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Case Report

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Atherogenic Biomarkers and Gingival Bleeding Among Smokers

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Abstract

Objectives: Smoking is a significant risk factor for gingivitis and has detrimental effects on both oral health and the cardiovascular system. This study aimed to evaluate the association between cardiovascular biomarkers and gingival bleeding among smokers.

Materials and Methods: This cross-sectional study comprising 60 smokers (mean age, 59.9±13.7 years) was conducted at an outpatient smoking cessation clinic. The smokers were divided into two groups based on the presence or absence of gingival bleeding, which was assessed by probing. α1-antitrypsin low-density lipoprotein complex (AT-LDL), an oxidatively modified LDL complex, causes progressive atherosclerosis. The clinical characteristics and blood markers including AT-LDL levels were measured in these patients.

Results: Significantly higher ($p=0.03$) levels of AT-LDL, an oxidized LDL complex that promotes atherosclerosis, were observed among smokers with no gingival bleeding on probing when compared to that among smokers with gingival bleeding. The pocket depths in smokers without gingival bleeding were significantly ($p=0.04$) lower than those among smokers with gingival bleeding.

Conclusion: The absence of gingival bleeding among smokers was associated with higher levels of AT-LDL. These findings could indicate reduced blood flow due to atherosclerosis among smokers with no gingival bleeding.

Keywords: Smokers, gingival bleeding, atherosclerosis, LDL, AT-LDL

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Introduction

Smoking is associated with various major cardiovascular risk factors that can exhibit detrimental effects on the heart and blood vessels. It is known to cause chronic and irreversible changes related to coronary atherosclerosis(1). Generally, a single puff of a cigarette consists of 10^{17} oxidant molecules that can cause oxidative stress(2). The oxidative stress can be assessed by directly measuring the production of reactive oxygen species in the peripheral blood cells or by measuring the amounts of lipid peroxidation products and oxidized proteins on the target molecules. Low-density lipoproteins (LDL) are more vulnerable to oxidization among smokers compared to non-smokers due to the higher levels of reactive oxygen species in the former(2). Oxidized LDL stimulates endothelial cell toxicity and vasoconstriction(3), and α1-antitrypsin low-density lipoprotein complex (AT-LDL) is an oxidatively modified LDL complex that contributes to advanced atherosclerosis. AT-LDL is found in human serum and atheromatous plaque, and the circulatory levels of AT-LDL appear to mirror the activity of foam cells in atherosclerotic lesions. Hence, AT-LDL levels are thought to be linked to oxidative stress and atherosclerosis caused by smoking(4,5). Our previous study demonstrated a decrease in AT-LDL levels after 3 months of smoking cessation and a further decrease after one year of smoking cessation; therefore, it could be considered as a valuable marker for oxidative stress among smokers(4). Serum amyloid A-LDL complex (SAA-LDL) is another inflammatory marker viewed as an oxidatively denatured form of LDL. Higher levels of circulating SAA-LDL were found to be associated with a higher susceptibility to atherosclerotic events(6). In addition, a study by Wada et al.(5) reported that higher SAA-LDL levels were associated with a longer duration of smoking.

Gingival health can be assessed by examining the gingival blood flow and gingival crevicular fluid. A study demonstrated an association between smoking and gingival health. An increase in gingival blood flow and gingival crevicular fluid was reported within a week after smoking cessation indicating recovery of the gingival microcirculation(7). One study suggested that smoking may lead to reduced gingival bleeding due to alterations in the blood vessels of the periodontium(8).

Smokers exhibit an 80% higher risk of presenting with periodontitis than non-smokers and quitters(9). Periodontitis is an inflammatory disease of the supporting tissues of the teeth; it induces progressive destruction of the periodontal ligament, resulting in periodontal pocket formation, gingival bleeding, and alveolar bone loss(10). A recent questionnaire-based study found a significant association between periodontal disease and a known family history of periodontal disorders as well as the smoking duration(11). Several previous studies support the association between periodontal disease and cardiovascular disorders(12,13). A global clinical trial found positive associations between the risk factors and biomarkers of cardiovascular diseases, tooth loss, and self-reported gum bleeding(13). Smokers demonstrate a unique characteristic of presenting with gingivitis in association with a reduced blood flow(7,8). However, to the best of our knowledge, the association between cardiovascular risk factors and gingivitis among smokers has not been reported so far.

The current study aimed to investigate the association between cardiovascular biomarkers and gingival bleeding among smokers.

Materials and Methods

Study Population

This cross-sectional study was conducted among 83 dentate smokers who visited the National Hospital Organization Kyoto Medical Centre outpatient clinic between January 18, 2017, and October 3, 2018, and reported a desire for smoking cessation. Those who provided written informed consent were included in the study, whereas those with advanced cancer (requiring palliative care), patients undergoing pharmacotherapy or any anticoagulation therapy for cardiovascular conditions and those in whom the gingival bleeding could not be assessed due to missing teeth were excluded.

The age, number of cigarettes per day, smoking years, Fagerström test of nicotine dependence (FTND) score, body mass index, waist circumference, blood pressure, and respiratory carbon monoxide (CO) levels were recorded. The FTND is a standard instrument consisting of items that are used to assess the intensity of the physical addiction to nicotine[14]. The items are summed to yield a total score of 0-10. The higher the FTND score, the more intense the patient's physical dependence on nicotine[14].

Blood was collected from the antecubital vein 2-3 h after a meal to determine the high-density lipoprotein (HDL-C), LDL-C, hemoglobin A1c (HbA1c), C-reactive protein (CRP), triglycerides (TG), SAA-LDL, and AT-LDL levels.

Periodontal Examinations

Clinical examination of the oral cavity was conducted using a mouth mirror and a calibrated periodontal probe. A single experienced dentist recorded the clinical parameters throughout the study using the same instruments. A calibrated periodontal probe with controlled force was used to assess the gingival bleeding to avoid trauma and false-positive bleeding from healthy tissues. The presence or absence of gingival bleeding was assessed. Gentle probing was performed by running a probe around the teeth up to a depth of 2 mm in the sulcus without applying any force apically. The WHO periodontal probe developed by the Japanese company YDM Corporation was used to assess the periodontal status of the patient; a recommended probing force of 20-25 g was used[15]. The periodontal pocket depth was classified into 3 groups: grade 0 [periodontal depth (PD)-0-3 mm], grade 1 (PD-4 to 5 mm) and grade 2 (PD>6 mm).

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) Statistics, version 17.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. The prevalence and association between the various parameters were evaluated. Comparisons between smokers with and without bleeding on probing were made using the Fisher's exact test, unpaired t-test, and Mann-Whitney U test. Data are presented as mean ± standard deviation for normally distributed data and as median (interquartile range) for data that were not normally distributed.

Results

The cross-sectional data of 83 smokers collected during the first visit to the smoking cessation clinic were analyzed. However, only 60 patients were included in this study due to the non-availability of data from the remaining patients (Figure 1).

For comparison purposes, the smokers were divided into two groups based on the presence or absence of gingival bleeding (Table 1). Table 1 shows the characteristics of the patients in the two groups. No significant differences in age, amount of smoking, years of smoking, FTND score, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, and respiratory CO levels were observed between the two groups. Furthermore, no significant differences were observed between a group with gingival bleeding and the group without gingival bleeding in the blood markers such as HbA1c, TG, creatinine, CRP, and SAA-LDL. The LDL-C level tended to be higher, and the HDL-C level tended to be lower among smokers with gingival bleeding, statistical significance notwithstanding (Table 1). The neutrophil-lymphocyte ratio, a marker of inflammation, tended to be higher among smokers without gingival bleeding when compared to that in smokers with gingival bleeding (p=0.12). AT-LDL showed a significant positive association (p=0.03), indicating that smokers with no

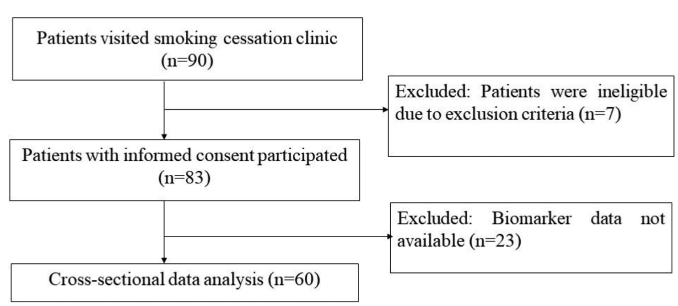

Figure 1. Flow chart of the study participants

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Table 1. Characteristics of the patients in the two groups who were classified according to the presence or absence of gingival bleeding

Variables	Gingival bleeding absent	Gingival bleeding present	p-value
Females, n (%)	8/33 (24%)	8/27 (30%)	0.77[a]
Age, years	62 (46.5, 73.0)	60 (50.0, 68.0)	0.56[c]
Smoking amount (cigarettes/day)	20 (10.0, 20.0)	20 (15.0, 25.0)	0.37[c]
Smoking years	37.1±14.2	37.6±12.4	0.89[b]
FTND score (points)	6 (4.5, 7.0)	7 (5.0, 8.0)	0.07[c]
Body Mass Index (kg/m²)	23.1±3.1	24.3±3.6	0.18[b]
Waist circumference (cm)	88±8.7	89.1±10.2	0.66[b]
Systolic blood pressure (mmHg)	129.9±18.8	133.5±22.8	0.50[b]
Diastolic blood pressure (mmHg)	77.4±12.9	79.1±14.6	0.63[b]
Hemoglobin A1c (%)	5.9 (5.6, 6.1)	5.8 (5.4, 7.2)	0.86[c]
LDL-C (mg/dL)	121.8±38.7	106.4±32.4	0.12[b]
HDL-C (mg/dL)	49.8±11.1	54.9±11.7	0.10[b]
Triglycerides (mg/dL)	144 (108.0, 253.0)	167 (121.0, 191.0)	0.91[c]
Creatinine (mg/dL)	0.83 (0.7, 0.9)	0.76 (0.7, 0.9)	0.28[c]
C-reactive protein (mg/dL)	0.10 (0.0, 0.2)	0.10 (0.1, 0.3)	0.80[c]
SAA-LDL (mg/dL)	7 (5.1, 9.5)	7 (4.0, 9.0)	0.58[c]
AT-LDL (mg/dL)	1.2 (1.0, 1.5)	1.1 (1.0, 1.2)	0.03[c]
Carbon monoxide (ppm)	16 (11.0, 21.5)	16 (11.0, 28.0)	0.96[c]
White blood cell count (x1000/μL)	6.3 (5.2, 7.8)	6.1 (5.1, 7.6)	0.82[c]
Neutrophil count (x1000/μL)	3.7 (2.9, 4.5)	3.2 (2.8, 4.6)	0.51[c]
Lymphocyte count (x1000/μL)	1.7 (1.5, 2.6)	2.3 (1.5, 2.6)	0.28[c]
Neutrophil-lymphocyte ratio	2.0 (1.3, 2.6)	1.5 (1.3, 2.2)	0.12[c]
Hematocrit (%)	42.4±4.6	43.3±4.9	0.43[b]
Grade 0 (PD-0-3 mm), n (%)	16/33 (48%)	6/27 (22%)	
Grade 1 (PD-4 to 5 mm), n (%)	11/33 (33%)	12/27 (44%)	0.04[c]
Grade 2 (PD>6 mm), n (%)	6/33 (18%)	9/27 (33%)	

[a]: Fisher's exact test, [b]: Unpaired t-test, [c]: Mann-Whitney U test. Data were presented as the mean ± standard deviation for normally distributed data and as median (Interquartile range) for the data which was not normally distributed
PD: Periodontal depth, FTND: Fagerström Test for Nicotine Dependence, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, SAA-LDL: Serum amyloid A-LDL, AT-LDL: α1-antitrypsin low-density lipoprotein complex

gingival bleeding exhibited higher levels of AT-LDL than those with gingival bleeding.

As shown in Table 1, a significantly fewer number of smokers without gingival bleeding presented with grade 1 and grade 2 pocket depths when compared to those with gingival bleeding (p=0.04); alternatively, the number of smokers with grade 0 pockets was higher among those without gingival bleeding. However, no association between the amount of smoking and the number of smoking years was observed.

Discussion

The purpose of the present study was to investigate the association between atherosclerotic biomarkers and gingival bleeding in smokers. Both SAA-LDL and AT-LDL are atherosclerotic factors; however, AT-LDL has been strongly associated with smoking. AT-

LDL levels have been linked to smoking habits, and a rapid decrease in these levels has been observed after smoking cessation, suggesting its role as a valuable biomarker of oxidative stress in smokers[5]. In the present study, the absence of gingival bleeding among smokers was associated with higher levels of AT-LDL. Additionally, tendencies toward an increase in LDL-C levels, decrease in HDL-C levels, and increase in the neutrophil-lymphocyte ratio were observed among smokers without gingival bleeding, thereby indicating the profile of the atherogenic lipoproteins in these patients. Smoking might reduce gingival bleeding owing to changes in the proportion of the blood vessels in periodontal tissues[8].

A global study by Vedin et al.[13] among never (31%), current (18%), and former smokers (51%) concluded that gingival bleeding was associated with a higher risk of cardiovascular disease. However, the majority of the subjects in that study were non-smokers, and the gingival bleeding was self-reported. Another study by Tamaki et al.[12] comprising 22 never-smokers with chronic periodontitis (30% of the sites in the oral cavity presented with gingival bleeding) reported higher levels of circulating oxidized LDL and oxidative stress among the subjects with chronic periodontitis compared to healthy patients. The discrepancies in these findings between the aforementioned studies and the current study may be due to differences in smoking status.

Gingival blood flow and crevicular fluid are well-known indicators of gingival health. Nicotine induces vasoconstriction and slows healing following periodontal therapy. Morozumi et al.[7] reported a considerable increase in gingival blood flow 3 days after smoking cessation. Gingival blood flow and gingival crevicular fluid act to improve the gingival microcirculation and periodontal health. Reduced inflammatory characteristics in the gingiva of smokers are related to a reduction in the number of inflammatory cells[16]. Smoking can drastically change the typical appearance of gingivitis and periodontitis by suppressing the signs of inflammation. As a result, less gingival bleeding among smokers does not always indicate a healthy gingiva. No gingival bleeding among smokers might reflect atherosclerosis[16]. Therefore, distinguishing between healthy gingiva and the absence of gingival bleeding in smokers is difficult, which could lead to difficulties in diagnosing gingivitis despite deterioration in the condition.

Healthcare providers, such as dentists, are the first points of contact for the oral health check-up of patients and are ideally supposed to take the smoking history of the patient. Patients with no gingival bleeding can be prone to atherosclerotic changes and must be treated accordingly and with more vigilance. The patients can be referred to a physician for further check-ups to evaluate the presence of other health conditions, such as cardiovascular diseases. However, the results of the present study do not indicate that smokers with presence of gingival bleeding are not at risk of cardiovascular events.

Our previous study[17] demonstrated an increase in periodontal pocket depth and gingival bleeding after 3 months of smoking cessation, thus indicating that the depth of the periodontal pocket increases with the increase in gingival flow, and these could be a part of the healing process. Therefore, reduced or no gingival bleeding with shallow pockets among smokers does not indicate healthy gingiva. The outcomes of the current and previous studies will be valuable in providing advice to patients who are undergoing smoking cessation programs. However, the dentists must advise their patients that quitting the smoking habit could cause an increase in gingival bleeding and pocket depth, initially.

This study has some limitations. The number of patients included in the study was limited. Moreover, causal interpretations were not possible, owing to the cross-sectional nature of the study. Additional studies using a significantly higher number of patients are required to observe the association between smokers and the AT-LDL levels.

Conclusion

The absence of gingival bleeding among smokers was associated with higher levels of AT-LDL, which could be connected with atherogenic events. The findings of this study indicated a reduction in blood flow due to atherosclerosis among smokers without gingival bleeding. These findings can be used by healthcare providers, particularly dentists, to assess and interpret correctly the dental health of smokers and, if necessary, recommend them to physicians to prevent the development of cardiovascular issues in the future.

Ethics

Ethics Committee Approval: Ethics approval for the study was obtained from the Ethical Review Committee at the National Hospital Organization Kyoto Medical Centre (Fushimi-Ku, Kyoto, Japan) (approval no.: - date: 14-042).

Informed Consent: A written informed consent was provided by all the patients who participated in the study.

Authorship Contributions

Surgical and Medical Practices: Hasegawa K, Concept: Hasegawa K, Design: Komiyama M, Data Collection and/or Processing: Yamakage H, Satoh-Asahara N, nalysis and/or Interpretation: Yasoda A, Wada H, Funamoto M, Shimizu K, Literature Search: Mittal S, Writing: Mittal S, Hasegawa K, Katanasaka Y, Sunagawa Y, Morimoto T, Takahashi Y, Nakayama T.

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References

1. Leone A. Relationship between cigarette smoking and other coronary risk factors in atherosclerosis: risk of cardiovascular disease and preventive measures. Curr Pharm Des. 2003;9:2417-23.
2. Yanbaeva DG, Dentener MA, Creutzberg EC, Wesseling G, Wouters EF. Systemic effects of smoking. Chest 2007;131:1557-66.
3. Tsimikas S. Oxidized low-density lipoprotein biomarkers in atherosclerosis. Curr Atheroscler Rep 2006;8:55-61.
4. Komiyama M, Shimada S, Wada H, et al. Time-dependent changes of atherosclerotic LDL complexes after smoking cessation. J Atheroscler Thromb 2016;23:1270-5.
5. Wada H, Ura S, Satoh-Asahara N, et al. α1-Antitrypsin low-density-lipoprotein serves as a marker of smoking-specific oxidative stress. J Atheroscler Thromb 2011;9:47-58.
6. Kotani K, Satoh N, Yamada T, Gugliucci A. The potential of serum amyloid A–LDL as a novel biomarker for cardiovascular disease risk. Clin Lipidol 2010;5:489-95.
7. Morozumi T, Kubota T, Sato T, et al. Smoking cessation increases gingival blood flow and gingival crevicular fluid. J Clin Periodontol 2004;31:267-72.
8. César Neto JB, Rosa EF, Pannuti CM, Romito GA. Smoking and periodontal tissues: a review. Braz Oral Res 2012;26:25-31.
9. Leite FR, Nascimento GG, Baake S, Pedersen LD, Scheutz F, López R. Impact of smoking cessation on periodontitis: a systematic review and meta-analysis of prospective longitudinal observational and interventional studies. Nicotine Tob. Res. 2019;21:1600-8.
10. Saini R, Marawar PP, Shete S, Saini S. Periodontitis, a true infection. J Glob Infect Dis 2009;1:149-50.
11. Ionel A, Lucaciu O, Bondor C, et al. Assessment of the relationship between periodontal disease and cardiovascular disorders: a questionnaire-based study. Clujul Medical 2016;89:534-41.
12. Tamaki N, Tomofuji T, Ekuni D, Yamanaka R, Morita M. Periodontal treatment decreases plasma oxidized LDL level and oxidative stress. Clin Oral Investig 2011;15:953-8.
13. Vedin O, Hagström E, Gallup D, et al. Periodontal disease in patients with chronic coronary heart disease: Prevalence and association with cardiovascular risk factors. Eur J Prev Cardiol 2015;22:771-8.
14. Heatherton TF, Kozlowski LT, Frecker RC. Fagerstrom KO. The Fagerström test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict 1991;86:1119-27.
15. Al Shayeb KN, Turner W, Gillam DG. Periodontal probing: a review. Prim Dent J 2014;1;3:25-9.
16. Sreedevi M, Ramesh A, Dwarakanath C. Periodontal status in smokers and nonsmokers: a clinical, microbiological, and histopathological study. Int J Dent 2012;2012:571590.
17. Mittal S, Komiyama M, Ozaki Y, et al. Gingival bleeding and pocket depth among smokers and the related changes after short-term smoking cessation. Acta Odontol Scand 2021;8:1-6.

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Fast-Track Extubation Experience in the Operating Room After Congenital Heart Surgery in Infants

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Abstract

Objectives: Early extubation applications after pediatric congenital heart surgery have increased in recent years because of the positive results of these studies. It remains controversial whether early extubation should be performed in the operating room or in the intensive care unit. In addition, there are differences between hospitals in early extubation practices after pediatric cardiac surgery. In this study, we aimed to contribute to the literature by presenting our first 12 cases of infants extubated in the operating room after congenital heart surgery.

Materials and Methods: Between May 2022 and December 2022, this study included the first 12 infant patients aged ≤1 year who underwent congenital heart surgery and were early extubate in the operating room.

Results: The cohort comprised 6 girls and 6 boys, with an 11-month-old male patient presenting with pulmonary hypertension. Seven patients underwent cardiopulmonary bypass, with temperatures set at 32 °C for 4 patients and 34 °C for 3 patients. No respiratory problems occurred in the patients. None of the infants required non-invasive ventilation. There was no need for reintubation in the early or late period.

Conclusion: Our findings suggest that a significant proportion of infant patients can be safely extubate in the operating room following congenital heart surgery. Early extubation offers the potential to decrease the need for sedation and inotropes, thereby averting complications associated with mechanical ventilation.

Keywords: Congenital heart defect, early extubation, operating room, infant

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Introduction

In recent years, the adoption of early extubation following pediatric congenital heart surgery has seen an upward trend due to encouraging study outcomes. This practice is also a pivotal element within the enhanced recovery after surgery protocols for pediatric cardiac surgery[1]. The definition of early extubation has varied, ranging from extubation in the operating room up to 6 h postoperatively. In some cases, neonatal extubation within 24 h of the operation is considered early.

Nevertheless, the question persists regarding whether early extubation is best performed in the operating room or in the intensive care unit, and there are divergences in practices among hospitals. In multicenter studies, the rate of early extubation in the operating room exhibits considerable variation, ranging from 25% to 94%[2,3].

Extubation in the operating room immediately after surgery is not a standardized procedure and is only undertaken in selected cardiac surgery centers. This study contributes to the existing literature by presenting our initial experience with 12 infants who underwent extubation in the operating room following congenital heart surgery.

Materials and Methods

Ethical approval was obtained from the Ethics Committee of University of Health Sciences Turkey, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital (approval no: 108, date: 15.05.2023). This study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all patients.

Between May 2022 and December 2022, this study included the first 12 infant patients aged ≤1 year who underwent congenital heart surgery and were early extubate in the operating room. The exclusion criteria were emergency surgery, preoperative inotrope administration, and preoperative intubation. Patient demographic data, details of the surgical intervention, duration of cardiopulmonary bypass (CPB), cross-clamp duration, anesthesia duration, inotropic requirements, postoperative near-infrared spectroscopy (NIRS) values, and intensive care unit and hospital stays were meticulously recorded.

Anesthesia induction was achieved using ketamine, midazolam, fentanyl, rocuronium, and low-dose sevoflurane inhalation. The tidal volume was maintained at 8-10 mL/kg with end-tidal carbon dioxide monitoring. Central venous and arterial catheterization was performed. Bispectral index (Medtronic, Minneapolis, MN, USA) and near-infrared spectroscopy (INVOS; Medtronic, Minneapolis, MN, USA) monitoring were performed. The depth of anesthesia was adjusted according to BIS monitoring. At the end of the surgery, we used sugammadex to eliminate the effect of the muscle relaxant. Pethidine and acetaminophen were used to treat postoperative pain. We determined the following as early extubation criteria: normal metabolic picture, low lactate value, hemodynamic stability, normal oxygenation, normal NIRS value, not long CPB and cross-clamp time. After extubation, the patients were taken to intensive care with oxygen support via a mask. Mild sedation was provided with ultra-low-dose midazolam. Intravenous analgesics were administered for pain.

Results

All 12 patients were successfully extubate in the operating room immediately after surgery and were subsequently transferred to the intensive care unit. The cohort comprised 6 girls and 6 boys, with the 11-month-old male patient presenting with pulmonary hypertension. None of the patients exhibited signs of syndromic disease. Arterial and central catheters were inserted under ultrasound guidance for all patients, and NIRS and bispectral index monitoring were universally applied. Seven patients underwent CPB, with temperatures set at 32 °C for 4 patients and 34 °C for 3 patients. The demographic and surgical data of the patients are summarized in Table 1.

On the first postoperative day, patients were closely monitored in the intensive care unit before transitioning

Table 1. Demographic and operation data of infants

	Age	Gender	Weight	Operation	CPB time	Anesthesia time	Postop NIRS	ICU stay	Hospital stay
Case 1	1 years	Female	7.6 kg	ASD	62 min	195 min	90	1 day	8 days
Case 2	1 years	Female	10 kg	ASD	57 min	215 min	75	1 day	7 days
Case 3	1 years	Male	9.8 kg	ASD	44 min	180 min	72	1 day	4 days
Case 4	1 years	Male	12 kg	ASD+Pulmonary valvotomy	87 min	245 min	75	1 day	7 days
Case 5	11 months	Male	10 kg	VSD	91 min	270 min	78	2 days	11 days
Case 6	5 months	Female	5 kg	VSD+ASD	56 min	235 min	94	1 day	15 days
Case 7	5 months	Female	7 kg	VSD+Coronary AV fistula closure	95 min	220 min	70	1 day	6 days
Case 8	4 months	Male	4 kg	PDA	No	90 min	68	1 day	9 days
Case 9	2 months	Female	6 kg	PDA	No	115 min	70	1 day	4 days
Case 10	1 month	Male	5 kg	ACoA+PDA	No	165 min	75	1 day	12 days
Case 11	1 years	Female	8 kg	ACoA+PDA	No	150 min	71	1 day	8 days
Case 12	1 years	Male	9 kg	ACoA+Aortic arch plasty+PDA	No	200 min	92	1 day	7 days

ASD: Atrial septal defect, VSD: Ventricular septal defect, PDA: Patent ductus arteriosus, CPB: Cardiopulmonary bypass, NIRS: Near-infrared spectroscopy, ICU: Intensive care unit

to the ward. No intraoperative or postoperative inotopes were required, and there were no complications during the perioperative period. No respiratory problems occurred in the patients. None of the infants required non-invasive ventilation. There was no need for reintubation in the early or late period. Importantly, no instances of mortality were observed in either the intraoperative or postoperative periods.

Discussion

In particular, in infants, complex cardiac surgeries, prolonged CPB duration, and hemodynamic instability often result in extended mechanical ventilation periods. Prolonged mechanical ventilation poses a risk of complications associated with intubation, the presence of an endotracheal tube, ventilator-induced lung injury, and oxygen-related infectious complications.

Fast-track anesthesia has been used for the last 30 years as a procedure that allows extubation in the first 6 h after cardiac surgery[4,5]. Ultrafast track anesthesia has been used for the last 20 years and is the method of extubations performed in the operating room or up to 1 h after cardiac surgery[6]. Ultrafast- track anesthesia application shortens extubation time, intensive care unit stay, and hospital stay in children undergoing cardiac surgery[4].

In fast-track anesthesia, it is important to use short-acting or low-dose medication for early extubation. The intraoperative use of opioids under anesthesia may influence extubation or the duration of mechanical ventilation. Respiratory depressant effects of these drugs in infants could lead to extubation failure within the first 24 h postoperatively[7]. Amula et al.[8] demonstrated that reducing the intraoperative opioid dose in infant cardiac surgery correlated with an increased rate of early extubation.

Postoperative extubation in the operating room is not a standard procedure and is performed only in a limited number of cardiac surgery centers[9]. Because the patient population in pediatric cardiac surgery is very heterogeneous, the experience of early extubation is less well defined. Early extubation results in a lower postoperative inotrope score, a shorter duration of catecholamine therapy, a decrease in ventilator-related complications, and a decrease in the hospital costs[4,9-12].

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Studies have indicated that fast-track extubation can be safely implemented in infants undergoing open heart surgery, leading to reduced intensive care and hospital stays, diminished inotropic support, and fewer postoperative transfusions[13]. The positive effects of early extubation in infants undergoing cardiac surgery extend to cost reduction, manifesting as decreased drug costs-especially those associated with respiratory care and mechanical ventilation-laboratory and imaging procedures, sedation, and analgesia[14].

Pediatric patients who have undergone cardiac surgery and are extubate may need reintubation. In a multicenter study, this rate was found to be 6% in patients extubate in the operating room and 10% in patients extubate in the intensive care unit[3]. Risk factors for reintubation after pediatric cardiac surgery include age, genetic disorders, complex surgery, the need for reoperation, developing complications (acute lung injury, chylothorax, diaphragm paralysis, seizure, and sepsis), hemodynamic instability, and upper airway obstruction[3,15].

Conclusion

Our findings suggest that a significant proportion of infant patients can be safely extubate in the operating room following congenital heart surgery. Early extubation offers the potential to decrease the need for sedation and inotropes, thereby averting complications associated with mechanical ventilation. Furthermore, cost reduction can be achieved by shortening the ICU stay through early nutrition and mobilization. The success of early extubation in the operating room hinges on the collaborative efforts of pediatric cardiac surgeons, anesthesiologists, and intensive care specialists that contribute to the fast-track strategy.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of University of Health Sciences Turkey, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital (approval no.: 108, date: 15.05.2023).

Informed Consent: Informed consent was obtained from all patients.

Authorship Contributions

Surgical and Medical Practices: Karaçelik M, Bilen Ç, Concept: Salman Önemli C, Evren Şahin K, Design: Salman Önemli C, Data Collection and/or Processing: Salman Önemli C, Karaçelik Ç, Analysis and/or Interpretation: Karaçelik M, Bilen Ç, Literature Search: Salman Önemli C, Evren Şahin K, Writing: Salman Önemli C, Karaçelik M.

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References

1. Fuller S, Kumar SR, Roy N, et al. The American Association for Thoracic Surgery Congenital Cardiac Surgery Working Group 2021 consensus document on a comprehensive perioperative approach to enhanced recovery after pediatric cardiac surgery. J Thorac Cardiovasc Surg 2021;162:931-54.
2. Rooney SR, Mastropietro CM, Benneyworth B, et al. Influence of early extubation location on outcomes following pediatric cardiac surgery. Pediatr Crit Care Med 2020;21:915-21.
3. Gupta P, Rettiganti M, Gossett JM, et al. Risk factors for mechanical ventilation and reintubation after pediatric heart surgery. J Thorac Cardiovasc Surg 2016;151:451-8.
4. Xu J, Zhou G, Li Y, et al. Benefits of ultra-fast-track anesthesia for children with congenital heart disease undergoing cardiac surgery. BMC Pediatrics 2019;19:487.
5. Engelman RM, Rousou JA, Flack JE, et al. Fast-track recovery of the coronary bypass patient. Ann Thorac Surg 1994;58:1742-6.
6. Djaiani GN, Ali M, Heinrich L, et al. Ultra-fast-track anesthetic technique facilitates operating room extubation in patients undergoing off-pump coronary revascularization surgery. J Cardiothorac Vasc Anesth. 2001;15:152-7.
7. Winch PD, Staudt AM, Sebastian R, et al. Learning from experience: Improving early tracheal extubation success after congenital cardiac surgery. Pediatr Crit Care Med 2016;17:630-7.
8. Amula V, Vener DF, Pribble CG, et al. Changes in anesthetic and postoperative sedation-analgesia practice associated with early extubation following infant cardiac surgery: experience from the pediatric heart network collaborative learning study. Pediatr Crit Care Med 2019;20:931-9.

9. Baehner T, Pruemm P, Vergnat M, et al. Effects of on-table extubation after pediatric cardiac surgery. J Clin Med 2022;11:5186.

10. Koski T, Salmi H, Nisula JK, et al. A retrospective analysis of the duration of mechanical ventilation in Scandinavian paediatric heart centres. Acta Paediatrica 2022;111:859-65.

11. Simeonov L, Pechilkov D, Kaneva A, et al. Early extubation strategy after congenital heart surgery: 1 year single-center experience. Cardiol Young 2022;32:357-63.

12. Montoro DV, Gomez JMG, Montoro AV, et al. Predictors early extubation after pediatric cardiac surgery: Fifteen months of institutional experience. PPC 2020;57:101224.

13. Murin P, Weixler VHM, Romanchenko O, et al. Fast-track extubation after cardiac surgery in infants:Tug-of-war between performance and reimbursement? J Thorac Cardiovasc Surg 2021;162:435-43.

14. McHugh KE, Mahle WT, Hall MA, et al. Hospital costs related to early extubation after infant cardiac surgery. Ann Thorac Surg 2019;107:1421-6.

15. Miura S, Hamamoto N, Osaki M, et al. Extubation failure in neonates after cardiac surgery: prevalence, etiology, and risk factors. Ann Thorac Surg 2017;103:1293-9.

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How Much Understandable of Patient Information Leaflets?

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Abstract

Objectives: Patient information leaflets play a crucial role in educating patients about their conditions and in sharing the responsibility for treatment and follow-up with their physicians. Purpose of this study indentifying the readability level of prospectuses according to national education system of our country and comparing the readability ratios among each other.

Materials and Methods: Fifteen oral anticoagulants and their equivalents, various readability analyses were performed, including the Gunning Fog Index (FOG), Automated Readability Index (ARI), Flesch-Kincaid Readability Analysis, Flesch Reading Ease (FRE), Ateşman, Coleman-Liau, and Powers-Sumner-Kearl (PSK).

Results: The metrics we extracted were calculated according to the formulas developed for criteria, such as Simple Measure of Gobbledygook, FOG, ARI, Flesch-Kincaid, FRE, Ateşman, Coleman-Liau, and PSK which are primarily scientifically accepted and have been developed to understand readability. According to the Ateşman scale, the average readability value of patient information leaflets is 53.2. It is observed that the readability value of the patient information leaflets for 15 oral anticoagulant drugs is between 50 and 59 on the Ateşman scale. Leaflets are moderately difficult to understand and requires high school education. IN terms of comparison patient information forms of Eliquis 2.5/5 mg and Pradaxa 150 mg were easier to read, unlike Pradaxa 110 mg.

Conclusion: All the 15 oral anticogulants' prospectuses requires simplifying an education level that equivalent to the average schooling years in Turkey, which is 6 years, instead of a high school-level education.

Keywords: Readability, prospectuses, oral anticoagulants, adverse effects

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Introduction

Patient information leaflets play a crucial role in educating patients about their conditions and in sharing the responsibility for treatment and follow-up with their physicians. This is especially critical for drugs with potentially fatal adverse effects that are used lifelong, such as oral anticoagulants (OACs). The importance of patient information leaflets and their comprehensibility to patients becomes increasingly vital in these cases[1]. In our study, we tested the readability of the prospectuses for OACs.

Materials and Methods

Within the scope of the research, 15 Turkish prospectuses for various mg types of the drugs Eliquis, Lixina, Pradaxa, Rivoksar, Rovaran, Venomia, and Xarelto were analyzed. These drugs are most frequently used in various branches, such as cardiology, neurology, pulmonology, and cardiovascular surgery, primarily for conditions like atrial fibrillation and vascular thromboembolism. To measure the intelligibility levels of 15 OACs and their equivalents, various readability analyses were performed, including the FOG, Automated Readability Index (ARI), Flesch-Kincaid Readability Analysis, Flesch Reading Ease (FRE), Ateşman, Coleman-Liau, and Powers-Sumner-Kearl (PSK)[1-4].

These methods and metrics are utilized to assess the readability levels of texts. They facilitate understanding of which age group and educational level the text is suited for and guide authors in crafting texts appropriate for their target audiences. Furthermore, these tools can identify necessary modifications to enhance the clarity of texts. In the package inserts, various text analyses were conducted using tools from general-purpose data and text mining, as well as natural language processing (NLP). The word frequencies in the consent form texts were calculated, and statistical analyses based on N-grams were performed. Additionally, the grammatical structures of the words in the texts were examined using the Part-of-Speech (POS) tagging method. Sentence parser analyses were employed to analyze the relationships between sentences and to identify significant relationships and connections within the texts. Analyses of noun-phrase pairs and topic modeling were also carried out.

Results

This study, conducted using text mining techniques, NLP, and artificial intelligence tools, aimed to enhance drug effectiveness and reduce problems arising from misuse by clearly conveying essential information such as dosage, frequency, and method of use to patients.

For all medication package inserts, readability analyses including FOG, ARI, Flesch-Kincaid Readability Analysis, FRE, Ateşman, Coleman-Liau, and PSK were used to measure their intelligibility levels[2-4]. Various text analyses were performed using tools from general-purpose data, text mining, and NLP. These analyses included calculating word frequencies in the texts, conducting statistical analyses based on N-grams, examining the grammatical structures of words using the POS tagging method[5], analyzing the relationships between sentences using sentence parser analyses, and identifying significant relationships and connections within the texts using noun-phrase pairs analyses and topic modeling.

A language model was developed in order to enhance the readability of the examined package inserts. This model learns the language patterns of pharmaceutical package prospectusus, produces new, more readable and understandable sentences and texts, summarizes the essential points and main ideas of the texts of prospectuses, and emphasizes important information.

To perform readability analyses of the prospectuses, it is necessary to calculate the grammatical features of the texts. For this reason, various metrics such as sentence structure, number of words, letters, characters, syllables, and multisyllabic words were extracted from the consent forms and are presented in the table below.

- Medication
- Number of sentences
- Number of words

• Number of letters

• Number of characters

• Number of syllables

• Number of multisyllabic words

• The metrics we extracted were calculated according to the formulas developed for criteria, such as Simple Measure of Gobbledygook, FOG, ARI, Flesch-Kincaid, FRES, Ateşman, Coleman-Liau, and PSK which are primarily scientifically accepted and have been developed to understand readability. From these calculations, readability values were obtained (Table 1, Figure 1).

Among the criteria shown in the table, the most crucial readability formula developed for Turkish texts was defined by Ateşman. According to the Ateşman scale, the average readability value of patient information leaflets is 53.2. It is observed that the readability value of the patient information leaflets for 15 OAC drugs is between 50 and 59 on the Ateşman scale.

Statistical Analysis

In the prospectuses, N-gram analysis, a text analysis method that calculates the number and distribution of consecutive word groups (N-grams), was also performed. N-gram analysis is used to obtain information, such as word frequency in texts, relationships among words, and grammatical structures. By measuring the frequency of specific word combinations in the text, N-gram analysis allows us to determine which word groups are more frequently used, providing insights into the content of the text and language usage. According to the N-gram results, the phrase "side effects" (128) appears with the highest frequency in the package inserts, indicating that statements about the possible side effects of the relevant drugs are frequently used. The phrases "15 mg" (123) and "once a day" (118) also have high n-gram frequencies, showing that statements providing information about the daily dosage and frequency of drug use are commonly included in the package inserts (Figure 2). Additionally, "blood clot" (102) is another phrase with a high n-gram frequency. The phrase "to your doctor or pharmacist" (82) also has a high frequency, suggesting that the need to consult a doctor or pharmacist when making decisions about drug use is heavily emphasized.

Table 1. Readability values of prospectuses according to various criteria

	SMOG	FOG	ARI	Flessch-Kincaid	FRES	Ateşman	Coleman-Liau	PSK	Readability value
Eliquis 2.5 mg	12.66	15.44	13.55	21.22	-40.01	61.2	34.67	14.78	9.66
Eliquis 5 mg	12.91	15.74	13.71		-40.42	60.12	34.75	14.81	9.93
Lixiana 15 mg	14.24	17.67	16.27	23.91	-55.66	49.44	37.34	14.06	14.32
Lixiana 30 mg	13.89	16.99	15.03	22.65	-47	53.96	35.86	14.58	11.95
Lixiana 60 mg	13.89	16.99	15.03	22.66	-47.07	53.94	35.87	14.57	11.94
Pradaxa 110 mg	14.29	17.05	15.24	22.09	-40.51	54.1	35.54	15.22	12.55
Pradaxa 150 mg	11.38	14.3	12.26		-31.42	70.04	33.52	15.05	7.05
Rivoksar 15 mg	14.62	17.68	17.01	23.52	-50.47	49.07	37.7	14.57	13.48
Rivoksar 20 mg	14.59	17.65	16.98	23.49	-50.38	49.25	37.68	14.57	13.41
Rivoran 15 mg	14.43	17.53	16.71	23.4	-50.49	50.05	37.53	14.5	13.05
Rivoran 20 mg	14.46	17.51	16.75	23.36	-49.89	50	37.5	14.56	13.19
Venomia 15 mg	14.92	18.56	16.8	23.75	-52.75	48.75	37.6	14.37	13.23
Venomia 20 mg	14.92	18.56	16.81	23.76	-52.82	48.72	37.61	14.37	13.23
Xarelto 15 mg	14.47	17.56	16.65	23.43	-50.54	49.84	37.42	14.51	13.15
Xarelto 20 mg	14.45	17.55	16.63	23.42	-50.54	49.97	37.42	14.5	13.08

SMOG: Simple Measure of Gobbledygook, FOG: Gunning Fog Index, ARI: Automated Readability Index, PSK: Powers-Sumner-Kearl

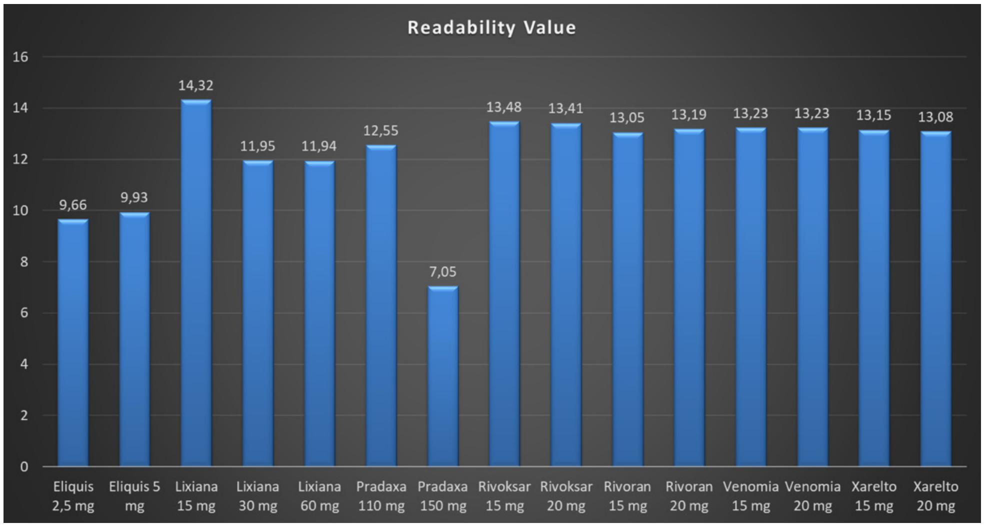

Figure 1. Readability values of patient information leaflets according to various criteria

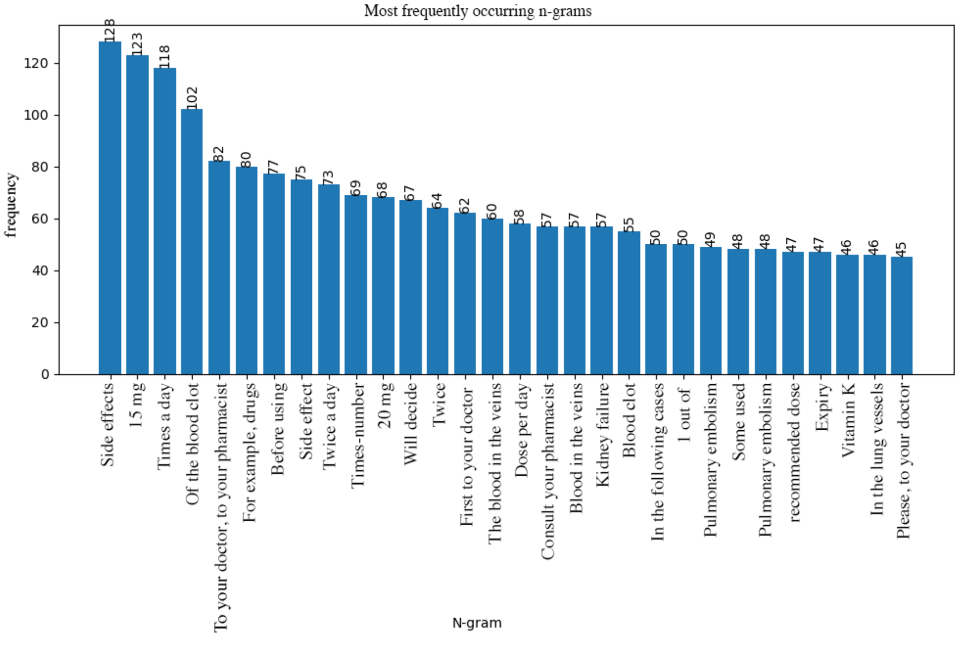

Figure 2. Column graph of the 30 most frequently used n-grams in the package inserts[1]

[1]The vertical elevation of the columns represents the frequency of the n-grams, while the x-axis shows the n-grams, and the y-axis displays the frequencies. In this way, it indicates which n-grams occur most frequently and which ones are less frequent.

Discussion

In this study, the readability levels of OAC drugs were evaluated using readability scales. Furthermore, by employing text mining techniques, NLP, and various artificial intelligence tools, it is aimed to clearly convey information such as dosage, frequency, and method of use to patients, thus enhancing drug effectiveness and reducing problems that may arise from misuse.

Conclusion

As a result of the analysis made on the package inserts of 15 OAC drugs, it was seen that the patient information forms of Eliquis and Pradaxa 150 mg were easier to read, unlike Pradaxa 110 mg.

We recommend simplifying the prospectuses to a level that requires an education equivalent to the average schooling years in Turkey, which is 6 years, instead of a high school-level education[6].

Ethics

Ethics Committee Approval: Ethical approval for the study was received from Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee (approval no.: AEŞH-BADEK-2024-139, date: 14.02.2024).

Informed Consent: Informed consent was obtained.

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References

1. Ay İE, Duranoğlu Y. An evaluation of the readability of package inserts of eye drops. Anatol Clin J Med Sci 2022;27:55-9.
2. Sørensen K, Van Den Broucke S, Fullam J, Doyle G, Pelikan J, Slonska Z, et al. Health literacy and public health: a systematic review and integration of definitions and models. BMC Public Health 2012;12.
3. Ateşman E. Measuring readability in Turkish. AU Tömer Language Journal. 1997;58:171-4.
4. Kincaid J, Jr RF, Rogers R, Chissom B. Derivation of new readability formulas (automated readability index, fog count and flesch reading ease formula) for navy enlisted personnel. Naval Technical Training Command Millington TN Research Branch; 1975.
5. Bezirci B, Yılmaz A. A software library for measurement of readability of texts and a new readability metric for Turkish. DEÜ FMD. 2010;12:49-62.
6. Yeşilyurt ME, Karadeniz O, Gülel FE, Çağlar A, Uyar SG. Mean and Expected Years of Schooling for Provinces in Turkey. Academia 2016;3:1-7.

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Association Between Albumin-Bilirubin Score and Ventricular Arrhythmia in Patients with Heart Failure

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Abstract

Objectives: Heart failure (HF) is a serious disease associated with increased morbidity and mortality. Hepatic dysfunction secondary to hepatic congestion and ventricular arrhythmia (VA) are frequently observed in patients with HF. The albumin-bilirubin (ALBI) score, which predicts liver damage, is a parameter that has been used in patients with HF in recent years. In this study, we investigated the predictive value of the ALBI score in detecting VA in patients with HF.

Materials and Methods: This study was planned as a single-center retrospective study. The study included 150 consecutive HF patients with reduced ejection fraction who had an implantable cardioverter-defibrillator. The ALBI score was calculated using the following formula: [log10 TB (mg/dL) × 0.66] + [albumin (g/dL) × -0.085]. Patients were divided into two groups: those with and without VA. A receiver operator characteristic (ROC) curve analysis was used to define the cut-off level of the ALBI score to predict VA.

Results: The mean age of the group was 55.3±10.8 years, and 78.7% of the patients were male. 28 patients (18.7%) had VAs. Male gender and HF hospitalization in the previous year were more common in the arrhythmia group. ALBI score was higher in the arrhythmia group ($p<0.001$). Sacubitril-valsartan and digoxin use were higher in the arrhythmia group, whereas beta-blocker and statin use were higher in the non-arrhythmia group. In multivariate logistic regression analysis, the ALBI score was found to be an independent predictor of VA. Male gender, hospitalization in the previous year, sacubitril-valsartan use, and digoxin use were other independent predictors of VA. ALBI score at a cut-off point of

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-3.66, predicts ventricular tachycardia with 74% sensitivity and 70% specificity in ROC curve analysis (area under the curve=0.732, p<0.001).

Conclusion: The ALBI score is associated with VA in patients with HF. It can be easily assessed and used as a predictor of VA in this patient group.

Keywords: Albumin-bilirubin score, heart failure, ventricular arrhythmia

Introduction

Heart failure (HF) is one of the leading causes of hospitalization and mortality worldwide[1]. It is a clinical syndrome with a prevalence of 1-2% in the adult population[2]. The incidence of HF is increasing and continues to be an important public health problem. Despite advances in treatment, HF still has a high mortality rate[3]. Approximately half of HF patients have HF with reduced left ventricular ejection fraction (LVEF). Reduced LVEF is associated with a high risk of sudden death due to congestive HF and arrhythmia in patients with HF[4]. Ventricular arrhythmia (VA) is such an important cause of mortality in HF patients that almost 50% of mortality is due to fatal VA, including ventricular tachycardia (VT) and ventricular fibrillation (VF) in these patients[5]. Implantable cardioverter-defibrillator (ICD) implantation is a modality that has been shown to reduce morbidity and mortality in patients with reduced LVEF[6]. ICD detects the frequency of VA and provides therapy. However, feasible and cost-effective markers beyond LVEF are required to estimate the risk of VA.

It has been shown that HF is not a single organ failure, but many organs are involved and interact with each other, including the kidneys, brain, lungs, intestines, and liver[7]. Although the relationship between the heart and liver is increasingly recognized, its clinical and prognostic value remains unclear. Hepatic dysfunction occurs due to hepatic congestion and perfusion disorder and is associated with the severity of HF and poor prognosis[8,9]. Previous studies have evaluated the association between various liver function tests and HF[10,11]. However, no clinically applicable marker of liver dysfunction has been clearly defined. Recently, a new model for assessing liver function, the albumin-bilirubin (ALBI) score, has been developed[12]. It is a predictive liver dysfunction score that has been generally investigated in studies on the prognosis of primary liver pathologies[13,14]. However, there is no study on the relationship between the ALBI score and VA, which is an important cause of mortality and morbidity in HF patients. The ALBI score may be an appropriate scoring system to predict the severity of cardiohepatic syndrome and the risk of VA. In this study, we investigated the predictor of ALBI score in detecting VA in patients with HF.

Materials and Methods

Study Population

This study was planned as a single-center retrospective study. The study population consisted of 150 consecutive reduced LVEF (≤40%) HF patients who presented to the outpatient clinic between January 2022 and December 2022 and had previously had an ICD implanted. Clinically stable patients older than 18 years receiving optimal medical treatment recommended by the guidelines were included in the study. Patients with chronic liver disease, acute or chronic hepatitis, acute or chronic biliary tract disease, chronic kidney disease, collagen vascular disease, acute infection, malignancies in their medical records, and patients who underwent heart transplantation or had ventricular assist devices were excluded. The study protocol was approved by the Ankara Bilkent City Hospital No. 2 Medical Research Scientific and Ethical Evaluation Board (TABED) (approval no.: TABED 2-24-

02, date: 07.02.2024). All procedures were conducted in accordance with ethical rules and the principles of the Declaration of Helsinki.

Analysis of Patient Data and Laboratory Data

Patients' medical records were used to obtain data about the medical history of patients, including cardiovascular risk factors and demographic parameters. Venous blood samples were obtained at admission. Parameters such as complete blood count, creatinine, N-terminal pro-brain natriuretic peptide (NT-proBNP), alanine transaminase, aspartate transaminase, total bilirubin, lipid profile, electrolyte parameters, and albumin levels were recorded. Transthoracic echocardiography was performed, and the left LVEF was calculated using the modified Simpson's method. ICD control was routinely performed. The medications used by the patients were noted during the routine outpatient clinic visit.

Definitions

HF was identified as a known HF symptom affirmed with reduced LVEF. Arrhythmia included documented non-sustained and sustained VT and VF within the ICD control. Patients with fasting blood glucose >126 mg/dL, those with a documented diabetes mellitus (DM) diagnosis, or those who use insulin or oral antidiabetics at admission were considered diabetic. Hypertension (HT) was defined as current antihypertensive use or a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. Current tobacco users were defined as smokers.

The ALBI score was calculated using the following formula: [log10 TB (mg/dL) × 0.66] + [albumin (g/dL) × -0.085][12].

Statistical Analysis

SPSS Statistics version 24.0 for Windows (SPSS Inc, Chicago, IL) was used for statistical analysis. Data are presented as numbers, proportions, mean and standard deviation, or median and interquartile range. The Kolmogorov-Smirnov test was used to determine the distribution patterns. Student's t-test or Mann-Whitney U test was used as appropriate. Categorical variables were evaluated using the chi-square test. Receiver operating characteristic curve analysis was performed to determine the cut-off level of the ALBI score to predict the presence of VA. The association between VA and other variables was investigated using multivariate logistic regression analysis. Any variable with a p-value <0.2 in the univariate logistic regression analysis was included in the multivariate logistic regression model. A two-tailed p-value <0.05 was considered significant.

Results

A total of 150 patients were included in the study. Patients were divided into two groups: those with and without VA. 55.3 percent of the patients had an ischemic etiology. The mean age of the patients was 55.3 years, and 118 (78.7%) were male. The mean LVEF of the patients was 23.74%. VA was detected in 28 (18.7%) patients during a periodic ICD battery check. The baseline demographics and clinical and laboratory parameters are shown in Table 1. There was no significant difference in terms of age, HT, DM, smoking, previous coronary artery bypass graft surgery, atrial fibrillation, and New York Heart Association class between the two groups. Male gender and HF hospitalization in the previous year were more common in the arrhythmia group. Creatinine, ALBI score, sacubitril-valsartan, and digoxin use were higher in the arrhythmia group. In addition, sodium and low-density lipoprotein cholesterol levels were lower in this group. LVEF did not differ between groups. Beta blocker and statin use was higher in the non-arrhythmia group. No significant difference was found between the use of renin-angiotensin system inhibitors, namely angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter-2 inhibitors.

The ALBI score at a cut-off point of -3.66, predicts VT with 74% sensitivity and 70% specificity in receiver operator characteristic curve analysis.

Table 1. Comparison of groups according to the baseline demographics and clinical and laboratory characteristics

Variables	Normal (n=122)	VT (n=28)	p-value
Age (years)	55.6±11.3	54.2±9.6	0.526
Male gender [n (%)]	92 (75.4)	26 (92.9)	**0.03**
Hypertension [n (%)]	55 (45.1)	11 (39.3)	0.367
Diabetes mellitus [n (%)]	57 (46.7)	13 (46.4)	0.573
Smoking [n (%)]	21 (17.2)	5 (17.9)	0.602
HF hospitalization in last year [n (%)]	22 (18.0)	20 (71.4)	**<0.001**
Previous CABG [n (%)]	24 (19.7)	8 (28.6)	0.214
Ischemic etiology in HF [n (%)]	67 (54.9)	16 (57.1)	0.456
Atrial fibrillation [n (%)]	38 (31.1)	9 (32.1)	0.484
NYHA Class	2.04±0.79	2.29±0.59	0.073
Hemoglobin (g/dL)	14.40±1.90	14.10±1.05	0.424
WBC (mcL)	8.15±1.72	8.17±1.76	0.846
Sodium (mEq/L)	139.21±6.97	128.81±13.22	**0.003**
Potassium (mEq/L)	4.38±0.49	4.38±0.46	0.981
Magnesium (mEq/L)	2.01±0.40	1.92±0.32	0.350
Calcium (mEq/L)	9.24±0.54	9.22±0.44	0.835
Glucose (mg/dL)	112.51±50.69	110.89±27.22	0.451
Creatinine (mg/dL)	1.02±0.24	1.18±0.39	**0.010**
AST (U/L)	30.01±19.22	29.8±21.22	0.455
ALT (U/L)	39.48±25.54	41.22±27.33	0.288
LDL-C (mg/dL)	95.42±56.21	82.33±20.21	**0.048**
HDL-C (mg/dL)	38.61±12.46	34.35±9.34	0.087
Triglyceride (mg/dL)	156.57±78.33	154.37±89.86	0.439
Albumin (g/dL)	4.36±0.55	4.23±0.48	0.116
Bilirubin (μmol/L)	15.39±8.22	15.55±7.45	0.488
ALBI score	-3.71±0.46	-3.44±0.36	**<0.001**
LVEF (%)	24.21±7.60	21.69±5.87	0.069
NT-pro BNP (ng/L)	2590±1720	2682±1674	0.650
TSH (mU/L)	2.41±2.03	2.40±1.31	0.981
Beta blocker [n (%)]	117 (95.9)	25 (89.3)	**0.034**
RAS blocker [n (%)]	96 (78.7)	21 (75.0)	0.418
Sacubitril-Valsartan [n (%)]	19 (15.6)	9 (32.1)	**0.044**
MRA [n (%)]	103 (84.4)	23 (82.1)	0.447
SGLT-2 inhibitors [n (%)]	65 (53.3)	15 (53.6)	1.000
Digoxin [n (%)]	21 (17.2)	11 (39.3)	**0.013**
Statin [n (%)]	66 (54.1)	8 (28.6)	**0.010**

HF: Heart failure, CABG: Coronary artery bypass graft surgery, NYHA: New York Heart Association, WBC: White blood cell, AST: Aspartate transaminase, ALT: Alanine transaminase, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, ALBI: Albumin-bilirubin, LVEF: Left ventricular ejection fraction, NT-pro BNP: N-terminal pro–B-type natriuretic peptide, TSH: Thyroid stimulating hormone, RAS: Renin angiotensin system, MRA: Mineralocorticoid receptor antagonist, SGLT-2: Sodium-glucose transport protein-2

The area under the curve of the ALBI score in predicting VA was 0.732 [95% confidence interval (CI): 0.677-0.822; p<0.001] (Figure 1). Univariate and multivariate logistic regression analyses were performed to assess the independent predictors of VA. Variables with p<0.2 in univariate analysis were evaluated in multivariate logistic regression analysis (Table 2). In multivariate logistic regression analysis, the ALBI index was found to be an independent predictor of VA (hazard ratio: 1.43, CI: 1.12-2.22; p<0.001). Male gender, hospitalization for HF in the previous year, sacubitril-valsartan use, and digoxin use were other independent predictors of VA (Table 2).

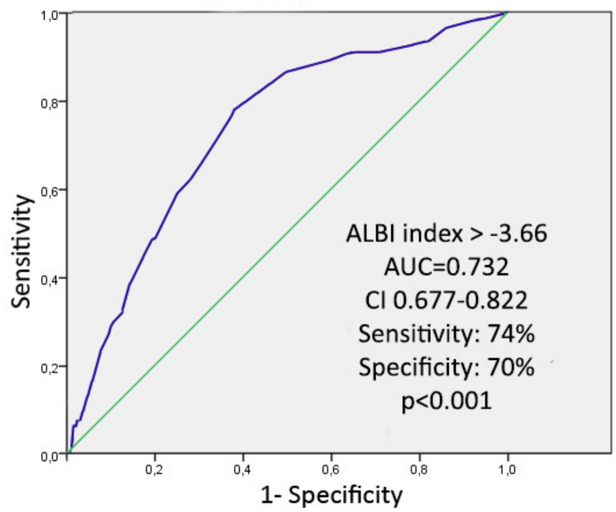

Figure 1. ROC curve ALBI
ROC: Receiver operator characteristic, ALBI: Albumin-bilirubin, AUC: Area under the curve, CI: Confidence interval

Discussion

This study analyzed the relationship between the ALBI score and VA in HF patients. The results showed that the ALBI score was independently associated with the development of VA in patients with HF. To the best of our knowledge, this is the first study to examine the relationship between ALBI score and VA in patients with HF.

HF is an important cause of morbidity and mortality caused by cardiac dysfunction, has structural and functional abnormalities, and has a higher incidence of arrhythmias than healthy people[15,16]. Data on the relationship between congestion and stage and arrhythmia frequency in patients with HF are limited. The use of ICD is widely used in patients with HF for arrhythmic events[6]. Because of its common use, it enables more detailed data

Table 2. Independent predictors of ventricular arrhythmia

Factor	Univariable		Multivariable	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Male gender	13.2 (2.11-28.22)	0.001	12.9 (1.24-26.61)	**0.001**
HF hospitalization in last year	32.23 (3.23-154.22)	0.001	24.46 (4.34-137.56)	**<0.001**
NYHA Class	1.77 (0.56-5.44)	0.288	-	-
Sodium	0.95 (0.89-1.22)	0.268	-	-
Creatinine	0.94 (0.066-13.63)	0.967	-	-
LDL-C	0.97 (0.094-1.105)	0.295	-	-
HDL-C	0.94 (0.87-1.127)	0.290	-	-
ALBI score	1.53 (1.32-2.11)	<0.001	1.43 (1.12-2.22)	**<0.001**
LVEF	1.12 (1.002-1.308)	0.04	1.066 (0.942-1.207)	**0.125**
Beta blocker	0.87 (0.67-1.25)	0.265	-	-
Sacubitril-Valsartan	3.53 (1.22-13.56)	0.03	2.56 (0.98-22.1)	**0.08**
Digoxin	2.55 (1.14-5.76)	0.008	2.12 (1.10-11.43)	**0.03**
Statin	0.65 (0.33-2.54)	0.256	-	-

HF: Heart failure, NYHA, New York Heart Association, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, ALBI: Albumin-bilirubin, LVEF: Left ventricular ejection fraction, OR: Odds ratio, CI: Confidence interval about arrhythmia to be recorded. Baman et al.[17] reported that frequent VAs cause left ventricular dysfunction. A previous study examined patients implanted with cardiac resynchronization therapy for HF[18]. Higher NT-proBNP levels and higher mortality rates were observed in the ALBI-positive group. However, no arrhythmia-related data were found. In our study, NT-proBNP was not an independent predictor of VA.

HF is a systemic disease that negatively affects other organ systems because of the failure to function as a pump. In patients with HF, not only left but also right ventricular function is impaired[19]. Therefore, congestion is mainly associated with increased right heart diastolic pressures and related symptoms[20]. The major result of these symptoms is hepatic congestion[21]. Liver dysfunction is one of the most common complications in HF patients[22]. In recent years, prognostic and clinical evaluations have been performed using different liver function parameters in patients with HF. Liver function tests such as albumin, bilirubin, alanine aminotransferase, and aspartate aminotransferase have been used to predict the prognosis of HF[23,24]. In some studies, the severity of HF was correlated with total bilirubin and albumin levels[25]. It was found that both high total bilirubin and low serum albumin levels are associated with poor outcomes in HF patients[26,27]. In our study, patients were divided into two groups, with and without arrhythmia, and no significant difference was found between albumin and total bilirubin levels in both groups.

Bilirubin is a marker of serum cholestasis. Elevated bilirubin levels are associated with acute liver congestion. In a study, it was shown that bilirubin levels increased as cardiac output decreased[28]. In another study, high bilirubin levels increased mortality in patients with HT-related HF[29]. Albumin is the most abundant plasma protein in the body and indicates hepatocyte function. Plasma albumin levels are known to decrease in inflammatory conditions. The cause of hypoalbuminemia in patients with HF is hepatocyte damage due to both chronic inflammation and hepatic congestion[30]. Therefore, the more progressive the HF, the lower the albumin level. Low albumin levels are associated with chronic congestive hepatopathy and poor prognosis in patients with HF[8,30].

The ALBI score, which includes serum bilirubin and albumin levels, was developed to assess liver function and predict survival in patients with chronic liver disease. It is a cost-effective and simple method to predict liver function. It was first published in 2015 and has been widely used in clinical practice until today[12]. Studies have shown that the ALBI score can reliably predict the prognosis and survival of patients with liver disease[31]. The ALBI score also predicts left and right ventricular dysfunction and associated liver dysfunction in patients with HF. In a study of patients with HF with reduced LVEF, it was shown that the group with a high ALBI score had a more severe poor prognosis[2].

In another study, there are findings suggesting that liver disease is associated with VA. Non-alcoholic fatty liver disease was found to increase the risk of VA by 3.5-fold[32]. In the same study, it was also shown that elevated gamma-glutamyl transferase was independently associated with VA. Systemic inflammation, cardiac lipotoxicity, and oxidative stress in liver diseases may lead to structural, electrical, and autonomic remodeling, leading to arrhythmogenic damage in the heart[33].

There has been no study between the ALBI score, which is used as a marker of liver function, and arrhythmia in HF patients. Our study is the first to demonstrate this relationship. According to our study, a relationship was found between the ALBI score and VA.

Study Limitations

This study has several limitations. First, this study has a single center design and has included a limited number of patients. Second, this was a retrospective cross-sectional study. The results should be supported by future prospective studies.

Conclusion

This is the first cross-sectional study to show that the ALBI score is independently associated with an increased risk of ventricular arrhythmias in patients with HF. The ALBI score is a cost-effective and simple index. It may provide preventive treatment and close follow-up in this patient group.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ankara Bilkent City Hospital No. 2 Medical Research Scientific and Ethical Evaluation Board (TABED) (approval no.: TABED 2-24-02, date: 07.02.2024).

Informed Consent: This study was planned as a single-center retrospective study.

Authorship Contributions

Concept: Özilhan MO, Açıkgöz SK, Design: Özilhan MO, Açıkgöz SK, Data Collection and/or Processing: Özilhan MO, Analysis and/or Interpretation: Açıkgöz SK, Literature Search: Özilhan MO, Writing: Özilhan MO, Açıkgöz SK.

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References

1. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol 2014;63:1123-33.
2. Sungur A, Sungur MA, Yıldırımtürk Ö. Effect of albumin-bilirubin score on prognosis in ambulatory heart failure patients with reduced ejection fraction. Turk Kardiyol Dern Ars 2023. Online ahead of print
3. Rocha BML, Menezes Falcão L. Acute decompensated heart failure (ADHF): A comprehensive contemporary review on preventing early readmissions and postdischarge death. Int J Cardiol 2016;223:1035-44.
4. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-83.
5. Zhang D, Tu H, Wadman MC, Li YL. Substrates and potential therapeutics of ventricular arrhythmias in heart failure. Eur J Pharmacol 2018;833:349-56.
6. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the american college of cardiology/american heart association task force on clinical practice guidelines and the heart rhythm society. Heart Rhythm 2018;72:e73-e189.
7. Harjola VP, Mullens W, Banaszewski M, et al. Organ dysfunction, injury and failure in acute heart failure: from pathophysiology to diagnosis and management. A review on behalf of the Acute Heart Failure Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur J Heart Fail 2017;19:821-36.
8. Xanthopoulos A, Starling RC, Kitai T, Triposkiadis F. Heart failure and liver disease: cardiohepatic ınteractions. JACC Heart Fail 2019;7:87-97.
9. Poelzl G, Ess M, Mussner-Seeber C, Pachinger O, Frick M, Ulmer H. Liver dysfunction in chronic heart failure: prevalence, characteristics and prognostic significance. Eur J Clin Invest 2012;42:153-63.
10. van Deursen VM, Damman K, Hillege HL, van Beek AP, van Veldhuisen DJ, Voors AA. Abnormal liver function in relation to hemodynamic profile in heart failure patients. J Card Fail 2010;16:84-90.
11. Samsky MD, Dunning A, DeVore AD, et al. Liver function tests in patients with acute heart failure and associated outcomes: insights from ASCEND-HF. Eur J Heart Fail 2016;18:424-32.
12. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol 2015;33:550-8.
13. Demirtas CO, D'Alessio A, Rimassa L, Sharma R, Pinato DJ. ALBI grade: Evidence for an improved model for liver functional estimation in patients with hepatocellular carcinoma. JHEP Rep 2021;3:100347.
14. Toyoda H, Johnson PJ. The ALBI score: From liver function in patients with HCC to a general measure of liver function. JHEP Rep 2022;4:100557.
15. Tomasoni D, Adamo M, Lombardi CM, Metra M. Highlights in heart failure. ESC Heart Fail 2019;6:1105-27.
16. Stehlik J, Feldman DS. Arrhythmias in heart failure: beyond sudden cardiac death. Curr Opin Cardiol 2013;28:315-6.
17. Baman TS, Lange DC, Ilg KJ, et al. Relationship between burden of premature ventricular complexes and left ventricular function. Heart Rhythm 2010;7:865-9.
18. Yamada S, Kaneshiro T, Yoshihisa A, et al. Albumin-bilirubin score for prediction of outcomes in heart failure patients treated with cardiac resynchronization therapy. J Clin Med 2021;10:5378.
19. Correale M, Tarantino N, Petrucci R, et al. Liver disease and heart failure: Back and forth. Eur J Intern Med 2018;48:25-34.
20. Rocha BML, Menezes Falcão L. Acute decompensated heart failure (ADHF): A comprehensive contemporary review on preventing early readmissions and postdischarge death. Int J Cardiol 2016;223:1035-44.
21. Laribi S, Mebazaa A. Cardiohepatic syndrome: liver injury in decompensated heart failure. Curr Heart Fail Rep 2014;11:236-40.

22. Matsue Y, Kagiyama N, Yamaguchi T, et al. Clinical and prognostic values of ALBI score in patients with acute heart failure. Heart Lung Circ 2020;29:1328-37.

23. Suzuki K, Claggett B, Minamisawa M, et al. Liver function and prognosis, and influence of sacubitril/valsartan in patients with heart failure with reduced ejection fraction. Eur J Heart Fail 2020;22:1662-71.

24. Biegus J, Hillege HL, Postmus D, et al. Abnormal liver function tests in acute heart failure: relationship with clinical characteristics and outcome in the PROTECT study. Eur J Heart Fail 2016;18:830-9.

25. Lau GT, Tan HC, Kritharides L. Type of liver dysfunction in heart failure and its relation to the severity of tricuspid regurgitation. Am J Cardiol 2002;90:1405-9.

26. Allen LA, Felker GM, Pocock S, et al. Liver function abnormalities and outcome in patients with chronic heart failure: data from the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. Eur J Heart Fail 2009;11:170-7.

27. El Iskandarani M, El Kurdi B, Murtaza G, Paul TK, Refaat MM. Prognostic role of albumin level in heart failure: A systematic review and meta-analysis. Medicine (Baltimore) 2021;100:e24785.

28. Kubo SH, Walter BA, John DH, Clark M, Cody RJ. Liver function abnormalities in chronic heart failure. Influence of systemic hemodynamics. Arch Intern Med 1987;147:1227-30.

29. Szyguła-Jurkiewicz B, Wojnicz R, Lekston A, et al. Effect of elevated bilirubin levels on the long-term outcome in patients with chronic heart failure due to hypertension. Pol Arch Med Wewn 2007;117:227-33.

30. Horwich TB, Kalantar-Zadeh K, MacLellan RW, et al. Albumin levels predict survival in patients with systolic heart failure. Am Heart J 2008;155:883-9.

31. Deng M, Ng SWY, Cheung ST, Chong CCN. Clinical application of Albumin-Bilirubin (ALBI) score: The current status. Surgeon 2020;18:178-86.

32. Mantovani A, Rigamonti A, Bonapace S, et al. Nonalcoholic fatty liver disease is associated with ventricular arrhythmias in patients with type 2 diabetes referred for clinically indicated 24-hour holter monitoring. Diabetes Care 2016;39:1416-23.

33. Chen Z, Liu J, Zhou F, et al. Nonalcoholic fatty liver disease: an emerging driver of cardiac arrhythmia. Circ Res 2021;128:1747-65.

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Intracerebral Hemorrhage after Discharge from Carotid Endarterectomy: An Extraordinary Complication Despite Standard Anticoagulation

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Abstract

Carotid artery disease is the most important source of cerebrovascular diseases, causing a high rate of morbidity and mortality. While there are medical and interventional treatment options for carotid artery disease, carotid endarterectomy (CEA) is the gold standard treatment for severe carotid artery stenosis. Our study focuses on a rare complication encountered in a 74-year-old female patient who underwent carotid endarterectomy for carotid artery disease. Our patient, who had a smooth postoperative course, developed intracranial hemorrhage after discharge. This complication, occurring under standard antiplatelet therapy, is quite rare in the literature. Our aim is to contribute this rare complication to the literature with our case report.

Introduction

Intracerebral hemorrhage (ICH) is described as the clinical situation regarding bleeding in intracranial area including parenchyma and meningeal spaces[1]. In the USA, approximately 50.000 individuals are suffering from intracerebral hemorrhage annually[1]. Only one of five can be healed functionally[1]. Also, the 30-day mortality rate can project to 50%[1]. Thus,

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intracerebral hemorrhage is related to poor outcomes. Risk factors may include male gender, aged population, Asian genetic background, alcohol consumption, high cholesterol levels, anticoagulation therapy, and drug use[1]. Coma, headache, vomiting, nausea, seizures, focal and generalized neurological symptoms can be seen in victims[1]. Computed tomography (CT), CT angiography, and magnetic resonance imaging (MRI) are common imaging techniques to diagnose[1]. Hence, intracranial hemorrhage after carotid endarterectomy (CEA) is an extremely rare clinical picture that is related to hyper-perfusion syndrome (HPS)[2]. It occurs less than 0,5% of all carotid endarterectomy cases[2]. The lack of the vascular autoregulatory mechanism in the affected hemisphere is blamed as a known pathophysiological event[2]. Seizures, headache, focal deficits may be seen as HPS related symptoms[2]. HPS is encountered more commonly, approximately 2,5% of all carotid endarterectomy cases[2]. ICH and HPS are related to high mortality and morbidity as a complication of the CEA[2]. Our aim is to declare an intracerebral hemorrhage after the CEA as a rare clinical entity. We believe that our study may contribute to the literature.

Case Presentation

A 74-year-old woman admitted to the cardiovascular surgery clinic for her complaint of left leg pain. That pain had been present for a year while walking 200 meters. The patient had a history of hypertension, diabetes mellitus, and hypothyroidism. There was no history of smoking or known cardiovascular disease, and any neurological disease. Physical examination revealed absent left femoral pulse and a murmur on the left carotid artery. Duplex ultrasonography showed monophasic flow in the left femoral and popliteal arteries. Bilateral carotid-vertebral artery duplex ultrasonography revealed a calcified plaque extending from the common carotid artery to the internal carotid artery on the right side, and a 70% stenosis and calcified plaque extending from the common carotid artery to the internal carotid artery on the left side. Angiography was performed for the lower extremities, carotid arteries, and coronary arteries in the same session. Left internal carotid artery was more than 90% stenotic. There was no significant stenosis in the coronary arteries, but a 70% stenosis was observed in the left iliac artery.

Endarterectomy was planned for the stenosis in the left internal carotid artery. Incision was made on the medial border of the left sternocleidomastoid muscle. Plaque location was identified, and arteriotomy was performed. Shunt was also employed. The plaque was removed with the help of a plaque elevator. Standard closure was performed after the successful process. The patient was also monitored with cerebral oxygenation during the operation. Afterwards, the patient's intensive care unit follow up was uneventfully done. The patient was discharged on the 4th postoperative day with routine medication.

Nausea and vomiting happened the day after the discharge. After a few hours, confusion happened. The patient's family admitted to the closest emergency department. Cranial CT scan showed intracerebral hemorrhage (Figure 1). The patient was intubated and transferred to our hospital. Afterwards, she underwent emergency surgery under general anesthesia by the neurosurgery department for hematoma evacuation and decompression. After the craniotomy, it was observed that the brain tissue was edematous and pulsatile. Widespread subarachnoid hemorrhage foci were seen in the temporal and frontal lobes. Hematoma evacuation and decompression were performed. The patient was followed up in the intensive care unit post-op while intubated. After approximately 1 month of follow-up in the ICU with a GCS score of 3, the patient passed away.

Discussion

Carotid artery stenosis can be defined as greater than 50% stenosis of internal carotid artery (ICA) according to The North American Symptomatic Carotid Endarterectomy Trial-NASCET classification[3]. Doppler ultrasound (DUS) may be beneficial as a first step imagine technique, and also provide detailed information about a plaque[3,4].

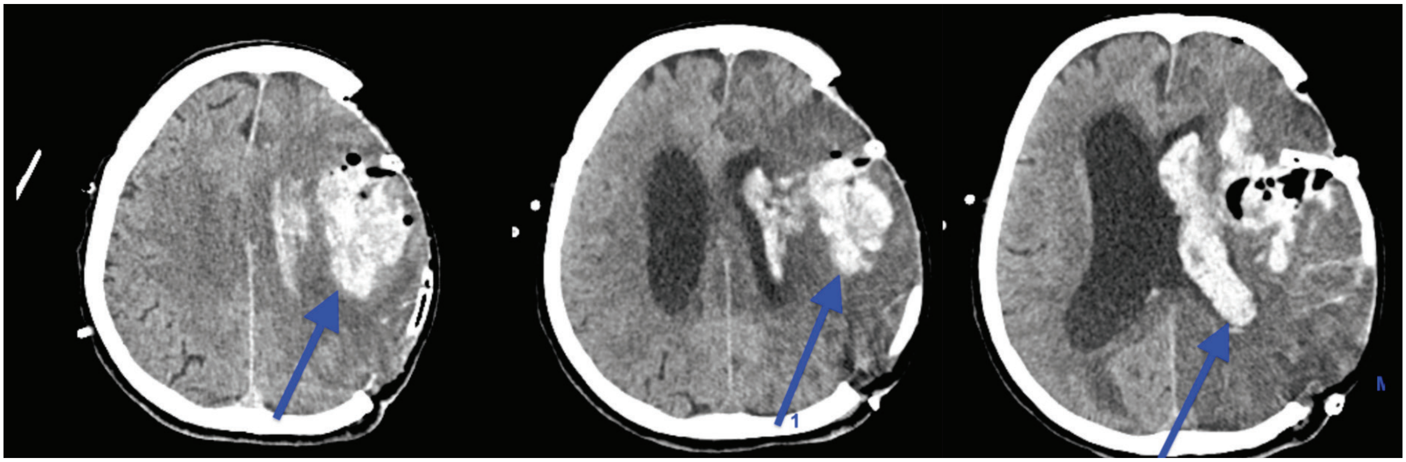

Figure 1. Arrows show hemorrhage areas on CT images in different sections
CT: Computed tomography

CT angiography (CTA) and MR angiography (MRA) also can be helpful to gain further information[3,4]. Digital subtraction angiography (DSA) is necessary when the plan of a surgery exists[3]. DSA is a gold standard technique for carotid artery imaging[4]. If there is significant narrowing, which is 60-99%, in carotid arteries in the asymptomatic patient whose life expectancy is greater than 5 years, CEA is recommended[4].

CEA can be defined as the best treatment for symptomatic critical stenosis of the internal carotid artery in order to prevent stroke[5]. Hence, carotid artery stenting (CAS) has advantages to be a more noninvasive technique, lack of risks regarding wound[3]. However, CEA provides significant advantages rather than CAS in terms of 30 days of stroke and death rates[6]. Thus, CAS is considered as an alternative to CEA[7]. Hence, CAS could be beneficial when the patient is in high risk for surgery which situations like previous radical neck surgery, cervical irradiation history, re-stenosis after CEA, older than 80 years age, major cardiac disease, or chronic obstructive pulmonary disease[4]. Given parallel to improvements in endovascular treatments, ischemic stroke rates lowered, but HPS and ICH became the usual suspect of morbidity and mortality after CAS[7]. Both HPS and ICH are existing as the complication of the carotid artery stenting[2]. Outcomes of both HPS and ICH regarding CAS are worse than outcomes regarding CEA[2]. In addition, more acute onset exists in CAS related ICH with a greater than 5% incidence[2].

There is a case in the literature, similar to our study, in terms of the age of the patient and clinical situation after CEA[8]. However, there are some differences. In our case, ICH occurred after uneventful discharge of the patient under standard antiplatelet therapy. Our patient had leaved the hospital by walking. Thus, it is hard to be linked between ICH and the operation. Conversely, ICH has occurred just after the procedure in other case[8]. Despite, their patient's prognosis is better than ours[8]. It seems where the event was happening could have been a critical role in prognosis. In their patient, they have intervened as soon as they can in hospital and ICU with the entire team. It shows the importance of the time of the intervention.

Intracerebral hemorrhage may be encountered after carotid surgery and interventions. Thus, it should be considered when planning the procedure. Although encountering such a rare complication is not sympathetic to a practitioner, it is our scientific duty to declare this seldom complication in order to contribute to the literature.

Ethics

Informed Consent: Informed consent was obtained.

Authorship Contributions

Surgical and Medical Practices: Concept: Design: Data Collection and/or Processing: Analysis and/or Interpretation: Literature Search: Writing: All authors contributed equally to the article.

Conflict of Interest: The authors declare no conflicts of interest concerning the authorship or publication of this article.

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References

1. Caceres JA, Goldstein JN. Intracranial Hemorrhage. Emerg Med Clin North Am 2012;30:771-94.
2. Timaran CH, Veith FJ, Rosero EB, Modrall JG, Valentine RJ, Clagett GP. Intracranial Hemorrhage After Carotid Endarterectomy and Carotid Stenting In The United States in 2005. J Vasc Surg 2009;49:623-9.
3. Aboyans V, Ricco JB, Bartelink MLEL, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J 2018;39:763-816.
4. Naylor R, Rantner B, Ancetti S, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on the Management of Atherosclerotic Carotid and Vertebral Artery Disease. Eur J Vasc Endovasc Surg 2023;65:7-111.
5. Russell DA, Gough MJ. Intracerebral Haemorrhage Following Carotid Endarterectomy. Eur J Vasc Endovasc Surg 2004;28:115-23.
6. Saratzis A, Naylor R. 30 Day Outcomes After Carotid Interventions: An Updated Meta-analysis of Randomised Controlled Trials in Asymptomatic Patients. Eur J Vasc Endovasc Surg 2022;63:157-8.
7. Abou-Chebl A, Yadav JS, Reginelli JP, Bajzer C, Bhatt D, Krieger DW. Intracranial Hemorrhage and Hyperperfusion Syndrome Following Carotid Artery Stenting. J Am Coll Cardiol 2004;43:1596-601.
8. Ogasawara K, Inoue T, Kobayashi M, Endo H, Fukuda T, Ogawa A. Intracerebral hemorrhage after carotid endarterectomy associated with asymptomatic perioperative cerebral ischemia detected by cerebral perfusion imaging: Case report. Surg Neurol 2004;62:319-22.