a single center study. Second, only HER2 positive breast cancer patients receiving a single chemotherapy protocol were included and results of the study cannot be generalized to all breast cancer patients. In addition, study participants received four different chemotherapeutic agents, and individual contribution of individual drugs to cardiotoxicity was not possible to assess.

CONCLUSION

In conclusion, diabetes mellitus, heart rate at the time of CI-CMP diagnosis, minimum LVEF during follow-up, development of clinical heart failure, and presence of visceral metastasis were independently associated with recovery of CI-CMP in HER2 positive breast cancer patients who received a chemotherapy protocol consisting of doxorubicin, Cyclophosphamide and Paclitaxel. Further studies are required the elucidate the factors associated with the recovery of CI-CMP. Particularly, relationship between diabetes and recovery of CI-CMP is notable and deserves further research.

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SARS-Cov-2 Infection in Patients with Inflammatory Bowel Disease: A Single-Center Study

Enver Akbaş[1]*, Mustafa Salih Akın[1]

1 Department of Gastroenterology, Faculty of Medicine, Istanbul Medipol University, Istanbul, TR

* Corresponding Author: Enver Akbaş E-mail: drenverakbas@gmail.com

ABSTRACT

Objective: Inflammatory bowel diseases (IBDs) are polygenic disorders. Patients with IBD, especially ulcerative colitis (UC), are more vulnerable to infections because of medications. Key COVID-19-related factors/risks have not been well-researched in IBD patients. In this study, we compared IBD patients with control patients who presented to our clinic with COVID-19 infection suspicion regarding COVID-19 PCR test positivity, COVID-19 pneumonia, hospitalization, and need for treatment at the intensive care unit (ICU).

Material and Methods: Thiscohort study included 480 IBD patients as cases and 9,269 age- and gender-matched control patients who came to our hospital for complaints/checkups and were tested for COVID-19 PCR.

Results: Covid-19 positivity was higher in IBD patients than in controls. COVID-19 pneumonia rates were higher in IBD compared to the pneumonia rate of Turkey — mainly due to the high prevalence of COVID-19 pneumonia in UC as none of the Crohn's disease (CD) patients experienced COVID-19 pneumonia. Hospitalization was significantly higher in UC than in CD and higher in IBD than in controls. Hospitalization at ICU was significantly higher in UC than in the controls. There were no IBD patients who died because of COVID-19 infection.

Conclusion: IBD patients have a significantly higher rate of COVID-19 PCR positivity, COVID-19 pneumonia, hospitalization, and the need for ICU than the controls; however, mortality is comparable.

Keywords: COVID-19, Crohn disease, inflammatory bowel diseases, ulcerative colitis

INTRODUCTION

Inflammatory bowel diseases (IBDs) (Crohn's disease (CD) and ulcerative colitis (UC)) are polygenic disorders caused primarily by intestinal microbiome contributions, defects in barrier function, and irregular host responses to microbial stimulation (1). Most IBD patients can be treated with aminosalicylates, antibiotics and corticosteroids, or a proper combination of these medications. Many, however, will need immunomodulators such as 6-mercaptopurine (Excella GmbH & Co. Feucht, Germany), as well as biologic treatment such as infliximab, when necessary (2). CD is chronic, affecting the entire gastrointestinal tract, and can cause extraintestinal complications. Patients with CD are at high risk for diseases such as cancer and should take biological drugs with/without immunomodulators (3).

UC is idiopathic and chronic with an unpredictable course, with exacerbation and remission periods. In patient with severe UC, in addition to aminosalicylates, topical or systemic corticosteroids, immunosuppressives, and biological agents are used (4). An excessive immune response is triggered against the target organ in IBD pathogenesis. This is also linked to a weakened immune system. Moreover, due to immunosuppressive, these patients are more vulnerable to infections.

COVID-19 has become one of the world's most serious public health crises and causes of death globally. The research for therapeutic and preventive options against the new SARS-CoV-2 is still ongoing. Two of the current priorities in this field are the active use of already-approved pharmacological agents, and the development of new treatments to reduce virus-related morbidity/mortality. Another is the production and spreading of safe and effective vaccines (5). In IBD, COVID-19 transmission rates, viral pneumonia prevalence in COVID-19 sufferers, hospitalization owing to severe disease, intensive care (IC) needs, and illness management have not been well-researched. Our study has the distinction of being Turkey's first study on the subject. It is also one of the most comprehensive studies, with the most cases reported in English literature.

MATERIAL and METHODS

This study was conducted to collect data on COVID-19 infection in 954 IBD patients followed up on at our center from 2014 to 2021. It is based on analysis of data from patients with IBD who were followed up by our center and underwent the COVID-19 PCR test because of complaints for Covid-19-like symptoms.

As a control group, 9,269 patients were age- and gender-matched to our IBD patients from 14,520 patients who presented to our center for various complaints or checkup purposes and underwent COVID-19 PCR testing between December 2020 and March 2021. The aim was to compare the IBD patients (i.e., cases) with the control cohort in terms of COVID-19 test positivity, COVID-19 pneumonia frequency, hospitalization due to COVID-19, need for IC and intubation, and, if applicable, fatality rates. COVID-19 pneumonia rates could be detected in the IBD group but not in the controls because not all patients testing positive had lung computed tomography (CT) scans. Therefore, the pneumonia rates in IBD were compared to the general average reported by the Turkish Ministry of Health as Turkey's overall Covid-19-related pneumonia status.

Ethical approval was provided by the Ethics Committee of Istanbul Medipol University Hospitals, on 10 March 2021 (decision No:267). Moreover, permission was received from the Turkish Ministry of Health for anonymous analysis of recorded patient data. All procedures were in accordance with the ethical standards of the committee on human experimentation and with the Helsinki Declaration of 1964 and later versions.

Statistical Analysis

Data were analyzed using SAS ®Version 9.4 (Carry, North Carolina, USA). Continuous variables were presented as mean±standard deviation, and categorical variables as overall or subgroup-specific frequencies and percentages. Relations between pairs of categorical factors were analyzed through Chi-Square/Fisher's Exact Test as appropriate. Distributions of continuous variables among categorical variable levels were compared through Wilcoxon-Mann-Whitney/Kruskal-Wallis test as appropriate.

Cases were matched with controls using the propensity score approach in SAS PSMATCH procedure with exact gender match. P-values are not adjusted for multiplicity; therefore, the results must be considered in the context of generating research hypotheses for future prospective studies. A p value <.05 was considered statistically significant.

RESULTS

The IBD cohort involved 954 patients (75.4% had UC, 24.6% had CD). Mean follow-up time was 5.2±4.0, 6.0±4.9 and 4.8±3.3 years among the entire cohort, females, and males, respectively. Regarding gender, 430 (44.61%) were female, and 534 (55.39%) were male. Of these, 480 (49.79%) were tested for COVID-19 through RT-PCR. Therefore, our case group consisted of 480 patients, while our control group consisted of 9,269 age- and gender-matched control cases tested for COVID-19 through RT-PCR at our center. Nearly all IBD patients were monitored in remission with or without the treatments available at the time.

The groups have compatible age and gender distribution as expected through matching. The average age was 40.4±11.6 years for the cases and 40.1±11.7 years for the controls (p=0.53); 64.4% of the cases and 63.1% of the controls were male (p=0.57).

Covid-19 test positivity (**Table 1**) was significantly higher in the IBD patients (34.38%) compared to the controls (28.97%) (p=0.011). CD patients had compatible Covid-19 positivity rate with the controls (p=0.73), whereas UC patients had a significantly greater proportion of COVID-19 positive cases than the controls (p=0.001).

Table 2 compares COVID-19 PCR test results per disease location. There were significantly higher COVID-19 PCR test positivity rates in UC involving the left colon (p=0.005), pancolitis (p=0.003), and CD involving the colon and terminal ileum (p=0.002) compared to the controls according to Montreal classification. The rate was significantly lower than the controls only in CD involving the terminal ileum (19.4%, p=0.041).

Table 1. COVID-19 PCR test data of IBD subgroups and control group. *Chi-Square test results against the controls

| | COVID-19 PCR Test | | | | | | |
| | Negative | | Positive | | Total | | *p** |
	n	Row%	n	Row%	n	Row%	
Ulcerative Colitis	213	62.83	126	37.17	339	100.00	0.001
Crohn's Disease	102	72.34	39	27.66	141	100.00	0.730
Controls	6584	71.03	2685	28.97	9269	100.00	

Table 2. Comparison of COVID-19 PCR test data with control group by IBD localization zones.

| | COVID-19 PCR Test | | | | | |
| | Negative | | Positive | | Total | |
	n	Row%	n	Row%	n	*p**
Ulcerative Colitis						
Rectum	63	72.41	24	27.59	87	0.780
Left Colon	93	60.78	60	39.22	153	0.005
Pancolitis	57	57.58	42	42.42	99	0.003
Crohn's Disease						
Terminal ileum	75	80.65	18	19.35	93	0.041
Colon	6	100.00	.	.	6	0.120
Colon+Terminal ileum	21	50.00	21	50.00	42	0.002
Controls	6584	71.03	2685	28.97	9269	

Among the all IBD patients who tested positive for COVID-19 PCR, 5.45% were those who did not receive treatment, 60% received mesalazine (Dr. Falk Pharma GmbH, Neuenburg, Germany) only, 30.91% received mesalazine and azathioprine, and 3.64% received anti-TNF. Compared to the control group, statistically significantly greater proportion of those receiving mesalazine and azathioprine tested positive for COVID-19 (43.6%, p=0.0005). Because of insufficient number of cases, no significant difference could be found between other subgroups and the controls.

Overall, the incidence of COVID-19 pneumonia in IBD patients was greater than the national Covid-19 related pneumonia incidence in Turkey (23.63% vs. 5.28%, respectively, p<0.0001) (see **Table 3 and Figure 1**). However, this difference was interestingly attributed to the high incidence of COVID-19 pneumonia found in UC patients (30.95% vs. 5.28%, respectively). None of the CD patients had COVID-19 pneumonia. Hospitalization due to Covid-19 also differed significantly among the groups.

In terms of admission to ICU and intubation, there was a significant difference between the IBD and control groups (p<0.0001) and between the UC and control groups (p<0.0001).

All nine patients who were admitted to ICU and were intubated had ulcerative pancolitis, and three were taking anti-tumor necrosis factor (anti-TNF) drugs, three were taking mesalazine, and azathioprine, and three were taking mesalazine only. There were significant differences in terms of gender between the UC, CD, and control groups among those with COVID-19; 34.55% of IBD patients with COVID-19 were female, and 65.45% were male. Moreover, males and females were significantly different regarding hospitalization, ICU treatment, and pneumonia (p<0.05).

Hospitalized patients were divided into treatment subgroups. Statistical analysis was not possible for those followed without treatment and those receiving anti-TNF because of insufficient numbers of patients. Patients receiving mesalazine only and those receiving mesalazine and azathioprine were not significantly different from the controls in hospitalization (6.25% vs. 4.84%, p=0.53, and 6.30% vs. 0.65, p=0.65), but more frequently required IC and intubation than the controls (3.13% vs. 0.6%, p=0.0031, and 6.28% vs 0.6%, p<0.0001). The disease was not lethal in any of our patients diagnosed with IBD and tested positive for COVID-19, resulting in a mortality rate of 0%.

Table 3. Pneumonia, hospitalization and IC statistics in IBD and control groups

| | IBD | | | | | | CONTROL | | |
| | Ulcerative Colitis (UC) | | Crohn's Disease (CD) | | Total | | Total | | |
	n	Col%	n	Col%	n	Col%	n	Col%	*p**
COVID-19's pneumonia									
Yes	39	30.95	0	0.00	39	23.64	N/A	5.28**	<0.0001[a], <0.0001[b],
No	87	69.05	39	100.00	126	76.36	N/A	94.72**	<0.0001[c], 0.14[d]
Hospitalization									
Yes	15	11.90	0	0.00	15	9.09	130	4.84	0.0008[a], 0.0373[b],
No	111	88.10	39	100.00	150	90.91	2555	95.16	0.0005[c], 0.20[d]
ICU Treatment									
Yes	9	7.14	0	0.00	9	5.45	16	0.60	<0.0001[a], 0.11[b],
No	117	92.86	39	100.00	156	94.55	2669	99.40	<0.0001[c], 0.66[d]
OVERALL TOTAL	126	100.00	39	100.00	165	100.00	2685	100.00	

*Chi-Square test results against the controls

**The percentage is the average data for the whole of Turkey.

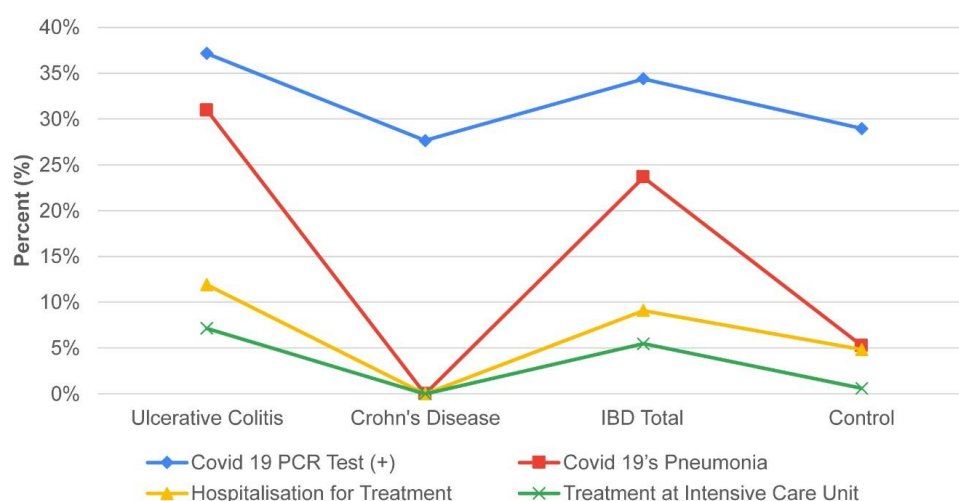[a] Case Group (IBD) vs. Control Group, bUC vs. CD, cUC vs. Control Group, dCD vs. Control Group

Figure 1. COVID-19 related results of case and control group participants.

DISCUSSION

Although the specific origin of IBD is unknown, most experts believe it is tissue damage caused by an overactive immune response to luminal bacteria in the intestines through various environmental effects in genetically susceptible people (6). IBDs affect millions of people and cause several symptoms/conditions, necessitating drug use, but they also put patients at risk of developing other complications (7). Coronaviruses bind to their targets in cells via angiotensin-converting enzyme-2 (ACE2) (8). Morphologically, epithelial cells in the lungs, intestines, kidneys, and blood vessels secrete ACE2 with the highest concentrations in the terminal ileum and colon (9). In studies on different biological samples of SARS-Cov-2 in COVID-19 patients, the virus was isolated from approximately 50% of fecal samples. Moreover, approximately 1/5 of patients continue to test positive through fecal samples after testing negative through respiratory tract samples (10). These findings explain why COVID-19 patients develop GIS symptoms and how SARS-Cov-2 also spreads through the fecal route. ACE2 secretion is increased in the inflamed bowel of IBD patients (11). Moreover, proteomics studies on IBD tissue samples revealed that ACE2 secretion increase was more pronounced in CD than UC (12). Aside from binding to ACE2, coronavirus envelope must also fuse with the host cell membrane for infection to occur. This is aided by specific fusion or "spike" proteins known to be up-regulated in IBD (13). These findings indicate that IBD patients' inflamed intestinal mucosa is an ideal entry point for the virus into tissues. However, the thesis that the GIS mucosa, apart from the respiratory tract mucosa, is another entry point for SARS-Cov-2 to the body has yet to be proven.

A study from Italia (14) reported a significant link of increased risk between active IBD and COVID-19 pneumonia and death from COVID-19; while deaths due to COVID-19 were not significantly related to corticosteroid and anti-TNF use, being older than 65 was the strongest predictor of death (14). A new IBD series reported a 5% mortality rate from Spain (15). COVID-19 infection rate was lower in IBDs than in controls, while the mortality rates were similar in another study from Spain (16). However, there are some issues with determining and accurately comparing data from IBD and control groups in all these study series. The limitation of our study is that not all IBD patients we followed were tested for COVID-19 PCR, but it is important to note that the control and case group cohorts were from the same center and were similar in age and gender.

CONCLUSION

We found that while IBD patients had an increased risk of COVID-19 infection and associated pneumonia, hospitalization, and ICU treatment, their mortality rates did not rise. There was no particular mortality risk regarding the prevalence and type of treatment, either. Therefore, it is recommended not to discontinue IBD patients' ongoing treatment during COVID-19 infection and to closely monitor the symptoms/signs of patients taking immunosuppressants. However, according to the guidelines, IBD patients over the age of 60 and/or those with comorbidity are at a higher risk of COVID-19 pneumonia and, therefore should avoid activities that increase the risk of disease transmission (17).

Although IBD patients have a higher risk of COVID-19 infection, we believe that the lack of a parallel increase in mortality is due to the immunomodulatory treatments, which protect them from "cytokine storm" — thought to be the main cause of COVID-19 infection-related mortality.

Author Contributions: EA, MSA: Concept, Data collection and/or processing, Analysis and/or interpretation, Literature review, **EA:** Writing, and Revision.

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Spontaneous hematomas, the new surgical challenge of COVID patients? Hematomas in COVID patients

Radu Mirica[1]*, Claudiu Ungureanu[1], Andrei Vacarasu[1], Danut Ciotirla[1], Razvan Iosifescu[1], Marius Zamfir[1], Alexandra Mirica[1], Niculae Iordache[1], Octav Ginghina[1]

1 Emergency Clinical Hospital 'Saint John', University of Medicine and Pharmacy 'Carol Davila', Bucharest, Romania

* Corresponding Author: Radu Mirica E-mail: mirica_rm@yahoo.com

ABSTRACT

Objective: There was a critical inconsistency in making therapeutic choices regarding anticoagulation in patients with COVID-19. This study aims to evaluate and determine the causes that led to the formation of hematomas, spontaneous bleeding or what is involved in this hypothesis and the elements related to this aspect.

Patients and methods: The present study is a case series analysis that aims to identify and verify the cause of spontaneous hematomas in COVID positive patients for whom surgery was required. Thus, we analysed patients who presented various spontaneous hematomas during the covid pandemic (March 2020 - May 2021) for which surgery was performed, having as a control group (CG) a homogeneous group in terms of age, covid infection severity, and comorbidities with the study group (SG).

Results: Regarding the preoperative and postoperative days, SG had average values of 4.76 ± 5.36 (Mean$\pm$SD) for preoperative days and 9.5 ± 9.327 for postoperative days. Given that one of the most suspected causes of hematomas was considered an anticoagulant overdose, we compared the anticoagulant doses and the type of anticoagulant, so the anticoagulant doses did not show statistically significant differences (0.836 ± 0.294ml in SG versus 0.866 ± 0.343ml in CG with p=0.588). As expected, hemoglobin (Hb) was significantly lower for SG with mean values of 7.266 ± 1.431mg/dl compared to CG that had mean values of 12.9 ± 2.092mg/dl (p=0.001). The correlation between the value of Hb (average value was 12.9 mg/dl, a minimum of 8.7 mg/dl and a maximum of 16.6 mg/dl) and the value of procalcitonin (average value was 0.13, a minimum of 0.02 and a maximum of 0.7) is statistically significant having p=0.012. In SG, hemoglobin can be correlated with ESR (erythrocyte sedimentation rate), p=0.008 and with procalcitonin, p=0.05. Both have a negative correlation explained by a proinflammatory status that can aggravate low hemoglobin levels, but without a direct link to high ESR and procalcitonin values.

Conclusions: The hypothesis of anticoagulant overdose is not supported or verified by the present study, we consider that additional thromboelastography tests are necessary to be able to completely refute it. Mortality did not increase statistically significantly.

Keywords: COVID-19, hematomas, hemostasis,

INTRODUCTION

The World Health Organization (WHO) named the newly found coronavirus in 2019 "COVID-19" and later declared it a pandemic in March 2020. General clinical signs of SARS-CoV-2 disease include fever, myalgia, weakness and it can go up to dyspnea and pneumonia. Also, it associates other disorders from the gastrointestinal area (vomiting, nausea), cardiovascular (myocardial infarction, arrhythmias) and renal (acute renal injury). Recent reports and studies also point to vascular damage that includes thrombosis and endothelial dysfunction [1-3].

Since the beginning of the COVID pandemic, there have been multiple studies in this direction, studies that have identified the procoagulant status of this infection, which is why anticoagulation was introduced in the treatment protocol.

As the focus on coagulopathy caused by COVID-19 increases, mortality can be explained by thrombotic phenomena [1,2].

A multicenter review in the United States detailed a thrombotic complication rate of 9.5%, despite the administration of the standard dose of prophylactic anticoagulation [3]. Furthermore, bleeding episodes have been identified in patients with COVID-19. In general, the number of patients with complications that lead to death varies from 4.8% to 8% [3, 4].

The early stage of this disease can be associated with high D-dimer, prolonged PT, and elevated levels of fibrinogen, indicating activation of coagulation pathways and thrombosis (Mehrdad Rostami)

Elevated plasma levels of CRP (C-reactive protein) and NT-proBNP (N-terminal B-type natriuretic peptide) are fully related to the lethal outcome of COVID-19, suggesting that irritation is a potent component of myocardial injury and underlying disease of mortality [2].

The disease progresses in 3 stages: the initial disease caused by dynamic contamination, an aspiration moment stage and, when extreme, a third stage characterized by hyperinflammation, cytokine storm, high levels of biomarkers of heart damage and remarkable morbidity and mortality. In some patients with COVID-19, the inflammatory reaction continues to intensify and it occurs in systemic inflammation, with a better measure on deceased people with dynamic thrombocytopenia. Regarding this famous decrease in platelet count, clots have been identified in the small vessels of the lungs, heart and liver of patients with COVID-19 [4] and extend the predominance of deep vein thrombosis in hospitalized patients with dynamic contamination [3, 5].

There is no current standardized approach to anticoagulation in patients with SARS-CoV-2 infection, while the potential dangers of death remain. Our thinking characterizes the anticoagulation therapy used in patients with COVID-19 and the associated death risk [2, 6].

There was a critical inconsistency in making therapeutic choices regarding anticoagulation in patients with COVID-19. It is well known that anticoagulation therapy is a non-lethal treatment with regular clinical controls. The choice to increase anticoagulation doses should subsequently be carefully considered. The dangers should be communicated, and the sharing of choices is ideal in such clinical situations [2, 7].

Through this study, we aimed to evaluate and determine the causes that led to the formation of hematomas, spontaneous bleeding or what is involved in this hypothesis and what the elements related to this aspect are

MATERIAL and METHODS

The present study is a case series analysis that aims to identify and verify the cause of spontaneous hematomas in COVID positive patients for whom surgery was required. Thus, we analyzed patients who presented various spontaneous hematomas during the covid pandemic (March 2020 - May 2021) for which surgery was performed having as a control group (CG) a homogeneous group in terms of age, COVID-19 severity and comorbidities with the study group (SG). Covid severity, O2 requirement, age, sex, hospitalization time (both preoperative and postoperative), discharge status, comorbidities, and biological analyzes

(complete blood count, coagulation testing, D-dimer) were analyzed for both groups. The data were collected from patients' files and from the digitized database of the 'Saint John' Emergency Clinical Hospital, Bucharest for the period March 2020 - May 2021. Descriptive and analytical statistics were performed using Microsoft Excel and SPSS Statistics 17.0 considering as statistically significant a p-value <0.05, all values being expressed in mean and standard deviation.

RESULTS

The SG group, the group of patients who underwent surgery for a spontaneous hematoma, had an average age of 70.83± 8.009 years. The CG was chosen to be uniform with the study group and presented an average age of 72.33 ±6.321 years. Also, the ratio of patients by gender was similar according to the graph below.(Figure 1)

Regarding the preoperative and postoperative days, SG had average of 4.76 ± 5.36 for preoperative days and 9.5± 9.327 values for postoperative days.

The total hospitalization days are the common parameter of the two groups, we compared them, and we obtained the following values: 14.17± 10.188 days for SG versus 14.93± 4.096 days for CG. This shows us that there is no statistically significant difference between the two groups and therefore, the appearance of a hematoma that required surgery did not prolong the total number of days of hospitalization. Also, for SG there is a statistically significant correlation between age and total days of hospitalization (p=0.049).

The state of discharge is shown according to the graphs below, in CG there were no deceased patients, although the severity of SARS-CoV2 pneumonia was similar for both groups. For SG, most patients (n=8) died, thus the comparative data between the two groups was statistically significant (p = 0.002). Also, for CG, there is a correlation between total hospitalization days and status upon discharge (p=0.005) meaning that a longer stay in hospital can negatively influence the discharge status. (Figure 2)

Given that one of the most suspected causes of hematomas was considered an anticoagulant overdose, we compared the anticoagulant doses and the type of anticoagulant, so the anticoagulant doses did not show statistically significant differences (0.836 ±0.294ml in SG versus 0.866 ±0.343ml in CG with p=0.588). Given that the type of anticoagulant used (Fraxiparin, Clexane or Heparin) was evenly distributed in the two groups, we cannot conclude that this was the cause of the hematomas.

As expected, hemoglobin (Hb) was significantly lower for SG, with mean values of 7.266 ±1.431mg/dl compared to CG which had mean values of 12.9 ±2.092mg/dl (p=0.001). The correlation between the value of Hb (average value was 12.9 mg/dl, a minimum of 8.7 mg/dl and a maximum of 16.6 mg/dl) and the value of procalcitonin (average value was 0.13, a minimum of 0.02 and a maximum of 0.7) is statistically significant having p=0.012. In SG, hemoglobin can be correlated with ESR (erythrocyte sedimentation rate), p=0.008 and with procalcitonin, p=0.05. Both have a negative correlation explained by a proinflammatory status that can aggravate low hemoglobin levels, but without a direct link to high ESR and procalcitonin values. (Figure 3)

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The difference in the number of leukocytes between the two groups was also with a statistical significance, SG had much higher values than those in CG (19.065 ±897/µl in SG vs 8.961 ±4.356/µl in CG) thus, we can raise the hypothesis that proinflammatory and infectious status can cause a more important state of anticoagulation. We also observed that patients in CG have lower values of leucocytes (average value was 8.96/µl, with a minimum of 2.77/µl and a maximum of 18.9/µl) also had a lower value of thrombocytes (average value was 346.000/µl with a minimum of 59.000/µl and a maximum of 890.000/µl), p=0.012. Leucocytes also correlate with C-reactive protein (average value was 36.64mg/dL with a minimum of 0.63 mg/dL and a maximum of 204 mg/dL), p= 0.012, being a statistically significant correlation. Another correlation was made in SG between preoperative days and the number of leucocytes (p=0.007) explained by the proinflammatory status, an increased number of leukocytes causing the operating team to operate earlier, even if the proinflammatory status could be given by the pneumological condition. Also, C-reactive protein was correlated with procalcitonin (p=0.046), both being involved in the proinflammatory status. (Figure 4)

The values of fibrinogen in CG (average value was 435 mg/dL with a minimum of 276 mg/dL and a maximum of 613 mg/dL) have a statistically significant correlation with procalcitonin (average value was 0.13, a minimum of 0.02 and a maximum of 0.7), p= 0.032 and with IL-6 (average value was 98.8 pg/mL with a minimum of 1.5 pg/mL and a maximum of 507 pg/mL), where p= 0.05.

Another correlation in CG was D-dimers (average value was 0.64 with a minimum of 0.27 and a maximum of 1.81) with IL-6 (average value was 98.8 µg/mL with a minimum of 1.5 µg/mL and a maximum of 507 µg/mL), p= 0.005. The higher the D-dimers was, the higher the value of IL-6 was. (Figure 5)

Moving to coagulation, in the same CG we also observed that aPTT (activated partial thromboplastin time), with an average value of 38s (a minimum of 22.4s and a maximum of 99s) has a more statistically significant correlation with fibrinogen (p=0.03), with ESR (average value was 43s with a minimum of 11s and a maximum of 89s), p=0.029, with procalcitonin (p= 0.001). We observed that IL-6 (average value was 98.8 with a minimum of 1.5 and a maximum of 507) has some interesting statistically significant correlation with the total hospitalization days (average value was 15 with a minimum of 11 and a maximum of 25), p=0.008, also with fibrinogen,(p= 0.05) and with D-dimer (p= 0.005).

Regarding platelets, in SG there is a negative correlation between them and age (p=0.022), also thrombocytes with ESR (p=0.046). This is explained by the procoagulant status in the context of sepsis, elderly patients consume platelets faster and cannot be produced in time due to age slowdown. (Figure 6)

In the case of the anticoagulant dose (average value was 0.9ml with a minimum of 0.4ml and a maximum of 1.6ml), we found that there is a statistically significant correlation with the total hospitalization days (p=0.05) and with Hb (p=0.05). It is known that the dose of anticoagulant increases aPTT, this being a positive correlation in SG with p=0.044. (Figure 7)
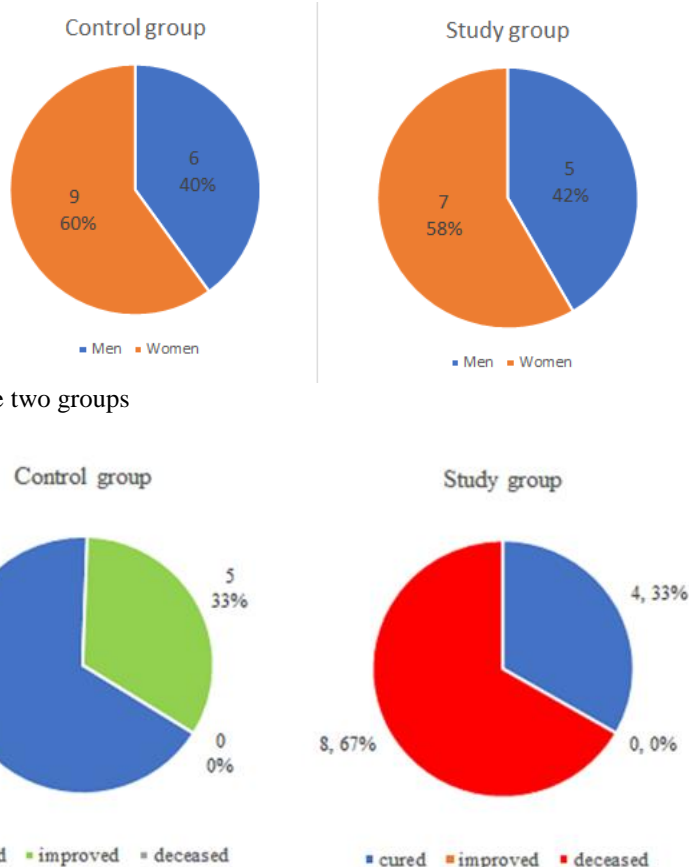

Figure 1: Gender division of the two groups

Figure 2: State of discharge for the two groups (cured/improved/deceased)
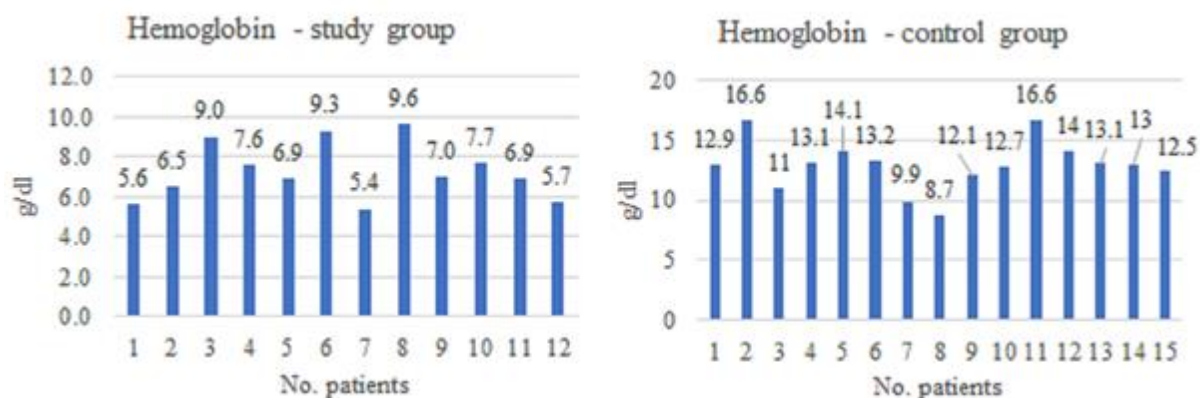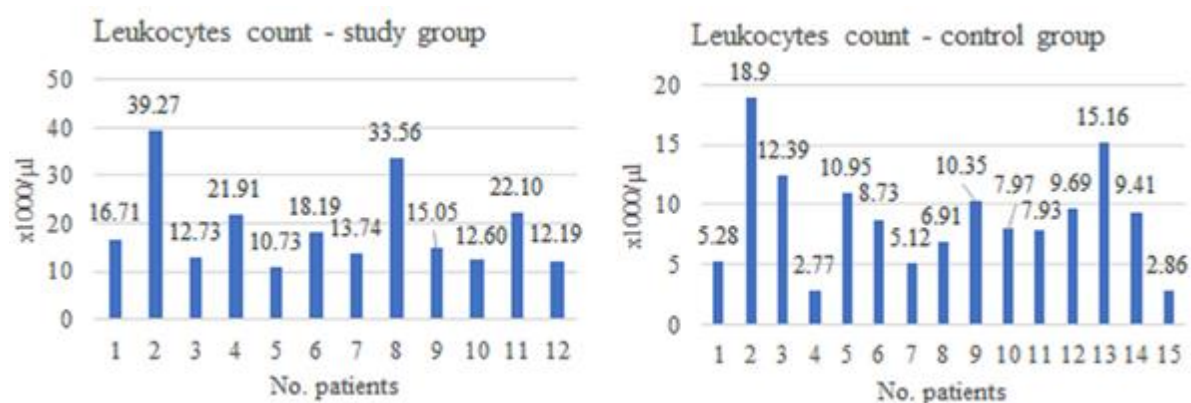
Figure 3: Hemoglobin evaluation for the two groups
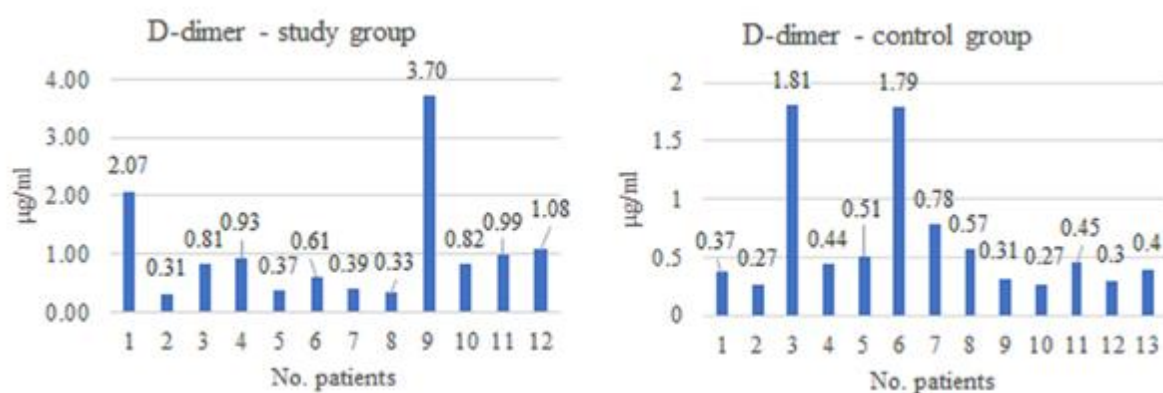

Figure 4: Leukocytes evaluation for the two groups
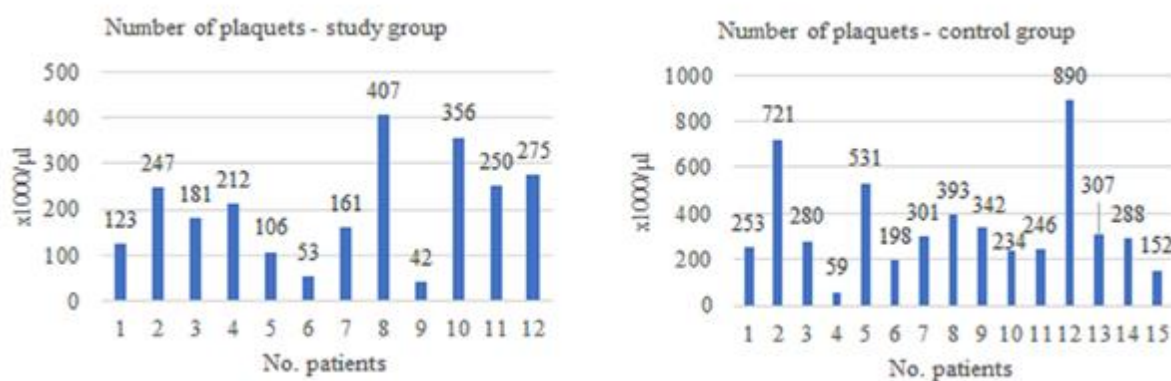

Figure 5: D-Dimers evaluation for the two groups
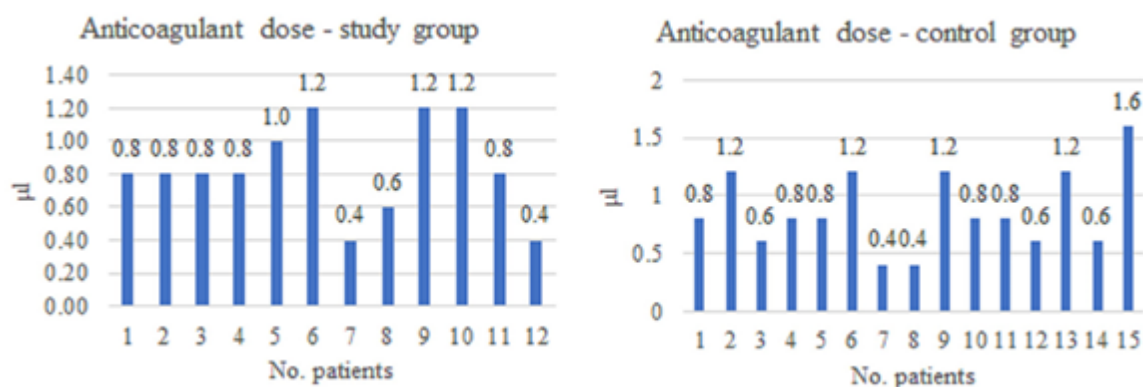

Figure 6: Platlets count evaluation for the two groups

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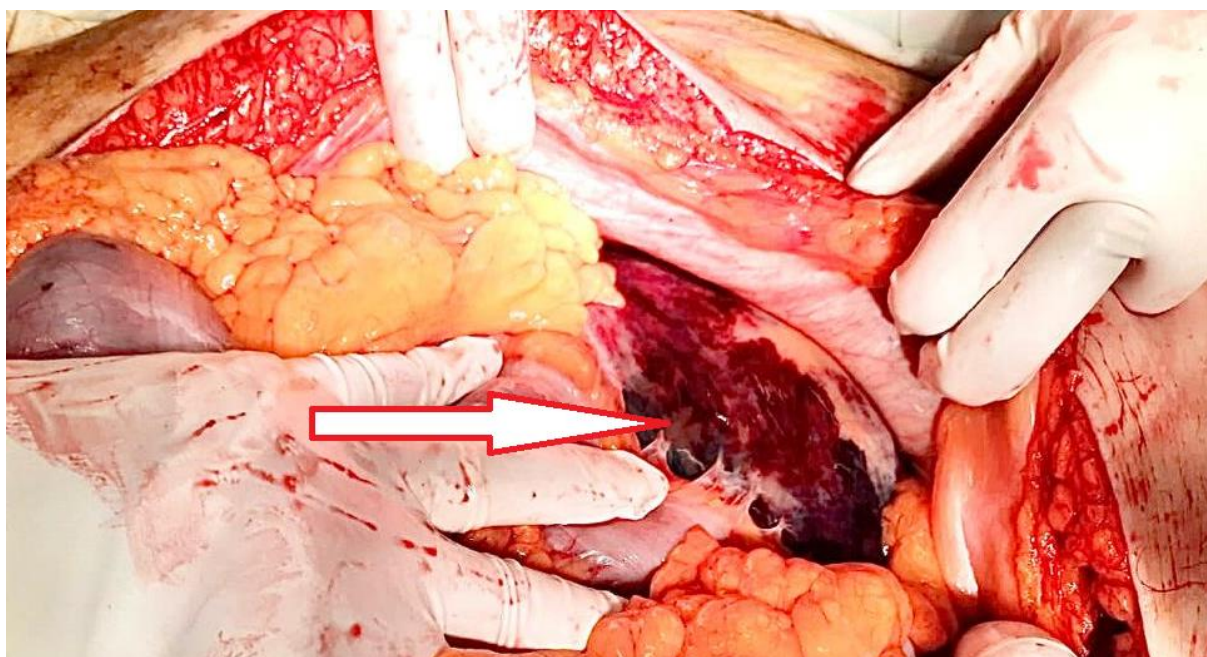**Figure 7:** Anticoagulant dose evaluation for the two groups

Figure 8: Retroperitoneal hematoma of the psoas muscle migrating to the pelvis

DISCUSSION

The main hypothesis studied both in the literature and in our study was that of the modified coagulation status within SARS-COV 2 infection. In the literature, 61% of patients were being treated with prophylactic doses of anticoagulation, while 7% and 29% were treated with sub-therapeutic and therapeutic anticoagulation (TA) doses, respectively. In 44% of patients, Musoke et al. found that the decision to escalate the dose of anticoagulation was based on laboratory values characterizing the severity of COVID-19 such as rising D-dimer levels. There were significantly higher rates of bleeding from non-CNS/non-GI sites (p = 0.039) and from any bleeding site overall (p = 0.019) with TA. TA was associated with significantly higher rates of inpatient death (41.6% vs 15.3% p < 0.0001) compared to those without [2].

What is noteworthy is the fact that both in the literature and in our study, the extremely serious cases that presented hematomas, also had an extremely severe COVID infection even with the association of IVCS. Critically ill patients with COVID-19 experience high rates of venous and arterial thrombotic complications.

The rates of bleeding may be higher than previously reported and re-iterate the need for randomised trials to better understand the risk-benefit ratio of different anticoagulation strategies. The International Society of thrombosis and hemostasis (ISTH) implemented DIC score, which takes into account INR value, fibrinogen, D-Dimers and platelets count, and established a score of risk for DIC [1,3].

This study by a team of surgeons highlights the importance of surgery in the treatment of this condition. The surgeon has a defining role in diagnosing and treating this pathology. First of all, he must make the differential diagnosis of hematomas with other pathologies with similar manifestations (neoplasms, digestive hemorrhages, inguinal hernias, etc.). Secondly, he must determine the urgency of these hematomas if there is active bleeding or it has stopped and conservative treatment may be attempted if the hematoma is not significant. Last but not least, it plays an extremely important role in draining and evacuating the hematoma through surgery (**Figure 8** - Retroperitoneal hematoma of the psoas muscle migrating to the pelvis)

There is currently available evidence that suggests the COVID-19 coagulopathy is an association of localized pulmonary platelet consumption, low-grade DIC (but rarely meeting the ISTH DIC criteria) and in some instances a thrombotic microangiopathy.

For the two groups, we evaluated the ISTH criteria for DIC (disseminated intravascular coagulation), and we noted no significant difference considering this parameter (p-value=0.0919). DIC does not influence the bleeding in CG and SG. It is proven that DIC can translate to transitory thrombocytopenia, but in our groups, only one patient (in the SG) had a score >5.

Severe COVID-19 illness is associated with increased platelet activation as well as platelet-monocyte aggregation. Platelets from severely ill COVID-19 patients can amplify inflammation and affect coagulability in these patients.

Incriminating COVID-19 for the coagulopathy associated with bleeding and hematomas, one does not forget that all severe infectious disorders are associated with changes in hemostasis laboratory values as well as thrombotic and bleeding events [8, 9]. Before the COVID-19 era, there were some hematomas, but the number was negligible compared to the rest of the cases.

A hypothesis suggests that bleeding can occur spontaneously [10], but other mechanisms may also imply trauma, as other studies indicate [11,12]. Another study indicates that percutaneous veno-venous extracorporeal membrane oxygenation (ECMO) can lead to hematoma formation [13]. We raise the idea that patient mobilization can also be incriminated – some of the patients included in SG have been transported in multiple units and submitted to multiple investigations. The surgeries represent an increased difficulty due to the associated medical conditions of the patients, technical difficulties given by the protective equipment, and last but not least due to the impossibility to identify a unique, clear source of bleeding, most often the bleeding being a diffuse bleeding [14-17].

Most studies reported that anticoagulant or antithrombotic therapies were used to treat these patients. Before the COVID-19 era, a study published by Gonzalez et al. [14] reported on 23 cases a preponderance of anticoagulated patients (65.21%) in the spontaneous etiology of retroperitoneal hematoma [16 - 18].

If we refer to the received anticoagulant doses, we notice that there are no statistically significant differences between the two groups, which is why we cannot support through our study the hypothesis of anticoagulant overdose as the direct cause of hematomas. We consider that additional thromboelastography tests are necessary in order to have a complete picture of this hypothesis.

Other studies suggested using coil embolization, a minimally invasive procedure [10-12], but in our group patients with hemodynamic instability required emergency surgery. Sahu et. Al [13] found in an analysis on 78 retroperitoneal hematomas that medical management alone can be successful in 59% of cases; which 38% underwent surgery and only 3% radiologic procedures. The same study reported that 2 of the 78 patients (2.56%) died from hemorrhagic shock [19, 20].

The studies of the coagulation cascade revealed by the literature require completion, as the hypothesis of microtraumas must also be studied much more detailed than before, with careful monitoring of these cases [19-21]. As expected, platelet count and hemoglobin levels are two of the variables directly related to the prognosis of these patients.

However, we assume the limitations of the study related to the small number of cases and the additional investigations necessary for molecular conclusions. Despite these limitations, the present study remains the only one in the literature to date with the highest number of cases and a similar control group in terms of gender distribution, age and covid severity.

CONCLUSION

Risk scores must be implemented in order to better identify these patients in order to avoid risky surgery for hemostasis or evacuation of hematomas. As expected, platelet count and hemoglobin levels are two of the variables directly related to the prognosis of these patients.

The surgeries represent an increased difficulty due to the associated medical conditions of the patients, technical difficulties given by the protective equipment and last but not least due to the impossibility to identify a unique, clear source of bleeding, most often the bleeding being a diffuse bleeding.

The hypothesis of anticoagulant overdose is not supported or verified by the present study, we consider that additional thromboelastography tests are necessary to be able to completely refute it.

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Surgical treatment of resectable and borderline resectable pancreatic cancer in tertiary cancer center: the 6-year experience

Yevhenii Trehub[1]*, Oleg Vasiliev[1], Anna Malovanna[2]

1 Department of Liver, Pancreatic Tumors and Oncovascular surgery, National Cancer Institute, Kyiv, Ukraine.
2 Department of Oncocoloproctology, National Cancer Institute, Kyiv, Ukraine

* **Corresponding Author:** Yevhenii Trehub **E-mail:** yev.trehub@gmail.com

ABSTRACT

Objective: The aim of the study is to analyze the short and long-term results of surgical treatment of resectable and borderline-resectable patients during 2015-2017 (1st period) and 2018-2021 (2nd period).

Material and Methods: A retrospective analysis of patients treated with pancreatic resection with (VR) and without portal or mesenteric vein resection (standard resection, SR) for exocrine pancreatic carcinoma in National Cancer Institute, Kyiv, Ukraine in 2015-2021.

Results: 188 patients underwent surgical treatment, among which 67 received concomitant portal/mesenteric vein resection. Postoperative mortality was 10.04% (14.93% and 6.61% in VR and SR group, respectively, p=0.11). Textbook outcome rate was 67.3% vs 72.7% in VR and SR groups, respectively (p=0.57). Comparing 2015-2017 and 2018-2021 time periods, TO rate did not change for VR – 67.9% vs 66.8% (p>0.99), but tended to increase in SR group – 62.2% vs 80.4% (p=0.089). Median overall survival was 17.03 month and did not differ between VR and SR. OS of all patients differed significantly between 2015-2017 and 2018-2021 – 13.8 vs 22.5 month (p=0.013). In multivariative analysis pancreatic head resection and lower tumor grade were positive prognostic factors, while age >65 and first study period – negative for OS.

Conclusion: Extended due to venous resection pancreatectomies lead to comparable with standard procedures short-term and long-term results. The tumor grade G1-2, patient age less than 65, pancreaticoduodenal resection, and treatment period 2018-2021 were independent factors for better prognosis. Further prospective data is necessary to obtain representative results.

Keywords: pancreatic cancer, borderline resectable pancreatic cancer, portal vein resection.

INTRODUCTION

Pancreatic cancer is the 7th leading cause of death among oncologic diseases (1). Surgical treatment is potentially the only method of achieving long-term survival, and the best results are achieved in patients who received a combination of surgery and chemotherapy, which was demonstrated in studies in the early 2000s (2) and formed the basis of the current treatment concept. However, no more than 20% of patients have a non-metastatic resectable process at the time of diagnosis (3). About 25% of patients will present with non-metastatic locally unresectable cancer, mainly due to the invasion to the major visceral vessels (4). Some of these patients still remain surgical candidates and the removal of the tumor in this case requires extended pancreatic resection with vascular plasty. To unify approaches to treatment and to analyze data, the classifications of resectability were proposed, most of which divides the tumor on resectable, borderline resectable and locally advanced. One of the most widely used classifications is the classification proposed by NCCN (5). Resectable tumors include non-metastatic tumors without vascular invasion, or contact with a superior mesenteric (SMV)/ portal vein (PV) less than 180'. This definition implies the minimum possibility of true invasion into the wall of the vein, although it does not exclude the intraoperative need for the venous resection: among cases of radiological tumor venous contact less than 180' up to 22% demonstrate true invasions, and up to 36% requires venous resection (6). In these cases, unplanned venous resection is associated with an increased frequency of R1-margin (7).

The borderline resectable tumors include tumors with radiological contact with SMV/ PV more than 180' or the presence of irregular venous contour or vein thrombosis; contact with the inferior vena cava; contact with the common hepatic artery with technical possability for reconstruction; contact with the superior mesenteric artery (SMA) less than 180'; contact with aberrant liver arteries when variant vascular anatomy is present; and the invasion of the celiac artery for the pancreatic body and tail tumors with intact gastroduodenal artery.

The resection of the arteries (with the exception of SMA and aorta) in the treatment of pancreatic cancer became standard procedures that lead to acceptable long-term results in thoroughly selected patients, but are associated with high postoperative mortality (8, 9). The tumors with a contact with SMA of more than 180', invasion of the aorta, non-reconstructable portal vein invasion belong to the locally advanced and such patients are mostly not surgical candidates, although in some cases surgical exploration after neoadjuvant therapy may be successful (10).

Early publications of Asian and Western centers demonstrated comparable short-term results of pancreatectomies extended due to venous resection compared with standard procedures (11, 12), but very scarce long-term results - median survival of 13 months, showed in 2006 in a systematic review (13).

After twenty years of accumulation of experience and with the advent of effective systemic therapy regimens, some centers demonstrate median survival up to 35 months (14, 15).

Pancreatic resections combined with vascular resections have been performed systematically at the National Cancer Institute since 2015. Today, this paper is the first analysis of the results of surgical treatment of patients with resectable and borderline resectable pancreatic cancer at the National Cancer Institute of Ukraine.

MATERIAL and METHODS

We performed a retrospective analysis of patients with exocrine pancreatic cancer, that received radical surgical treatment at the National Cancer Institute (Kyiv, Ukraine) from January 2015 to July 2021. Inclusion criteria were:

1) histologically confirmed pancreatic adenocarcinoma (based on postoperative histological exam);
2) absence of arterial invasion (in the common hepatic artery, SMA or the celiac artery);
3) absence of radiological or pathological signs of distant metastases at the time of surgical treatment;
4) performance of standard or extended (due to resection of adjacent visceral organs, SMV or PV) surgical procedure (pancreaticoduodenectomy, distal pancreatectomy (or radical antegrade modular pancreatosplenectomy), total pancreatectomy).

We define the type of vein resection in accordance with the ISGPS classification:

1) wedge resection;
2) wedge resection with a patch insertion;
3) segmental resection with end-to-end anastomosis;
4) segmental resection with an interposition of a graft.

Patients were divided into two groups - a group of standard pancreatic resections (SR) - 121 patients, and a group of pancreatic resection group combined with resection of SMV/ PV (VR) - 67 patients.

An analysis of subgroups of patients receiving treatment in the first time period (2015-2017 years) and the second period (2018-2021 years) was performed.

Postoperative mortality was defined as mortality during the same hospitalization.

Major postoperative complications were defined as grade 3b and higher according to Clavien-Dindo classification.

The failure-to-rescue rate was defined as the ratio of postoperative mortality to the number of patients with major postoperative complications.

Textbook outcome was defined as the absence of postoperative and 90-day mortality, major postoperative complications and readmission within 90 days after surgery in patients followed-up at least 90 days after index surgery.

The overall survival was counted from the date of operation to the date of death.

Statistical analysis was performed using GraphPad Prism software version 9.2.0 and SPSS version 22.0.

RESULTS

During a 6-year period, 188 patients underwent surgical treatment for pancreatic adenocarcinoma (men, 83; mean age, 57.7 years). Pancreaticoduodenectomy was performed in 131 cases (48 with venous resection), distal pancreatectomy in 43 patients (10 with venous resection), total pancreatectomy in 14 patients (9 with venous resection). Patients' characteristics are shown in **Table 1**.

In the VR group, the wedge resection of the vein (type 1) was performed in 6 cases (8.96%), segmental resection with end-to-end anastomosis (type 3) in 60 cases (89.6%), interposition of venous autograft (type 4) in 1 case (1.5%).

Postoperative mortality was 10.04% in the general group. In the SR group, postoperative mortality was 6.56%, in the VR group - 14.93% (differences are statistically insignificant, p=0.11). 90-day mortality was 13.07% in the general group; 10.74% and 20.9% in the SR and VR groups, respectively (p=0.092). (**Table 2**)

Major postoperative complications occurred in 17.02% of patients, 16.53% against 17.91% in SR and VR, respectively (p=0.969). Bleeding was the cause of postoperative death at 12.5% and 40% of cases in patients without with venous resection, respectively, although difference is statistically insignificant (p=0.31). The failure-to-rescue rate differed significantly: 40.0% and 83.36% in the SR and VR groups, respectively (p=0.0276).

The type of pancreatic resection did not affect neither postoperative, nor 90-day mortality: postoperative mortality was 8.4%, 7.1% and 6.97% after pancreaticoduodenectomy, total pancreatectomy and distal pancreatectomy, respectively (p=0.958); 90-day mortality - 12.98%, 14.3% and 18.6%, respectively (p=0.659).

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The length of postoperative hospital stay did not differ significantly between the SR and VR groups - the average length of stay was 15.8 versus 18.16 (p=0.1563).

Among patients who were followed up 90 days or more after resection (140 patients), the textbook outcome was achieved in 70.7%; 72.7% vs. 67.3% in the SR and VR groups, respectively (p=0.57).

When comparing time periods (2015-2017 versus 2018-2021), mortality was significantly different in the general group - 16% versus 5.3%, respectively (p=0.0213). The 90-day mortality also differed for time periods in the general group - 21.3% vs. 9.7% (p=0.0337), and there was a trend in the SR group - 18.2% vs. 6.5% (p=0.0659). The incidence of major complications did not differ between time periods in the general group and subgroups; however, there was a change in the failure-to-rescue rate in the VR group – 100% versus 50% (p=0.0114).

The frequency of the textbook outcome did not change in the VR group (67.9% vs. 66.8%, p>0.99), but tended to increase in the standard resection group (62.2% vs. 80.4%, p=0.089). (**Table 3**)

The median overall survival for all patients was 17.03 months. 1 year survival accounted for 60.02%, 3-year - 28%. The overall survival was not significantly different between patients with and without venous resection (p=0.41): median 15.1 versus 17.3 months, 1-year survival rate 52.4% versus 64.49%, 3-year 35.19% vs. 23.38%. (**Figure 1**)

In univariate analysis, overall survival differed between patients who received treatment in 2015-2017 and 2018-2021: median 13.8 versus 22.5 months. (p = 0.013). (**Figure 2**) The difference remains when analyzing the subgroup of standard resection: 11.4 against 22.5 months. (p = 0.02), but not in the subgroup of venous resection: 15.1 months versus not reached (p = 0.366).

Information about the tumor grade was available in 114 patients: G1-2 in 76, G3 in 38. The frequency G3 was not significantly different between groups of standard and venous resections (29.1% versus 42.9%, p = 0.1965). The tumor grade (G1-2 against G3) did not significantly affect the survival in the general group in univariate analysis: 17.8 versus 9.63 months. (P = 0.08). In the group of venous resection, differences were significant: 36.5 versus 4.33 months. (p = 0.04).

In multivariate analysis (**Table 4**), the resection of pancreatic head (RR 0.3, CI 0.1-0.87, p=0.027), and tumor grade G1-2 (RR 0.4, CI 0.197-0.83, p=0.014) were factors associated with improved overall survival. Age over 65 years at the time of treatment (RR 3.7, CI 1.47-9.36, p=0.05) and the first (2015-2017) treatment period (RR 2.13, CI 0.97-4.69, p=0.061) were factors associated with decreased survival.

The presence of pathologically confirmed regional lymph node metastases, advanced pT stage (3-4), the performance of venous resection and neoadjuvant chemotherapy did not affect the survival in multivariate analysis.

Table 1. Study groups' characteristics.

	Standard resection	Venous resection	p
Total number	121	67	
Pancreaticoduodenectomy, n (%)	83 (68.6%)	48 (71.6%)	n.s.
Distal pancreatectomy, n (%)	33 (27.3%)	10 (14.9%)	n.s.
Total pancreatectomy, n (%)	5 (4.1%)	9 (13.4%)	n.s.
Males, n (%)	51 (42.1%)	32 (47.8%)	n.s.
Females, n (%)	70 (57.9%)	35 (52.2%)	n.s.
Age	14-78 yrs, mean 57.39 (CI 95% 55.58-59.16)	39-77 yrs, mean 58.39 (CI 95% 56.29-60.48)	n.s.
pT1*	4	2	n.s.
pT2*	32	7	*p=0.0177*
pT3*	52	38	*p=0.0066*
pT4*	6	2	n.s.
pN0*	63	33	n.s.
pN+*	34	16	n.s.
G1**	5 (6.3%)	1 (2.9%)	n.s.
G2**	51 (64.6%)	19 (54.3%)	n.s.
G3**	23 (29.1%)	15 (42.9%)	n.s.

Table 2. Short-term outcomes.

	Standard resection	Venous resection	p
Postoperative mortality, n (%)	8 (6.6%)	10 (14.93%)	p=0.11
90-day mortality, n (%)	21 (10.74%)	14 (20.9%)	p=0.092
Major complications, n (%)	20 (16.53%)	12 (17.91%)	p=0.969
Failure-to-rescue, %	40%	83.36%	*p=0.0276*
Death due to hemorrhage, n (%)	1 (12.5%)	4 (40%)	p=0.3137
Length of stay, mean (CI 95%)	15.81 (CI 95% 13.79-17.83)	18.16 (CI 95% 15.19-21.14)	p=0.1563
Textbook outcome	72.7%	67.3%	p=0.57

Table 3. Comparison of the sort-term outcomes in the first (2015-2017) and second (2018-2021) study periods.

	2015-2017	2018-2021	p
Number of patients	75	113	
Standard resection, n (%)	44 (58.7%)	77 (68.1%)	n.s.
Venous resection, n (%)	31 (41.3%)	36 (31.9%)	n.s.
Mortality, n (%)	12 (16%)	6 (5.3%)	*p=0.0213*
a)　**Standard, n (%)**	5 (11.4%)	3 (3.9%)	n.s.
a)　**Venous resection, n (%)**	7 (22.6%)	3 (8.3%)	n.s.
90-day mortality, n (%)	16 (21.3%)	11 (9.7%)	*p=0.0337*
a)　**Standard, n (%)**	8 (18.2%)	5 (6.5%)	p=0.0659
a)　**Venous resection, n (%)**	8 (25.8%)	6 (16.7%)	n.s.
Major complications, n (%)	18 (24%)	16 (14.2%)	n.s.
a)　**Standard, n (%)**	11 (25%)	10 (13%)	n.s.
a)　**Venous resection, n (%)**	7 (22.6%)	6 (16.7%)	n.s.
Failure to rescue, %	66.7%	37.5%	n.s.
a) Standard, %	45.5%	30	n.s.
b) Venous resection, %	100%	50%	*p=0.0114*
Textbook outcome, %	64.6%	76%	n.s.
a) Standard, %	62.2%	80.4%	p=0.089
b) Venous resection, %	67.9%	66.8%	n.s.

Table 4. Multivariate analysis of risk factors influencing overall survival

Risk factors	p	HR	CI 95,0% for HR
Pancreaticoduodenectomy	*0,027*	*0,302*	*0,105-0,873*
Tumor grade G1-2	*0,014*	*0,406*	*0,197-0,834*
Venous resection	0,663	1,194	0,538-2,648
pN+	0,684	1,172	0,545-2,519
pT1-2	0,831	1,090	0,495-2,400
Neoadjuvant chemotherapy	0,983	226,837	-
Age older than 65 years	*0,005*	*3,713*	*1,473-9,359*
Year of treatment 2015-2017	*0,061*	*2,128*	*0,966-4,689*
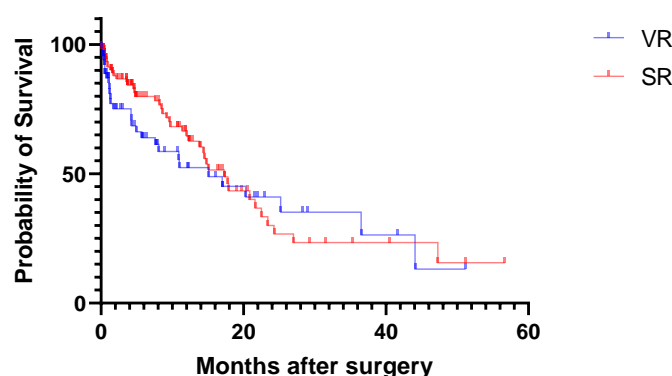
Figure 1. Overall survival of patients underwent standard (SR) and combined with venous (VR) pancreatic resection.
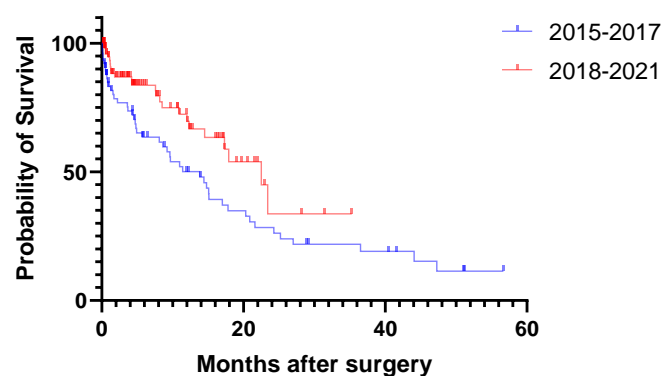
Figure 2. Overall survival of patients underwent surgical treatment in 2015-2017 vs 2018-2021 periods.

DISCUSSION

This work is the first analysis of the results of surgical treatment of patients with pancreatic cancer in the National Cancer Institute of Ukraine.

The first attempts of resection of a portal vein during surgery for tumors of the pancreatic head belong to Child, who published two cases of two-stage obstructive resection of PV in 1952 (16). In the same year, McDermott proposed a technique for simultaneous pancreaticoduodenectomy with resection of the portal vein and application of the mesocaval anastomosis (17). This was followed by certain reports on successful cases, but the systematization of experience began only in the 1990s.

In the earliest series of pancreatic resections extended due to vascular plasty in the 1990s, Fortner and Sindelal demonstrate 26% and 20% postoperative mortality and median survival of 13 months (18-21). In the 2006 systematic review, which includes 52 series of observations from 1966 to 2005, the experience of 1646 extended pancreatic resections was summarized, while 919 of them belong to Asian authors, and only 338 - European (13). Despite the improvement in short-term results compared to the Fortner's historical cohort (mortality in the general group 5.9%), the overall survival remained at the same level (the median 13 months).

In 2006, the NCCN first introduced the concept of "borderline resectable pancreatic cancer", which was based solely on anatomical criteria. In 2008, it was first proposed to add biological and conditional criteria of borderline resectability (22). In 2016, international consensus clearly defined the criteria of biological borderline resectability as a CA-19-9 level above 500 U/mL or regional lymph node metastases confirmed by biopsy or PET/CT (23) and highlighted the importance of neoadjuvant therapy in this categories of patients.

The accumulation of experience and the use of modern chemotherapy regimens led to a meaningful improvement in long-term results in the publications of recent years. Barnes demonstrates median survival at 31 months in patients with borderline resectable cancer who received neoadjuvant chemotherapy and surgery, compared with 13 months in those received only chemotherapy (24). Similar results were demonstrated by MagGino (25), Javed (26), Byun (27), Kishi (28). Multicenter series, that are the most relevant representers of the "real-world data", declare more modest, but still acceptable results: the median overall survival is 18-24 months (29-31).

Our results are consistent with the literature data. In the first period (2015-2017), short-term and long-term results were significantly worse than in the second period, and were similar to the results of early European and Asian publications. The median survival of 22.5 months in the general cohort in the 2018-2021 period is in line with the global trend.

We associate an unsatisfactory high mortality rate in the first period with an extremely high rate of failure-to-rescue in the treatment of major postoperative complications in patients undergone venous resections. These trends are typical for pancreatic surgery: with a constant rate of postoperative complications, the rate of treatment failure (and therefore mortality) decreases over time and with an increase in the number of annually performed procedures (32-34). A similar trend is observed in the textbook outcome rate (35), although we found its increase only in the subgroup of standard, but not venous resections.

In our cohort, vein resection was not a risk factor overall survival. The fact of resection of SMV/ PV did not affect the survival in the Kishi's 2019 work (36), while the presence of true invasion into the vein wall did. Previously, similar results were reported by Nakao in 2012 (37), and confirmed in meta analyzes in 2016 and 2017 (36, 38).

The status of regional lymph nodes and the pT-stage of the tumor did not affect the survival in our analysis. These data contradict most literature data (38-40). We associate these results with the absence of routine adherence tp the standardized pathological protocol in the clinic. For the same reason, we have not analyzed the influence of R-status, lymphovascular and perineural invasion for survival. We plan to conduct a separate analysis of cases where the standardized pathological protocol was performed.

We noted the extremely low frequency of use of neoadjuvant therapy in our series. Despite the trend of the treatment paradigm change towards the wider use of neoadjuvant chemo or chemoradiotherapy in resectable cancer, and established principles for its use in borderline resectable cancer, the "real-world data" from Australia, New Zealand and Singapore published in 2020, demonstrate that the neoadjuvant is used in only 16% cases (41). Also, we cannot exclude the possibility of data loss during the primary documentation registration in our cohort. Initiated in 2021 in our clinic, a prospective data collection will allow us to perform appropriate analyses in the future.

We did not analyze the impact of the CA-19-9 level on long-term results, because information about it is almost uniformly absent in the primary documentation in the first study period (2015-2017). We are planning an appropriate analysis of patients who have this information in the future.

CONCLUSION

Extended pancreatic resections with venous plasty make it possible to achieve short- and long-term results comparable with standard procedures. The tumor grade G1-2, the patient's age less than 65, the pancreatic head resection and the period of treatment 2018-2021 were independent factors of the improved survival. Further prospective studies are necessary to obtain representative data.

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Relapsing Secondary Spontaneous Pneumothorax during COVID-19 infection

Nilay Embel[1], Muhammed Ziya Öcal[1], Ismail Ertuğrul Gedik[1]*

1 Çanakkale Onsekiz Mart University, Faculty of Medicine, Department of Thoracic Surgery, Çanakkale, TR

* Corresponding Author: Ismail Ertuğrul Gedik **E-mail:** ertugrulgedik@gmail.com

ABSTRACT

Objective: COVID-19 infection has been reported to cause spontaneous pneumothorax with variable clinical manifestations and prognoses. We would like to present a case of a patient who developed spontaneous pneumothorax during COVID-19 infection.

Case Presentation: A 40-year-old male patient developed spontaneous pneumothorax during COVID-19 infection. A prolonged air leak developed and the patient was discharged with a Heimlich valve. Then the pneumothorax relapsed twice. The surgical treatment of pneumothorax was postponed because of a persistently increased state of inflammation secondary to COVID-19 infection. Our patient recovered completely with carefully timed surgical intervention.

Conclusion: Surgery for the treatment of cases with pneumothoraces during COVID-19 infection has been reported to be as low as 2% compared to 25% in standard pneumothorax admissions. This might be secondary to the generally less favorable general conditions and higher morbidity and mortality of the COVID-19 patients in contrast to the general population who develop spontaneous pneumothorax. The diagnosis and management of these patients may become challenging as symptoms and signs of spontaneous pneumothorax tend to be similar to COVID-19 and these patients may require tailored management.

Keywords: Pneumothorax, COVID-19, Thoracic Surgical Procedure

INTRODUCTION

COVID-19 infection has been reported to cause spontaneous pneumothorax with variable clinical manifestations and prognoses (1). We would like to present a case of spontaneous pneumothorax in a patient who developed during COVID-19 infection and recovered completely with carefully timed surgical intervention.

Case Presentation

A 40-year-old male patient presented to the emergency department with complaints of right-sided chest pain and difficulty in breathing. His medical history revealed that these complaints started 3 hours before admission. His chest pain aggravated with inspiration, and he was on the eighth day of COVID-19 treatment. His past medical history revealed no chronic disease or medication, but he was smoking a pack of cigarettes/day for 20 years and he has been diagnosed priorly with a bulla of 5x3 cm diameter on his right middle lobe (Figure 1). His blood pressure was 138/96 mm Hg, heart rate was 114/min, fever was 36,8°C, and respiratory rate was 38/min. He had severe dyspnoea. His physical examination revealed diminished right-sided respiratory sounds on lung auscultation. Other routine examinations revealed no additional abnormality. His Thoracic Computer Tomography (CT) revealed a right-sided pneumothorax (Figure 1).

Chest tube thoracostomy was performed, and the patient was hospitalized at the COVID-19 clinics. He had a prolonged air leak for ten days and was transferred to the Thoracic Surgery Clinics. The chest tube was replaced with a 36 Fr Pezzer drain, and the drain was connected to a Heimlich valve. The patient was discharged from the hospital on his 13th day. After a 2-week outpatient clinic follow-up, the Pezzer drain was removed from the patient as his right lung was completely expanded and the air leak stopped. The patient has been re-admitted to the Thoracic Surgery outpatient clinics with a relapsing right-sided pleuritic chest pain and dyspnoea one week after the removal of the chest drain. His posterior-anterior (PA) chest x-ray revealed recurrent right-sided pneumothorax and fibrothorax with an elevated right diaphragm (Figure 2).
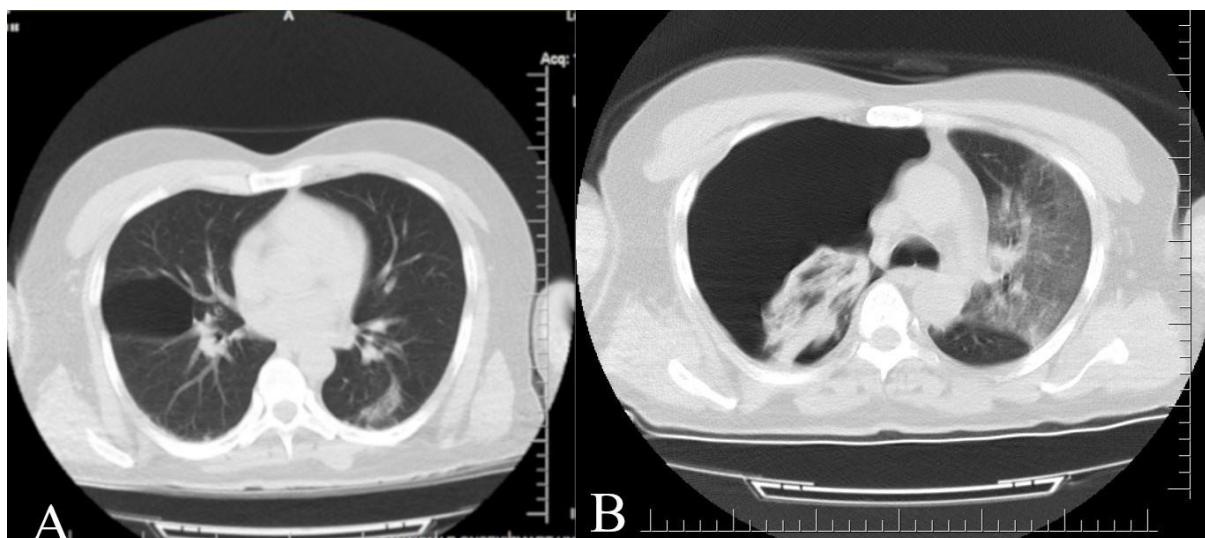
Figure 1: A) CT image revealing bulla on the right middle lobe. B) CT image revealing the right-sided pneumothorax.
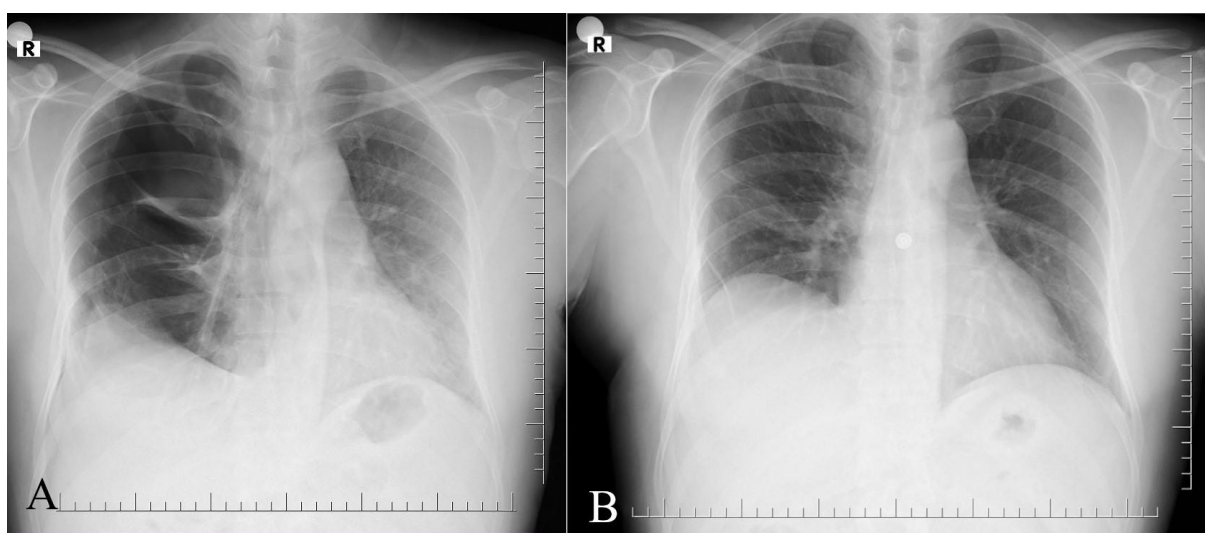

Figure 2: A) PA chest x-ray revealing recurrent right-sided pneumothorax and fibrothorax with an elevated right diaphragm. B) PA chest x-ray of the patient on his 10th postoperative month.

He had leucocytosis (14000/mm3), an elevated C-reactive protein, and a d-dimer value (respectively). The patient was hospitalized, but as his laboratory tests still revealed an increased state of inflammation, the spontaneous pneumothorax surgery was postponed, and a right-sided chest tube thoracostomy was performed instead with a 28 Fr Pezzer drain. The right lung re-expanded, the drain was removed on the fifth day, and the patient was discharged on the sixth day of hospitalization. Two weeks later, the patient was re-admitted to the outpatient clinics with dyspnoea and recurrent right pleuritic chest pain. PA chest x-ray revealed a recurrent right-sided pneumothorax. The patient was hospitalized, and pre-operative preparations were performed. Total decortication of the right lung and bullectomy with a right postero-lateral thoracotomy was performed on the bulla with the dimensions of 5x3 cm on the right middle lobe which has been detected 2 years before the development of pneumothorax. The patient was discharged from the hospital on the seventh day. The patient is still being followed up in the 10th postoperative month (Figure 2).

DISCUSSION

Pneumothorax has been defined as the pathological presence of air in the pleural cavity (2). Although the main clinical presentation of COVID-19 infection includes fever, cough, and dyspnoea 1-2% of COVID-19 patients have been reported to develop pneumothorax (3). Pneumothorax has been reported in both mechanically and non-mechanically ventilated patients with COVID-19 infection (4).

Cases of pneumothorax that occurred during the COVID-19 infection are usually male patients and more than half of them are older than 60 years of age and never-smokers (4). Our case was male but differed in contrast to these findings as he was 40 years of age and was an active smoker.

The most common symptoms and signs of pneumothorax during COVID-19 infection are fever, cough, dyspnoea, and pleuritic chest pain (3). Among these symptoms, only pleuritic chest pain can lead the physician to the diagnosis of pneumothorax.

Approximately 30% of these patients who develop pneumothorax present a change in clinical condition, as in our patient (3).

Patients who develop pneumothorax during COVID-19 infection are treated in the same fashion as other pneumothoraxes. It has been reported that almost 90% of the patients who develop pneumothorax during COVID-19 infection are treated either conservatively or with chest tube thoracostomy (3). We tried to treat our patient with chest tube thoracostomy but failed to achieve complete remission. Thus we started to treat our patient with surgery. Surgery for the treatment of pneumothoraxes during COVID-19 infection has been reported to be as low as 2% compared to 25% in standard pneumothorax admissions (3,5). This might be secondary to the generally less favourable general conditions and higher morbidity and mortality of the COVID-19 patients in contrast to the general population who develop spontaneous pneumothorax.

Prognosis of patients with spontaneous pneumothorax has usually been reported in terms of recurrence rather than mortality. The estimated recurrence rate after the first pneumothorax is reported to be up to 50% over a one to five-year follow-up period. The risk of recurrence is the highest in the first 30 days following the first episode which is similar to our patient as his first recurrence developed in the first month of follow-up (6). The recurrence rates of pneumothorax during COVID-19 infection remain obscure as no article is present yet to report findings of the long-term follow-up of these patients.

The exact mortality in spontaneous pneumothorax has not been reported (6). Despite pneumothorax cases that develop during COVID-19 infection can be as high as 30%, articles on this topic do report that pneumothorax in COVID-19 patients with ARDS has higher mortality. However these articles do not report pneumothorax as the exact cause of death in these patients. Nevertheless, pneumothorax is reported as a contributing factor to mortality in COVID-19 patients (4).

CONCLUSION

In conclusion, pneumothorax can develop in COVID-19 patients. The diagnosis and management of these patients may become challenging as symptoms and signs of pneumothorax tend to be similar to COVID-19, and these patients may require tailored management.

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