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ORIGINAL RESEARCH

Vitamin K epoxide reductase complex subunit 1 gene promoter polymorphism - a potential genetic basis for survival from thromboembolism in COVID-19

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Abstract

Introduction. The coronavirus induced disease 2019 (COVID-19), caused by the severe acute respiratory coronavirus 2 (SARS-CoV-2), which was identified in patients in China in 2019, was pronounced a pandemic in March 2020. It resulted in more than 7 million deaths worldwide. As hypercoagulation emerged as its key pathological hallmark, the objective of this study was to investigate if a polymorphism within the *VKORC1* gene, which plays a role in the vitamin K-dependent blood coagulation pathway, contributed to the survival from thrombosis in individuals who developed some form of it during their COVID-19.

Methods. This was an observational, case-control study. Characterization of the *VKORC1* -1639G>A (rs9923231) polymorphism-associated genotypes was carried out in cases (N=16), volunteers who developed some form of thromboembolism during COVID-19, but who survived from it, and controls (N=32), volunteers who did not develop any form of thromboembolism during COVID-19, by using polymerase chain reaction restriction fragment length polymorphism method, followed by Sanger sequencing of the *VKORC1* gene promoter-specific, polymerase chain reaction-amplified products.

Results. Our preliminary data indicate that the variant or A allele, which is associated with intermediate or low blood coagulability, is more frequently present within the *VKORC1* gene of individuals who developed some form of thromboembolism during their COVID-19, but who survived from it, than the wild-type or G allele, which is associated with standard or high blood coagulability.

Conclusion. These results warrant further studies into the role of the *VKORC1* promoter-associated polymorphism in the COVID-19-associated coagulopathy, as the specific *VKORC1* genotypes could become genetic biomarkers for prediction of a thrombotic state during COVID-19, and possibly, other thrombosis-associated diseases and disorders.

Keywords: COVID-19, Hypercoagulability, Thrombosis, Venous thromboembolism, Vitamin K epoxide reductase

INTRODUCTION

The coronavirus induced disease 2019 (COVID-19), caused by the severe acute respiratory coronavirus 2 (SARS-CoV-2), which was identified in patients in China in 2019 [1], was pronounced a pandemic in March 2020. It resulted in more than 776 million confirmed cases [2] and 7 million deaths worldwide [3]. Early during the pandemic, it was recognized that COVID-19's pathophysiology was not restricted to the lungs, as it could progress to a systemic disease and affect other organs. In addition, hypercoagulation termed COVID-19-associated coagulopathy (CAC) has emerged as its key pathological hallmark, exhibiting either as venous thromboembolism (pulmonary embolism and deep vein thrombosis), or arterial thromboembolism (ischemic stroke, systemic arterial embolism, acute coronary syndrome, limb artery thrombosis, mesenteric artery thrombosis, etc.) [4]. Various systematic reviews and meta-analyses reported high prevalence of venous thromboembolism: 28%, 22.7% and 24.1% among the intensive care units' (ICU) patients, and 10%, 7.9% and 7.7% among general wards' patients, respectively [5] [6] [7]. However, a sensitivity analysis showed that the prevalence of venous thromboembolism was probably lower, i.e., 15.7% in ICU patients. Furthermore, a reported overall prevalence of arterial thromboembolism in patients diagnosed with COVID-19 was 1-5%, i.e., lower than that of venous thromboembolism [8].

Biomarkers measured in hospitalized COVID-19 patients were used to estimate the severity of COVID-19 pathogenesis and predict the course of the disease: biomarkers of the inflammatory and immune system activation were interleukin (IL)-6 and C-reactive protein (CRP), whilst biomarkers of coagulation, and the consequent thrombosis risk, were platelet count, activated partial thromboplastin time (aPTT), prothrombin time, D-dimer, fibrinogen, von Willebrand (vWF) factor activity, vWF antigen, lupus anticoagulant, etc. It was established that the most severe clinical stage of CAC is characterized with high D-dimer and fibrinogen concentrations, prolonged prothrombin time and reduced platelet count, accompanied with high incidence of venous thromboembolism [9]. However, the reported incidence of thrombosis was different in different racial/ethnic groups, with a significant disparity in the incidence of thrombotic events between African Americans, Caucasians and Asians [10]. It was suggested that an inherent antithrombotic state in the Asian population, termed "East Asian Paradox" [11], was responsible for a significantly lower thrombosis rate of 1.86% in the examined 5,807 patients from the Japanese population [12] compared with a substantially higher thrombosis rate of 40.8% in the examined 184 patients from the European population [13].

One of the genetic factors, which contribute to the "East Asian Paradox", is the variant sequence within the vitamin K epoxide reductase complex subunit 1 (*VKORC1*) gene, which encodes the enzyme vitamin K epoxide reductase (VKOR) - the molecular target of warfarin, the most commonly prescribed oral anticoagulant drug worldwide. VKOR regulates the synthesis of the reduced form of vitamin K and, thus, indirectly controls the levels of the vitamin K-dependent procoagulant factors (II, VII, IX, X) and anticoagulant factors (proteins C and S). *VKORC1* is one of four genes whose variations in sequence give rise to large inter-individual variability to sensitivity to warfarin [14] [15] [16]. A variant sequence in the promoter region of the *VKORC1* gene (*-1639G>A*, rs9923231) is significantly associated with an individual's response to warfarin, with carriers of the variant or A allele, who are prevalent in East Asian populations, requiring reduced therapeutic doses of warfarin. Because the consequence of the presence of the variant or A allele in an individual is a phenotype of an enhanced endogenous anticoagulation, it was hypothesized that its presence could be, at least in part, responsible for the low incidence of CAC in East Asian populations [17].

In order to investigate if the *VKORC1 -1639G>A* polymorphism-associated genotypes/alleles may influence a survival from CAC, we examined them in 16 cases - individuals who developed some form of thromboembolism during their COVID-19 and survived from it, and 32 controls - individuals who did not develop any form of thromboembolism during their COVID-19.

METHODS

Patients and study design

This study was an observational, case-control study. For the case group of volunteers, inclusion criteria were age ≥ 18 years, history of COVID-19 diagnosis, and development of a thromboembolic event (either venous or arterial thromboembolism) during the course of COVID-19. Exclusion criterion was inability to provide written, informed consent. The cases were matched with volunteers who did not develop a thromboembolic event during their COVID-19. Two controls were randomly selected for each case, individually matched by biological sex and age (within 4 years age-range). The recruitment of volunteers took place after they were infection free, from January 2022 until January 2024. The study followed the ethical guidelines of the Declaration of Helsinki (2013) and was approved by the Bioethical Committee of the Sarajevo Medical School on the 23rd November 2021 (SMS-23112021). In addition, written, informed consent was obtained from all volunteers in the study.

Human, genomic DNA extraction and characterization of the *VKORC1 -1639G>A* (rs9923231) polymorphism-associated genotypes

Approximately 3ml of whole blood was obtained from all volunteers in ethylenediaminetetraacetic acid (EDTA)-containing tubes. Genomic DNA extraction and characterization of the *VKORC1 -1639G>A* (rs9923231) polymorphism-associated genotypes was described in a protocol deposited on Protocols.io (https://www.protocols.io/) which can be accessed through the following digital object identifier (DOI): dx.doi.org/10.17504/protocols.io.j8nlko8mdv5r/v1 [18].

Statistical methods

Descriptive statistics was used to summarize the results of the study (Table 1). In addition, a Chi-squared test was used to compare allele frequencies between cases and controls. Statistical significance (p) was set at 0.05.

Availability of data and materials

The dataset generated and analyzed during the current study was deposited in the Harvard Dataverse repository, which can be accessed through the following digital object identifier (DOI): https://doi.org/10.7910/DVN/JCCWCO [19]. In addition, this dataset was deposited in a database associated with clinical variations titled ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/). The results are public and can be accessed through the accession numbers: SCV004807478 and SCV004812937 [20]. In addition, details of individual human, genomic DNA samples, which were generated in this study, were also deposited on the National Centre for Biotechnology Information data platform within a BioProject database (https://www.ncbi.nlm.nih.gov/bioproject/). They can be accessed through the accession number: PRJNA1095829 [21]. Human, genomic DNA sample material, which was generated in this study, is available on request from the corresponding author.

RESULTS

In this study, an association between the *VKORC1 -1639G>A* (rs9923231) polymorphism-associated genotypes and survival from COVID-19-associated thrombosis was examined. In the case group, 13 volunteers

(81%) had venous thromboembolism and 3 volunteers (19%) had arterial thromboembolism. In this group, 3 volunteers (19%) had the wild-type, *VKORC1-GG* or the most thrombogenic *VKORC1* genotype, 7 volunteers (44%) had *VKORC1-AG* or the *VKORC1* genotype with an intermediate thrombogenic effect, and 6 volunteers (37%) had *VKORC1-AA* or the least thrombogenic *VKORC1* genotype. In the case group, the wild-type, G allele frequency was 0.41 or 41%, while the variant or A allele frequency was 0.59 or 59% (Table 1, Fig. 1). In contrast, in the control group, 11 volunteers (34%) had the wild-type, *VKORC1-GG* genotype, 14 volunteers (44%) had *VKORC1-AG* genotype, and 7 volunteers (22%) had *VKORC1-AA* genotype. In the control group, the wild-type, G allele frequency was 0.56 or 56%, while the variant A allele frequency was 0.44 or 44% (Table 1, Fig. 1). In order to establish whether a statistically significant difference exists between cases and controls, with regard to allele frequencies, a Chi-squared test was performed. With a degree of freedom of 1, a value of 2.0625 was obtained (p=0.1510).

DISCUSSION

Multiple patient characteristics (e.g. age, biological sex, race, existing medical condition, prescribed pharmacological agents, different biomarkers, etc.) were previously studied in order to understand which determining factors affect patients' outcomes following COVID-19 diagnosis. We examined an association between a genetic factor with an established effect on blood coagulation, the *VKORC1 -1639G>A* polymorphism, and survival from a thromboembolism in COVID-19. A trend towards a decrease in the frequency of the wild-type or G allele (0.41) and an increase in the frequency of the variant or A allele (0.59), in cases - individuals who developed a thromboembolic event during their COVID-19, but who survived it, was detected. In controls - individuals who did not de-

Table 1. Clinical, demographic and the VKORC1 -1639G>A (rs9923231) polymorphism-associated genotype characteristics of the study's volunteers.

Demographic and genetic characteristics of human volunteers	Survived cases Human volunteers with thromboembolic event during COVID-19 N=16	Controls Human volunteers without thromboembolic event during COVID-19 N=32
Age in years (Mean ± SD; Range in years)	55±14; 31-74	55±13; 29-77
Biological sex (N, % M; N, % F)	9, 56%; 7, 44%	18, 56%; 14, 44%
VKORC1-GG (N, %)	3, 19%	11, 34%
VKORC1-AG (N, %)	7, 44%	14, 44%
VKORC1-AA (N, %)	6, 37 %	7, 22%
G allele frequency (%)	41%	56%
A allele frequency (%)	59%	44%

F = female biological sex; N = number of human volunteers; M = male biological sex; SD = standard deviation; VKORC1-GG = homozygous, wild-type genotype; VKORC1-AG = heterozygous, variant genotype; VKORC1-AA = homozygous, variant genotype.

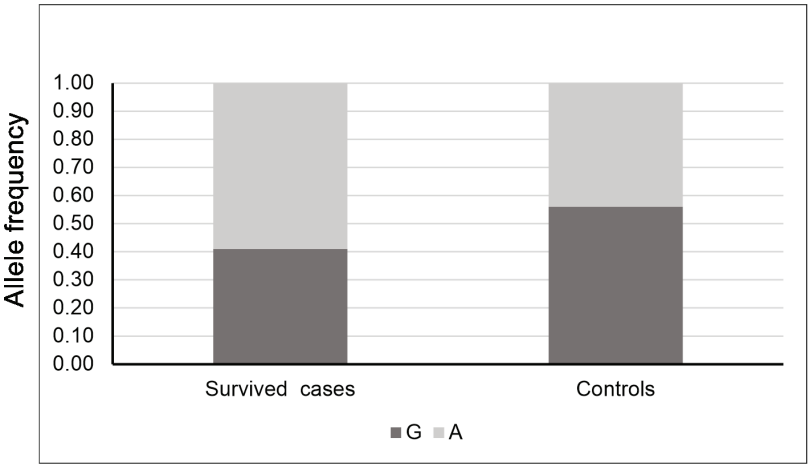

Figure 1. Allele frequencies at the VKORC1 -1639 locus in survived cases and controls.

Allele frequencies for the wild-type, VKORC1 -1639G (G) allele, and the variant, VKORC1 -1639A (A) allele were calculated and compared between survived cases (N=16), volunteers who developed a thromboembolic event during their COVID-19, and controls (N=32), volunteers who had no thromboembolic event during their COVID-19 disease. In the survived cases, the wild-type or G allele frequency was 0.41 or 41%, while the variant or A allele frequency was 0.59 or 59%. In the controls, the wild-type or G allele frequency was 0.56 or 56%, while the variant or A allele frequency was 0.44 or 44%.

velop a thromboembolic event during their COVID-19, we detected the opposite trend: the wild-type or G allele at 0.56 and the variant or A allele at 0.44. Although these differences in allele frequencies between cases and controls were not statistically significant (p=0.1510), the results of this study indicate that having the A allele during a thromboembolic event in COVID-19 contributed, at least in part, to survival from it (Fig. 2).

To our knowledge, this is the first study on this topic and its results warrant further investigations of the G/A alleles within the *VKORC1* gene promoter in individuals who survived a thromboembolic event in COVID-19, as the knowledge of the intrinsic *VKORC1* polymorphism effects on blood coagulability could improve prediction of thrombosis, monitoring, treatment and overall clinical outcomes for future patients. As data and samples, which have been generated through this study, will be made available to other researchers, we hope that this study will contribute to future research on this topic.

Limitations of the study are small sample size and unavailability of detailed information on the volunteers who were analyzed (e.g. date of their COVID-19 disease, which would indicate an infection with a specific SARS-CoV-2 variant, pharmacological agents that were prescribed/administered to them during their thrombosis and/or after it, and the presence of any comorbidities). However, in the control group of volunteers, the obtained allele frequencies (G: 0.56; A: 0.44) were similar to the average allele frequencies reported for the population of the Americas (G: 0.586; A: 0.414) [16], suggesting that the results of this study could have implications for a wider, global populations and their health outcomes.

CONCLUSION

In conclusion, our preliminary results indicate that, in the individuals who develop COVID-19-associated thrombosis, the presence of the variant or A allele within the *VKORC1* gene promoter, at least in part, offers a better chance of survival, due to its association with an intermediate or low blood coagulation. Our results also suggest that individuals with the wild-type or G allele within the *VKORC1* gene promoter, due to its association with high or standard blood coagulation, should be carefully monitored for early signs of thromboembolic events and/or pre-emptively treated when necessary.

Acknowledgement: The authors are grateful to all volunteers who took part in this study and the funders, the Ministry for Science, Higher Education and Youth of Canton Sarajevo, Bosnia and Herzegovina.

Declaration of Patient Consent: Written, informed consent was obtained from all volunteers in the study.

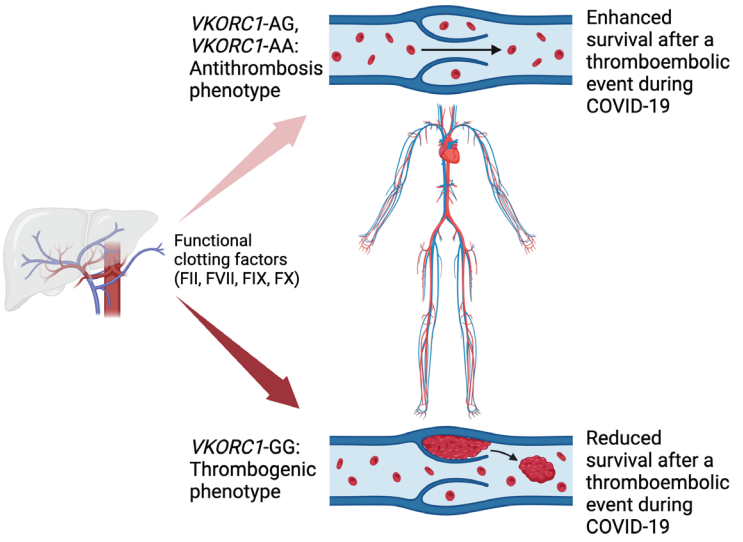

Figure 2. A hypothesized effect of the VKORC1 -1639G>*A* polymorphism on survival from COVID-19-associated thromboembolism.
Our results indicate that individuals with the variant or A allele within the VKORC1 -1639 locus, giving rise to the VKORC1-AG and VKORC1-AA genotypes, survived a thromboembolic event during COVID-19, compared with individuals with the wild-type or G allele, giving rise to the VKORC1-GG genotype. Image created with BioRender.com.

Authors' Contribution: Mirsada Causevic: Conceptualization, Funding acquisition, Investigation, Project administration, Methodology, Writing - original draft, reviewing & editing. Amina Sahbaz: Investigation, Methodology, Validation, Visualization, Writing - reviewing & editing; Nedim Galijasevic: Data curation, Methodology, Resources; Lamija Sikalo: Data curation, Methodology, Resources; Slobodan Jankovic: Funding acquisition, Formal analysis, Methodology, Writing - reviewing & editing; Edin Begic: Conceptualization, Funding acquisition, Methodology, Resources.

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Conflict of Interest: None.

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ORIGINAL RESEARCH

Morning Stiffness Correlates with Disease Activity, Blood Pressure and Cholesterol Levels in Patients with Seropositive Rheumatoid Arthritis

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Abstract

Introduction. Morning stiffness (MS) is the hallmark of rheumatoid arthritis (RA) and it has important implications on daily life of the patients. There are conflicting reports of its association with disease activity.

Methods. This observational study included 125 patients with seropositive RA from Health Care Center, Visoko. We obtained data on patient's gender and age, duration of RA, pain in hands and feet, MS and its duration, hospital admission, blood pressure, laboratory values and treatment modalities.

Results. MS lasted up to 30 minutes in 71 (56.8%) patients, 30 to 60 minutes in 40 (32%) patients, and more than 60 minutes in 14 (11.2%) patients. There was no difference in the duration of MS between genders. Patients with longer MS were younger and had a longer duration of illness. Patients with MS longer than 30 minutes had higher blood pressure and cholesterol levels. ESR in the second hour and CRP correlated with a duration of MS. Patients on methotrexate had a longer duration of MS. No significant differences in the duration of MS were observed for leflunomide, corticosteroids and supportive treatment modalities.

Conclusion. Duration of MS correlates with RA disease activity and remains an important burden for patients. Usage of newer treatment options, such as biologic disease-modifying antirheumatic drugs (DMARDs), may be required.

Keywords: biomarkers, disease activity, rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease affecting around 1% of the world population. It is more common in women than men, with peak incidence around 50 years of age. It is assumed that RA develops in genetically predisposed

individuals exposed to an external factor that triggers an autoimmune reaction (1, 2).

Clinical features of RA include constitutional symptoms, joint pain and swelling predominantly and symmetrically affecting the small joints of the hands and feet, although other joints lined by a synovial membrane may be affected (1, 3). The hallmark of RA is morning joint stiffness lasting longer than an hour, which is described as a limitation of motion after a period of rest (1, 4). However, this is not specific to RA, and this finding can be present in other inflammatory joint disorders (3). It can be explained by the circadian rhythm of pro-inflammatory cytokines like the tumor necrosis factor (TNF) and interleukin-6 (IL-6) (5). Morning stiffness (MS) may temporarily improve with active exercise and heat application (1).

MS is no longer included in classification criteria for RA, last published by the American College of Rheumatology (ARC) and the European Alliance of Associations for Rheumatology (EULAR) in 2010, but physicians still use it to help differentiate inflammatory arthritis from degenerative arthritis (6). There are conflicting reports of its association with disease activity, but there is evidence that MS is associated with local joint inflammation and elevated markers of systemic inflammation (7-9). It has an important impact on everyday activities and the well-being of patients with RA. It is the most common reason for early retirement of patients with RA (10). Previous studies showed that in the arthralgia preceding clinical arthritis, MS already reflects systemic and subclinical joint inflammation (11).

The aim of this study was to determine the significance of MS in patients with RA, especially its association with disease activity.

METHODS

Patients and study design

This observational study included 125 patients from the Public Institution "Health Care Center" Visoko. We collected data from the medical records of the patients with seropositive RA in the year 2022.

Methods

We obtained data on the following: patient's gender, age, duration of RA, pain in hands and feet, morning stiffness and its duration, hospital admission, systolic and diastolic blood pressure. We obtained data on laboratory values: erythrocyte sedimentation rate (ESR) in the 1st hour, ESR in the 2nd hour, white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets, fasting blood glucose, urea, creatinine, cholesterol, triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), C-reactive protein (CRP). We collected data on the following treatment modalities: methotrexate, leflunomide, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), topical NSAIDs, protein pump inhibitors (PPIs), vitamin D, glucosamine chondroitin, pomegranate extract supplement, omega-3 fish oil, calcium, herbal gel.

Statistical Methods

Data analysis was performed using the SPSS Windows software package (version 25, SPSS Inc., Chicago, Illinois, USA) and Microsoft Excel (version 2311 of Microsoft Corporation, Redmond, WA, USA). Mann-Whitney U test was used to assess differences in the duration of MS based on gender, hospital admission and treatment modalities. The effect size was small for r=0.10-0.29, moderate for r=0.30-0.49, large for r=0.5-1.0. To assess differences in the duration of MS based on laboratory values, patient's age, duration of illness and blood pressure, we used the Kruskal Wallis test. The level of statistical significance was set at $p < 0.05$.

RESULTS

Basic patient information

Most patients were female, 91 (72.8%). There were 34 (27.2%) male patients. The mean age was 62.3±11.4 years (range 43-100 years). The mean duration of RA was 5.3±1.8 years (range 1-10 years).

Regarding symptoms, all patients reported pain in hands and feet and MS. MS lasted up to 30 minutes in 71 (56.8%) patients, 30 to 60 minutes in 40 (32%) patients, and more than 60 minutes in 14 (11.2%) patients. 124 (99.2%) patients had swollen joints. 44 (35.2%) patients were admitted to the hospital due to rheumatoid arthritis.

There was no difference in the duration of MS between genders (U=1514, z=-0.20, p=0.83, r=0.01). Patients with MS longer than 30 minutes were younger (Median (Mdn) of 67 years for patients with MS<30min vs Mdn of 55 years for patients with MS 30-60min), χ^2=30.39, p<0.001. Patients with longer MS had a longer duration of illness (χ^2=54.67, p<0.001).

Patients with MS > 30 min had higher systolic BP (Mdn=140mmHg) and diastolic BP (Mdn=90mmHg), χ^2=36.70, p<0.001 and χ^2=22.50, p<0.001, respectively.

Hospitalized patients had a longer duration of MS (U=1035, z=-4.36, p<0.001, r=0.38).

Laboratory values and duration of morning stiffness

Comparations of laboratory values based on the duration of MS are presented in Table 1. Patients with longer MS had higher ESR in the second hour (χ^2=7.73, p=0.02). Patients with MS> 30 min had higher CRP (Mdn=11 mg/L vs 9mg/L; χ^2=6.16, p=0.04) and higher cholesterol (Mdn=6 vs 5.5 mmol/L; χ^2=6.44, p=0.04).

Patients with MS > 60 min had higher urea blood nitrogen (Mdn=6.05 vs 5.65 mmol/L; χ^2=6.62, p=0.03). ALT was significantly higher in patients with MS 30-60 minutes compared to patients with shorter or longer duration of MS (Mdn=22 U/L vs 19 U/L), χ^2=6.57, p=0.03.

Table 1. Comparing laboratory values between patients based on duration of their morning stiffness.

	Mdn for patients with morning stiffness <30 min (n=71)	Mdn for patients with morning stiffness 30-60 min (n=40)	Mdn for patients with morning stiffness >60min (n=14)	χ^2	Df	P
ESR in the 1st hour	27 mm	30.5 mm	34.5 mm	4.30	2	0.11
ESR in the 2nd hour	55 mm	62 mm	70.5 mm	7.73	2	0.02
WBC count	7×10^{12}/L	7.05×10^{12}/L	5.95×10^{12}/L	3.71	2	0.15
RBC count	4.5×10^{12}/L	4.55×10^{12}/L	4.4×10^{12}/L	0.97	2	0.61
Hemoglobin	136 g/L	137 g/L	133.5 g/L	2.20	2	0.33
Hematocrit %	0.41 L/L	0.40 L/L	0.39 L/L	2.31	2	0.31
MCV	88.5 fL	88.8 fL	89.15 fL	1.77	2	0.41
MCH	29.8 pg	29.9 pg	29.8 pg	0.28	2	0.86
MCHC	336 g/L	340 g/L	341 g/L	0.63	2	0.72
Platelets	277×10^{9}/L	293×10^{9}/L	299×10^{9}/L	2.32	2	0.31
Fasting blood glucose	5.5mmol/L	6.05mmol/L	6.35mmol/L	2.98	2	0.22
Urea	5.4mmol/L	5.65mmol/L	6.05mmol/L	6.62	2	0.03
Creatinine	72 µmol/L	74.5µmol/L	73 µmol/L	0.33	2	0.84
Cholesterol	5.5mmol/L	6 mmol/L	6 mmol/L	6.44	2	0.04
Triglycerides	2.3mmol/L	2.85mmol/L	2.8mmol/L	1.90	2	0.38
AST	20 U/L	25 U/L	22 U/L	4.80	2	0.09
ALT	19 U/L	22 U/L	19 U/L	6.57	2	0.03
CRP	9 mg/L	11 mg/L	11.5 mg/L	6.16	2	0.04

Mdn-median; ESR-erythrocyte sedimentation rate; WBC-white blood cell; RBC-red blood cell; MCV-mean corpuscular volume; MCH-mean corpuscular hemoglobin; MCHC-mean corpuscular hemoglobin concentration; AST-aspartate aminotransferase; ALT-alanine aminotransferase; CRP- C-reactive proteine; χ2 Chi-Square; Df - Degree of freedom; p -level of significance.

Treatment and duration of morning stiffness

Patients on methotrexate had longer duration of MS (U=1449, z=-2.74, p=0.006, r=0.24). No significant differences in the duration of MS were observed for leflunomide, corticosteroids, and supportive pharmacological and non-pharmacological treatment (Table 2).

Table 2. Duration of morning stiffness based on treatment modalities.

	Mann-Whitney U	z	P	R
Methotrexate	1449	-2.74	0.006	0.24
Leflunomide	1421	-0.23	0.81	0.02
Corticosteroids	879	-0.31	0.75	0.02
NSAID	626	-0.93	0.35	0.08
Topical NSAID	1207	-1.22	0.22	0.10
PPI	787	-0.32	0.74	0.02
Vitamin D	1710	-0.30	0.75	0.02
GC	1075	-0.70	0.48	0.06
Pomegranate extract supplement	1065	-0.49	0.62	0.04
Omega-3 fish oil	607	-0.19	0.84	0.01
Calcium	1276	-0.31	0.75	0.02
Herbal gel	780	-0.38	0.69	0.03

NSAID-non-steroidal anti-inflammatory drug; PPI-proton pump inhibitor; GC-glucosamine chondroitin

DISCUSSION

Higher ESR and CRP were found in patients with longer duration of MS, which goes in favor that MS is correlated with RA disease activity. Correlation between ESR and MS was also confirmed in the QUEST-RA study (12).

As previously reported, we confirmed no significant difference in MS duration between genders (12, 13). Large QUEST-RA database suggested no correlation between MS duration and duration of illness, while we found longer MS in patients with a longer duration of RA. On the contrary, the Japanese study reported that MS duration was higher in patients with a shorter duration of illness (14). Patients in our study were not treated with the biologic and targeted synthetic disease-modifying antirheumatic drugs (DMARDs); rather, they were treated with conventional DMARDs. Since evidence confirms that biologic DMARDs markedly improve MS, this could be one of the reasons why there is a higher burden of MS in patients with a longer duration of illness in our study (15). These drugs should be more accessible in Bosnia and Herzegovina to improve RA disease activity and symptom control (16).

We identified an inverse correlation between age and duration of MS, with younger patients having longer MS. Higher burden of MS in younger patients was previously reported (13). MS may be more noticeable in younger patients, as it may impact their daily activities more (13).

Previous reports suggest that patients with RA have higher average blood pressure compared to patients without RA, and our results indicated that patients with MS longer than 30 minutes have higher blood pressure, with its median in values diagnostic for hypertension (17, 18). Inflammation has its role in the pathogenesis of hypertension, including pro-inflammatory cytokines like TNF-α and IL-6, whose circadian elevation is also considered responsible for MS, which may explain this correlation (19). A similar concept can be applied to explain why patients with MS longer than 30 minutes had higher cholesterol levels, since cholesterol is linked to chronic inflammation (20). Patients with MS longer than 60 minutes had higher urea levels, and previous studies have shown that uremic toxins increase the levels of TNF-α and IL-6 and cause an exacerbation of the inflammatory state, but it should be noted that urea levels were still in the reference range in patients with longer MS duration in our study (21).

Since patients on methotrexate had a longer duration of MS, the question remains as to why methotrexate, being a standard of care for patients with RA, is not sufficient for symptom control and if other treatment modalities should be tried. One of the possible explanations may be poor patient compliance. CAPRA-1 and CAPRA-2 studies showed that the evening administration of modified-

release prednisone alleviates MS, by reducing the nocturnal levels of pro-inflammatory cytokines (22, 23). We did not confirm the difference in MS duration for patients on glucocorticoid treatment, however, our patients were prescribed standard methylprednisolone or prednisone to be taken in the morning.

It is difficult to alleviate stiffness with standard treatment, and usage of newer treatment options, such as biologic DMARDs, may be required. Reducing both systemic and local inflammation should be the focus.

Our study has several limitations. First, our sample size is small, and conducting more detailed research, especially randomized controlled studies, is necessary. It is not specified how long the patients were on a particular treatment before data collection, and whether they were taking treatment regularly. We did not report MS severity, which can be assessed using a numerical rating scale or the visual analogue scale (VAS). MS severity showed a stronger correlation with measures of disease activity than a duration of MS, although its assessment can be more subjective and it can overestimate the actual data (8, 24, 25). Also, we did not correlate the duration of MS with other patient-reported outcomes, such as physical function and pain. It was previously found that the duration of MS correlated better with functional disability than with ESR and swollen and tender joint counts (12, 26).

CONCLUSION

Duration of MS correlates with RA disease activity, systolic and diastolic blood pressure and cholesterol levels. Shorter MS duration was not associated with observed treatment modalities. MS in RA remains an important burden for patients, and its monitoring should be continued in clinical practice and research studies.

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ORIGINAL RESEARCH

Objective Response Rate According to Response Evaluation Criteria in Solid Tumors in Patients with Metastatic Colorectal Cancer and Their Influence on Progression Free Survival and Overall Survival

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Abstract

Introduction. Colon cancer is one of the most common forms of cancer, affecting both sexes equally. The objective tumor response rate (ORR) is an important parameter that proves the effectiveness of treatment in oncology; one of the ways to evaluate ORR is the response evaluation criteria in solid tumors *Response evaluation criteria in solid tumors* (RECIST).

The aim of the research is to determine and compare the impact of the objective response rate in patients with metastatic colorectal cancer and the impact on *overall survival* (OS) and *progression-free survival* (PFS).

Methods. The work is based on a retrospective (2014-2020) clinical study, with follow-up of patients over a period of 5 years. The research included a total of n=101 patients diagnosed with colorectal cancer (stages II and III according to the *American Joint Committee of Cancer* -AJCC). Research included n=101 patients, 52% male, 48% female. The youngest patient is 18 years old, and the oldest patient is 80 years old.

Results. The average age is 59.69 years. The obtained data show that the largest percentage of *Colorectal Cancer*-CRC patients are in the third age. Adenocarcinoma is the most common pathohistological verification of colon cancer (77.23%). Overall survival and progression-free time in relation to objective response to therapy (ORR) according to RECIST criteria did not show statistical significance. One patient had a complete response (CR) to therapy, six patients (5.94%) had a partial response (PR) to therapy. Stable disease (SD) was verified in 32.67%, and disease progression (PD) was confirmed in 60.39% of subjects.

Conclusion. The extent of objective response to therapy has no influence on overall survival and survival without disease progression in patients with metastatic colorectal disease.

Key words: colorectal, cancer, response evaluation criteria in solid tumors.

INTRODUCTION

Objective response rate (ORR) refers to the percentage of individuals in a study or treatment group who exhibit a partial or complete response to the therapy within a specified timeframe (1, 2). A partial response refers to a decrease in tumor size or

the amount of cancer in the body, while a complete response means the total disappearance of all signs of cancer. In clinical trials, assessing the objective response rate helps evaluate the effectiveness of a new treatment (2). The Response Evaluation Criteria in Solid Tumors (RECIST) is a set of guidelines used to assess tumor response in cancer patients undergoing treatment. It defines whether tumors shrink, remain stable, or grow (progress) during therapy (1). Only patients with measurable disease at baseline should be included in studies where the primary endpoint is objective tumor response. These criteria are designed to evaluate tumor changes, not necessarily to assess overall patient improvement, as they focus on the tumor rather than the patient's overall condition (1, 2). Measurable disease is the presence of at least one measurable lesion. If measurable disease is limited to a solitary lesion, its neoplastic nature should be confirmed cytologically/histologically (1). Measurable lesions are lesions that can be accurately measured in at least one dimension with a longest diameter ≥20 mm using conventional techniques or ≥10 mm using helical computed tomography (CT), scanning (1).

Non-measurable lesions are all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with helical CT scan) (1).

The theoretical basis for the RECIST criteria is that the sum of the longest diameters of individual tumors correlates more directly with the extent of cell death than the sum of two-dimensional measurements (4). According to the RECIST criteria, a partial response (PR) is defined as a reduction of at least 30% in the sum of the longest diameters of target lesions, while disease progression (PD) is defined as a 20% or greater increase in this sum. If tumors are assumed to be spherical, a 30% decrease in total diameter, which corresponds to a 65% reduction in tumor volume, is equivalent to a 50% reduction in the sum of the two-dimensional products (2, 3). Colorectal cancer originates from the epithelial cells lining the colon or rectum. It is primarily a disease of older adults, with colon cancer being one of the most common cancer types, affecting both men and women equally, and peaking in incidence during the seventh decade of life. Approximately 91% of new cases are diagnosed in individuals over 50 years old, with the average age at diagnosis ranging from 60 to 65 years. Colorectal cancer is relatively uncommon in younger individuals, with only about 9% of cases diagnosed before the age of 50, and 5-8% diagnosed before the age of 40 (4). Most colon cancers develop from malignant changes in colon polyps, with over 95% of cases arising from polyps, typically as adenocarcinomas (5). Over the past two decades, the incidence of colon cancer has been steadily and significantly increasing. In 2018, the global incidence of colorectal cancer was 19.7 per 100,000 people across all age groups and both sexes, according to GLOBOCAN (6). In Bosnia and Herzegovina, data from the International Agency for Research on Cancer (IARC) report approximately 663 new cases of colorectal cancer in women and 826 new cases in men annually, with 836 deaths expected each year from the disease (6).

In 5-10% of cases, colorectal cancer has a hereditary component, with 3-4% of these cases linked to Hereditary Non-Polyposis Colorectal Cancer (HNPCC), also known as Lynch syndrome, which is associated with microsatellite instability (MSI) in specific DNA regions. This includes conditions like familial adenomatous polyposis, non-polyposis colorectal cancer, familial colorectal cancer, and hereditary adenocarcinomatosis syndrome (7, 8). The majority of colon cancers result from mutations in the Wnt signaling pathway, leading to increased activation of this pathway (9).

The aim of this research is to determine and compare the impact of objective response rate (ORR) in patients with metastatic colorectal cancer and its influence on overall survival (OS) and progression-free survival (PFS).

METHODS

Patients and study design

This study is based on a retrospective clinical analysis conducted between 2014 and 2020, with a follow-up period of 5 years. It involved a total of 101 patients diagnosed with colorectal cancer (stages II and III according to the AJCC) who underwent surgery at the Clinical Center University of Sarajevo (CCUS) and subsequently received adjuvant chemotherapy.

Methods

After adjuvant chemotherapy, patients were followed. Those patients whose distant metastasis was verified during the follow-up period were included in the study. Some patients were surgically treated and for some patients, the diagnosis was made by biopsy. After adjuvant chemotherapy, patients were followed up. Those patients with verified distant metastasis during the follow-up period were included in the study.

Overall survival (OS) calculation was done from the operation (the appearance of metastases) until the end of the study, until the last written finding or until the death of the patient. PFS calculation was also done from the appearance of metastases to verified disease progression, which was established by radiological reevaluation. ORR in patients was verified on the basis of periodic oncological examinations, and on the basis of RECIST criteria. OS, PFS and ORR data were taken from patient medical histories at the Clinic of Oncology, CCUS.

Statistical Methods

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software for Windows. The Mantel-Cox test was applied to compare observed survival times with the expected survival times, under the null hypothesis that the survival functions of the two groups are identical. The Kaplan-Meier method was used to estimate the probability of survival past a certain time point, accounting for censored data. Additionally, a t-test was conducted to compare the means of two groups and assess whether there were significant differences between them.

RESULTS

Overall survival and progression-free time in relation to objective response to therapy (ORR) according to RECIST criteria did not show statistical significance. Our research (Figure 1) shows a slightly higher percentage of patients with PD, and a smaller percentage of patients with SD.

One patient had a complete response to therapy (0.99%). Six patients (5.94%) had a partial response to therapy. Stable disease was verified in (n=33) patients or 32.67%, and disease progression was confirmed in (n=61) patients or 60.39%.

Figure 1. Objective response rate to therapy in the examined group of patients

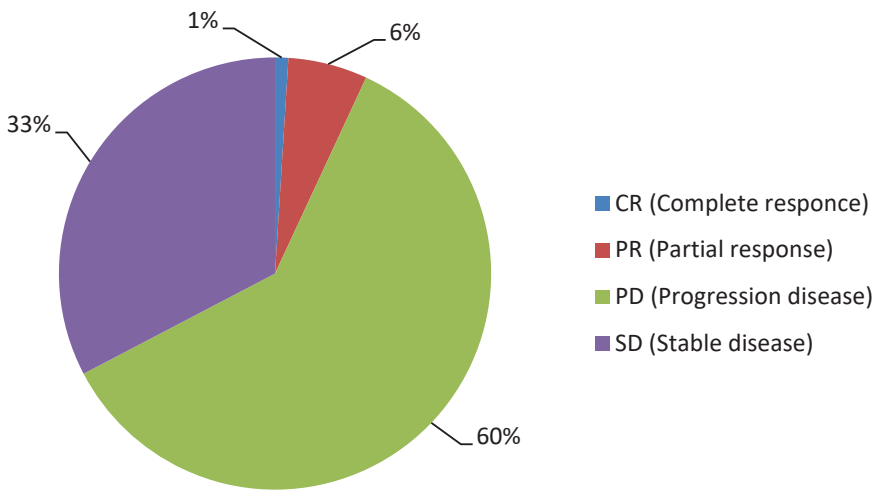

Table 1. Overall survival in relation to objective response to therapy

		t-test for equal means						
		t	df	Sig. (2-end)	Mean value t difference	Standard error of difference	95% Interval trust the difference	
							Lower	Top
In total	Probably	-	99	.066	-4.883	2.629	-10.100	.334
survival	equal variations	1.857						
(months)	Equal	-	72.613	.045	-4.883	2.393	-9.653	-.113
	variations are not likely	2.040						

df-degree of freedom; sig. - level of significance.

The t-test of independent samples did not reveal a statistically significant difference in the length of overall survival (OS) between patients with stable (9.77±10.15) and progressive disease (PD) (14.66±12.98), t=-1.86, p=0.66, (95% CI: -10.10-0.33). The average difference in OS length by group was 4.88 days.

The t-test of independent samples did not establish a statistically significant difference in the length of survival without disease progression (PFS) between patients with stable (SD) (8.45±7.43) and progressive disease (PD) (9.61±7.18), t=- 0.742, p=0.46, (95% CI: -4.27-1.94). The average difference in the length of PFS by groups was 1.16 days.

Discussion

The study included n=101 patients, of which n=53 or 52% were male, and n=48 or 48% were female (10,11). The largest number of patients are in their third age. Looking at the age structure, we notice that the largest proportion of patients (n=86) or 85.15% are over 50 years of age, while younger patients (up to 50 years of age) make up only 14.85% (n=15) and of these, only n=2 patients or 1.98% are under 30 years of age. The obtained data on the sex structure correspond to the data from the literature (10).

By reviewing the age structure, we can see that the largest proportion of patients (n=86) or 85.15% are over 50 years of age, while younger patients (up to 50 years of age) make only 14.85% (n=15) (10), and of these younger than 30 years only n=2 patients or 1.98%. The youngest patient included in the research is 18 years old, and the oldest patient is 80 years old. American Cancer Society research from 2020 shows that patients under the age of 50 make 12% of patients. The obtained data correspond to the data of the consulted literature, which supports the fact that the largest percentage is made up of patients in their third age (12, 13).

Overall survival and progression-free time in relation to objective response to therapy (ORR) according to RECIST criteria did not show statistical significance. *Lucidarma O. et al.* in their prospective two-month study had 57% of patients with stable disease (SD) and 43% with progressive disease (PD) (14). Our research shows a slightly higher percentage of patients with PD and a smaller percentage of patients with SD.

Table 2. Survival without disease progression in relation to the objective response to therapy

		t-test for equal means						
		t	df	Sig. (2-end)	Mean value t difference	Standard error of difference	95% Interval trust the difference	
							Lower	Top
Progression free survival	Likely equal variances	- .742	99	.460	-1.163	1.566	-4.270	1.945
	Equal variations are not likely	- .733	55.783	.467	-1.163	1.587	-4.342	2.017

df-degree of freedom; sig. - level of significance.

Of the total number of patients with metastatic colorectal cancer included in the study, n=62 or 61.39% survived to the end of the study. Five-year survival ranges from 50 to 59% for patients with colorectal cancer in many countries (7). Patients with liver metastases have a median survival of 5 to 20 months without treatment (15). *Valderama et al.* state that in 14–18% of patients, metastases are recorded at the first examination, 10–25% of patients have liver metastases during the first operation, and the incidence of liver metastases additionally "jumps" after the use of *Computed Tomography Scan* (CT) diagnostics. The mentioned research says that even about 70% of patients with colorectal cancer will develop liver metastases (15).

Shahab D. et al. indicate in their research that in locally advanced colon cancer, 15–20% of patients are treated with neoadjuvant chemoradiotherapy, achieving a pathologically complete response to therapy (16, 17). The benefit of adjuvant chemotherapy is controversial in patients with rectal cancer. An eight-year study by *Shahab D et al.* shows a difference in 5-year OS for patients who received neoadjuvant chemoradiotherapy plus adjuvant (94%) and patients who received only neoadjuvant chemoradiotherapy (84%) (16, 17).

Conclusion

The extent of objective response to therapy has no influence on overall survival and survival without disease progression.

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Declaration of Patient Consent: Written, informed consent was obtained from all volunteers in the study.

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ORIGINAL RESEARCH

Enhanced Survival Outcomes with FOLFIRINOX in Initial Metastatic Pancreatic Cancer: Single-Center Study

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Abstract

Introduction. The aim of this article is to evaluate the efficacy and outcomes of FOLFIRINOX as a first-line treatment for initial metastatic pancreatic cancer patients at the Clinical Center University of Sarajevo.

Methods. The research presents a retrospective analysis was conducted on 33 patients treated with FOLFIRINOX, between January 2021 and January 2023. Baseline characteristics, tumor markers (CEA, CA 19-9, CA 125), neutrophil-to-lymphocyte ratio (NLR), neutrophil-to-platelet ratio (NPR) and initial metastatic site were evaluated using Cox regression analysis in order to identify predictive and prognostic factors for progression-free survival (PFS) and overall survival (OS).

Results. The median age of patients was 64 (range 38-76). There were 18 males and 15 females. The median OS was 21.7 months (95% CI, 10.5-32.9) and the median PFS was 10.0 months (95% CI, 8.2-11.8). A statistically significant negative correlation was found between NLR and OS (r=-0.464, p=0.045). Patients with initial liver metastasis had a numerically worse median OS (16.3 months, 95% CI, 5.1-27.5), compared to those with non-liver metastasis (OS not reached, p=0.058). Tumor markers, NLR, NPR, and initial metastatic site were not independent predictors of PFS and OS.

Conclusion. FOLFIRINOX demonstrates significant efficacy in treating metastatic pancreatic cancer in a real-world setting. Personalized approaches, including genetic profiling and microbiome analysis, along with AI integration, offer promising avenues to enhance treatment outcomes and quality of life for patients.

Keywords: metastatic pancreatic cancer, enhanced outcomes, overall survival, progression-free survival.

INTRODUCTION

Pancreatic cancer is acknowledged as one of the most formidable challenges in oncology, characterized by its aggressive progression and poor prognosis. The disease is among the poorest in terms of prognosis and the disease ranks as the sixth leading cause of cancer mortality in both sexes combined (1).

Taking into account the advances in medical research, the five-year survival rate has recently improved by approximately 13% – a moderate but significant increase which reflects improvements in treatment and early detection methods (2). However, for patients with unresectable pancreatic cancer, the five-year survival rate remains below 5%, implying the particularly dire prognosis for those whose cancer cannot be surgically removed (2). In the United States, the projected figures for 2024 indicate 66,440 new cases and 51,750 deaths, emphasizing the deadly nature of this disease (2). In Bosnia and Herzegovina, the situation mirrors the global challenge, with estimated 502 new cases and 489 deaths reported in 2022, suggesting a high fatality rate that nearly matches the incidence (3).

Considering the recent advancements in treatment, FOLFIRINOX has emerged as a crucial therapy for metastatic pancreatic cancer. Introduced in the early 2010s, FOLFIRINOX presents a combination regimen of fluorouracil, leucovorin, irinotecan and oxaliplatin. The ACCORD trial, published in 2011, demonstrated that FOLFIRINOX significantly extended median overall survival to 11.1 months, compared to 6.8 months for patients treated with gemcitabine, marking a valuable improvement in the management of this disease (4). Despite its intense side effects and the necessity for careful patient selection, FOLFIRINOX is a good example of the shift in the approach towards aggressive combination therapies that target multiple aspects of tumor growth and survival, with the aim of extending lifespan and improving the quality of life for patients suffering from this devastating disease.

Besides the recent promising increase in survival rates, there is also an ongoing need for advancements in both therapeutic approaches as well as diagnostic techniques, in order to change the overall dismal survival statistics. The American Society of Clinical Oncology (ASCO) guidelines emphasize the importance of early testing for actionable genomic alterations in patients who are likely to become candidates for additional treatment after the first-line therapy. This includes testing for microsatellite instability, mismatch repair deficiency, BRCA mutations and NTRK gene fusions (5).

Pancreatic Ductal Adenocarcinoma (PDAC) patients with somatic/germline mutations in the DNA Damage Repair (DDR) pathway, such as BRCA1, BRCA2 and PALB2, may benefit from platinum-based therapies and PARP inhibitors such as Olaparib. Similarly, KRAS mutations, prevalent in about 95% of PDAC cases, are being targeted with the new therapeutics like Sotorasib and Adagrasib, which have shown promising results in many clinical trials. Besides that, immunotherapy is showing up as a potential treatment for a subset of PDAC patients with mismatch repair deficiency (dMMR) and/or high microsatellite instability (MSI-H), within which medications like Pembrolizumab demonstrate particular efficacy. These advancements underscore the importance of personalized medicine in the future management of pancreatic cancer, setting the ground for better outcomes through targeted and immune-based therapies (6).

An additional advantage of early testing for actionable genomic alterations is the opportunity it provides for patients to qualify for clinical trials specifically targeting these genetic changes.

METHODS

Patients and Study Design

This retrospective cohort study was conducted at the Clinic of Oncology, Clinical Center University of Sarajevo. We included patients diagnosed with initially metastatic pancreatic cancer who were treated from January 2021 to January 2023. The stu-

dy aimed to evaluate the efficacy of FOLFIRINOX as a first-line treatment and to identify potential predictive and prognostic biomarkers.

Methods

Within the study, 33 patients with a confirmed diagnosis of initially metastatic pancreatic cancer were included. Eligibility for inclusion required patients to be treated with FOLFIRINOX as their first-line treatment. We excluded patients deemed unfit for FOLFIRINOX based on predefined clinical criteria including performance status and organ function tests. The criteria for being deemed unfit were rigorous and aligned with the latest oncological guidelines.

Data were collected retrospectively from electronic medical records and patient files, thoroughly maintained by the Clinic of Oncology. We extracted demographic information, clinical history, treatment details and follow-up outcomes. The primary collected variables included:

The primary analyzed outcomes were overall survival and progression-free survival, defined from the start of the treatment to the date of the last follow-up or death.

We evaluated several potential predictive and prognostic factors including:

- Tumor Markers: Carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA 19-9) and cancer antigen 125 (CA 125).
- Inflammatory Markers: Neutrophil-to-lymphocyte ratio (NLR) and neutrophil-to-platelet ratio (NPR).
- Metastatic Site: Initial sites of metastasis were recorded and classified.

Statistical Methods

- analysis was performed using SPSS software (Version 25, IBM Corp., Armonk, NY, USA). Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Multivariate analysis was conducted using Cox proportional hazards regression models to identify independent predictors of survival. A two-sided p-value of less than 0.05 was considered statistically significant.

RESULTS

This study analyzed the outcomes of 33 patients with initially metastatic pancreatic cancer treated with FOLFIRINOX as a first-line treatment at the Clinic of Oncology, Clinical Center University of Sarajevo, from January 2021 to January 2023.

The median age of the patients was 64, ranging from 38 to 76 years, with a distribution of 18 males and 15 females. We have not identified a statistically significant difference in progression-free survival and overall survival between gender groups.

The median overall survival (OS) for the cohort was 21.7 months, with a 95% confidence interval (CI) of 10.5 to 32.9 months.

The median progression-free survival (PFS) was 10.0 months, with a 95% CI of 8.2 to 11.8 months.

A statistically significant negative correlation was found between the NLR and overall survival of patients (correlation coefficient r = -0.464, p = 0.045).

Patients presenting with initial liver metastasis exhibited a worse median OS of 16.3 months (95% CI: 5.1 to 27.5 months), compared to those with non-liver metastatic sites, where the median OS was not reached. The difference approached statistical significance (log-rank p-value = 0.058). The impact of metastatic sites on survival outcomes is illustrated in Figure 1.

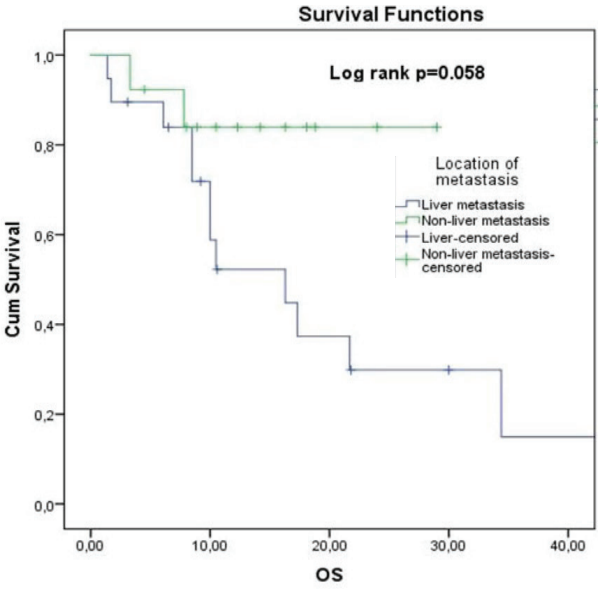

Figure 1 Kaplan-Meier survival analysis of patients divided in two groups based on the location of metastatic disease.

Metastatic sites were located predominantly in the liver (52.6%), followed by the lungs (23.6%), retroperitoneal lymph nodes (13.1%), peritoneum (5.3%), stomach (2.7%) and bones (2.7%). The detailed distribution of metastatic sites among patients is presented in Table 1.

Table 1 Frequency and percentage distribution of metastatic sites among the patients.

Location of Metastasis	Frequency (n)	Percent (%)
Liver	20	52.6
Lungs	9	23.6
Retroperitoneal lymph nodes	5	13.1
Peritoneum	2	5.3
Stomach	1	2.7
Bones	1	2.7
Total	38	100

Survival analysis was performed, dividing the patients into two groups based on the location of metastatic disease. The survival curves highlighted the differential impact of metastatic sites on survival outcomes and are shown in Figure 1.

The study assessed tumor markers (CEA, CA 19-9, CA 125), NLR, neutrophil-to-platelet ratio (NPR) and the initial site of metastasis for their potential as predictive and prognostic markers. However, none of the noted parameters were identified as independent predictive or prognostic markers for PFS and OS.

DISCUSSION

Patients with initially metastatic pancreatic cancer who were treated with FOLFIRINOX at our site achieved better PFS and OS results compared to the clinical studies that established this regimen. Within our study, the median overall survival (OS) was 21.7 months, and the median progression-free survival (PFS) was 10.0 months, significantly higher than the 11.1 months OS and 6.8 months PFS reported in the ACCORD trial (4). This difference in outcomes may be attributed to several factors, including advancements in supportive care.

Considering the timeline of the ACCORD trial, it should be pointed out that since then, there have been significant improvements in supportive care which help patients to better manage the intense side effects associated with the FOLFIRINOX regimen. Enhanced supportive care can lead to improved tolerability, allowing patients to maintain optimal dosing and treatment schedules, which can be crucial in achieving the best outcomes (1, 7).

When it comes to the patient selection process and the management in general, our study likely benefited from implementing refined criteria for selecting patients, but also from the advancements made in the initial diagnostic management of pancreatic cancer. This includes more precise diagnostic tools and closer monitoring, which can contribute to better overall outcomes (2, 4, 8). Besides that, this aspect aligns with the findings from other studies as well, such as Yoon et al., which also reported better survival rates due to enhanced supportive care and closer patient monitoring (8).

It is interesting to note that variations in healthcare practices, accessibility to advanced care, and demographic differences can also significantly influence treatment outcomes. Studies indicate that regional differences impact survival rates and treatment effectiveness, suggesting that local healthcare infrastructure and practices play critical roles in the success of complex treatments like FOLFIRINOX (9).

Even though the previously noted findings indicate that FOLFIRINOX really does offer improved survival benefits, we need to take into consideration that this regimen is at the same time associated with higher toxicity and cost. Economic evaluations suggest that while remaining more expensive, the cost-effectiveness of FOLFIRINOX may be justified by the significant survival benefit that it brings (7, 10). Moreover, quality of life considerations are paramount, as treatment intensity must be balanced against potential quality of life deterioration. Gourgou-Bourgade et al. highlighted that FOLFIRINOX significantly reduces quality of life impairment compared with gemcitabine, despite its higher toxicity profile (7).

The recent NAPOLI-3 clinical trial demonstrated an improvement in median survival to 11.1 months (95% CI 10.0–12.1) for patients treated with the NALIRIFOX regimen (liposomal irinotecan, oxaliplatin, leucovorin, and fluorouracil), compared to 9.2 months (95% CI 8.3–10.6) for those receiving nab-paclitaxel-gemcitabine. These findings position NALIRIFOX as a promising new first-line treatment option for patients with metastatic pancreatic cancer.

Aside from the quality of life considerations and survival benefits of FOLFIRINOX, we found that survival outcomes can be impacted by liver metastasis as well. Precisely, our findings indicated that patients with initial liver metastasis had a worse median OS compared to those with non-liver metastases. This observation aligns with existing research indicating that liver metastases in pancreatic cancer are associated with weaker prognosis. The general physiological role of the liver in drug metabolism and the aggressive nature of liver-invading tumors likely contribute to worse outcomes. Studies have shown that liver metastases are often linked with higher tumor burden and more aggressive disease, impacting the effectiveness of systemic treatments and overall patient survival (6, 11).

Genetic profiling can change treatment outcomes through identification of patients who are more likely to respond to different chemotherapy regimens based on their genomic information, thus highlighting the potential benefits of integrating precision medicine into treatment protocols for metastatic pancreatic cancer (5). For instance, the presence of certain DNA repair gene mutations may make cancer cells more susceptible to the DNA-damaging agents in FOLFIRINOX. Further research into these predictive biomarkers could refine patient selection criteria, potentially leading to even better clinical outcomes and more personalized treatment approaches (12).

When we bring up patient profiling, it is important to highlight that the use of artificial intelligence (AI) in healthcare is transforming the development of that process and the customization of treatment plans in general. AI can analyze extensive datasets, including genetic profiles, clinical histories and treatment responses, to identify patterns that predict which patients are most likely to benefit from specific chemotherapy regimens. These AI algorithms provide clinicians with data-driven insights, enhancing the precision of treatment plans and optimizing patient outcomes (13, 14). Future research should investigate the incorporation of AI tools in routine clinical practice in order to further refine patient selection and personalize treatment strategies, particularly in pancreatic cancer.

The composition of the gut microbiome can influence the body's response to chemotherapy and also modulate the immune response against tumors. Studies indicate that certain bacterial populations can enhance the effectiveness of chemotherapy, while others may contribute to resistance or increased toxicity. Including microbiome analysis into patient profiling could lead to even more personalized treatment modalities aimed at improving outcomes and reducing side effects (15). Chrysostomou et al. highlighted that gut microbiota modulation could impact the efficacy and toxicity of cancer chemotherapy and immunotherapy, suggesting that microbiome-targeted in-

terventions might be a valuable addition to cancer treatment protocols (15).

Innovative targeted therapies, based on genomic results, could potentially improve survival and quality of life in PDAC (Pancreatic Ductal Adenocarcinoma) patients. PDAC patients with somatic/germline mutations in the DNA Damage Repair (DDR) pathway, such as BRCA1, BRCA2, and PALB2, may benefit from platinum-based therapies and PARP inhibitors like Olaparib (5). Similarly, KRAS mutations, prevalent in about 95% of PDAC cases, are being targeted with new therapeutics like Sotorasib and Adagrasib, which have shown promising results in clinical trials (6). Besides that, immunotherapy is also showing up as a potential treatment for a subset of PDAC patients with mismatch repair deficiency (dMMR) and/or high microsatellite instability (MSI-H), within which medications like Pembrolizumab demonstrate particular efficacy (5, 7). These advancements emphasize the importance of personalized medicine in the future management of pancreatic cancer, making space for better outcomes through targeted and immune-based therapies (8).

Although the study provides valuable insights, several limitations must be acknowledged. First, the relatively small sample size of 33 patients may reduce the statistical power of our analysis and limit the generalizability of our findings to broader patient populations. The retrospective design of the study introduces inherent limitations, including the potential for selection bias and incomplete data collection. Moreover, the biomarker analysis in this study was limited to tumor and inflammatory markers (CEA, CA 19-9, CA 125, NLR, NPR). While these markers have been associated with prognostic outcomes in other studies, our analysis did not include genomic or molecular profiling, which could offer more precise predictive insights, especially in the context of emerging targeted therapies and personalized medicine.

As this study was conducted at a single institution, the results may not be broadly applicable to other healthcare settings or regions with different treatment protocols and patient populations.

In summary, while this study contributes to the growing body of evidence supporting the use of FOLFIRINOX in metastatic pancreatic cancer, these limitations should be considered when interpreting the results. Further research with larger, multicenter cohorts, prospective designs, and comprehensive biomarker and quality of life assessments is warranted to refine treatment strategies and optimize outcomes for this patient population. The limitations of our research pertain to the small sample size of patients and the lack of information on the molecular profile of patients.

CONCLUSION

The results of our study correlate with the outcomes of therapy with FOLFIRINOX in pivotal clinical trials and confirm the efficacy and safety of this combination in a real-world setting.

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Declaration of Patient Consent: Written, informed consent was obtained from all volunteers in the study.

Authors' Contributions: ES, AD, US, EK, EB-G, JR, AA, LM, SC, BH, AP and SB gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author had role in article drafting and in process of revision. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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ORIGINAL RESEARCH

Correlation Between MRI Findings, ODI, and VAS Score in Lumbar Disc Herniation

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Abstract

Introduction. Magnetic resonance imaging (MRI) is the preferred method for diagnosing the causes of lumboischialgia, as it offers the highest sensitivity and specificity compared to other imaging techniques. In clinical practice, there is often a notable discrepancy between patients' clinical symptoms and the radiological findings. While there are various clinical tests for lumboischialgia, the Oswestry Disability Index (ODI) and the Visual Analogue Score (VAS) are the most commonly used and reliable. This article aims to explore the correlation between patients' subjective pain experiences and their level of disability due to lumboischialgia and disc herniation as detected by MRI.

Methods. In this prospective clinical study, a total of 100 patients of both genders, aged 18 to 65 years, were included. These patients were referred for magnetic resonance imaging of the lumbar spine due to complaints of lumboischialgia. MRI of the lumbar spine was performed, and the extent of degenerative changes was evaluated. Participants completed a questionnaire regarding their subjective pain experience and functional status, and the Oswestry Disability Index (ODI) and Visual Analogue Score (VAS) were calculated.

Results. The statistical analysis revealed a significant correlation between the severity of disc herniation (classification) and the intensity of spinal pain ($p = 0.010$), as well as with the disability index ($p = 0.003$).

Conclusion. A statistically significant relationship was confirmed between the levels of pain and disability and the degree of intervertebral disc herniation observed on MRI images of the lumbar spine.

Keywords: lumbal disk herniation, lumboischialgia, pain.

INTRODUCTION

Back pain is one of the most prevalent clinical conditions among middle-aged individuals, affecting over 85% of the global population at least once in their lifetime. This condition is a leading cause of visits to family medicine practitioners, work absenteeism, and high healthcare costs. It significantly impacts quality of life, often leading to anxiety, depression, and other psychosomatic changes, particularly in cases of chronic pain.

Back pain encompasses a range of spinal disorders that are among the most common ailments in modern society. Epidemiological data indicate that between 50% and 80% of adults will experience low back pain (lumbar syndrome) at some point in their lives. Although low back pain can occur at any age, it is most prevalent between the ages of 35 and 55, affecting both sexes equally. After menopause, women are somewhat more likely to experience it, and during pregnancy, between 49% and 76% of women report low back pain. It is the leading cause of disability in adults under 45 and ranks third among those over 45. Approximately 5% of men and 2.5% of women suffer from sciatica, with pain most commonly localized in the lumbar or cervical spine. Back pain serves as a symptom rather than a standalone disease, with a wide range of potential causes—up to 150 different factors are noted. The most common cause is degenerative changes in the intervertebral discs and the small joints of the vertebrae. Lumbar disc herniation occurs when disc material is displaced beyond the normal boundaries of the intervertebral space, leading to pain, weakness, or tingling in specific dermatomes or myotomes. This condition typically affects the L4-L5 and L5-S1 levels, causing pain that can radiate to the gluteal region, down the back of the leg, across the top of the foot, and into the big toe if originating from the L5 nerve root. If stemming from the S1 nerve root, the pain may travel along the gluteal area, down the back of the leg, to the heel, lateral side of the foot, and into the little toe. This type of pain is particularly challenging due to its high incidence and chronic nature. Magnetic resonance imaging (MRI) is the preferred diagnostic tool for identifying the causes of lumboischialgia, owing to its superior sensitivity and specificity compared to other imaging methods. MRI provides detailed anatomical visualization and effectively highlights pathologies, particularly in soft tissues, without the use of ionizing radiation. In addition to radiological techniques, various clinical tests are employed to evaluate and diagnose the patient's condition. The Oswestry Disability Index (ODI) and the Visual Analogue Score (VAS) are the most commonly used and reliable tools. These assessments include questions about the intensity of lumbar pain and the impact on nine daily activities (such as personal care, lifting, walking, sitting, standing, sleeping, sexual activities, social life, and travel). Several studies have explored the relationship between radiological findings and patient symptoms related to lumbar pain; however, many had methodological limitations, often relying on retrospective symptom descriptions without standardized approaches. Utilizing standardized tools, like ODI and VAS, has improved the accuracy and reproducibility of symptom assessments.

The aim of our study was to determine whether there is a correlation between patients' subjective pain experiences and their level of disability related to lumboischialgia and disc herniation, as detected by MRI.

METHODS

Patients and Study Design

Following approval from the Ethical Committee (0302-56/13) of the University Clinical Center of Sarajevo, this research was conducted as a randomized prospective study from 2021 to 2023 at the Radiology Clinic of the University Clinical Center of Sarajevo. The study included 100 patients of both genders, aged 18 to 65, who presented a clear clinical picture of lumboischialgia and were referred for MRI. Medical documentation provided insights into clinical findings (from neurologists, orthopedists, or neurosurgeons), laboratory results, and demographic data.

Patients were excluded if they did not have a confirmed clinical diagnosis of lumboischialgia, had undergone prior spinal surgery, had other conditions affecting the clinical presentation (such as post-stroke status, amputations, or severe diabetes with neuropathy), or if their symptoms were due to other pathological processes in the lumbar

spine (including inflammatory processes, tumors, or trauma) rather than degenerative changes. Additionally, patients with incomplete medical records or those who declined to participate were not included.

Methods

All eligible patients underwent an MRI scan of the lumbar spine while lying supine, with a pillow placed under their knees, using an appropriate spinal coil. No prior preparation was required, and no intravenous contrast medium was administered.

MRI was performed using 1.5 Tesla machines (Magnetom Avanto, Siemens; Toshiba Titan; GE Signa Exite). A standard protocol was employed for the lumbosacral region, including T1 and T2 turbo spin echo (TSE) sequences in sagittal orientation, T2 TSE in coronal orientation, fat-suppressed T2 trim in sagittal, and axial T1 and T2 TSE sequences.

The MRI scans were analyzed for lumbar disc herniation, using Jensen's and MSU classification systems. Jensen's classification divides disc herniation into four categories:

1. **Bulging**: Minor bulging of the disc without disruption of the annulus fibrosus.
2. **Protrusion**: Larger disc bulge with partial annulus fibrosus defect.
3. **Extrusion**: Complete rupture of the annulus fibrosus and posterior longitudinal ligament.
4. **Sequestration**: The central part of the disc breaches the annulus fibrosus and enters the spinal canal.

Using the MSU classification, we determined the size and location of the herniations based on a single measurement at the point of greatest extrusion, at the level of the intrafacet line (a transverse line joining the medial edges of the right and left facet joints).

The size of the herniated disc was categorized as follows:

1. A herniation extending to or less than 50% of the distance from the posterior aspect of the normal disc to the intrafacet line.
2. A herniation extending more than 50% of that distance.
3. A herniation that fully extends beyond the intrafacet line. In cases of caudal or cranial (maximal) extrusions, the measurement was taken from the posterior edge of the vertebra instead of the disc.

Three points (A, B, and C) were marked along the intrafacet line to quantify the location of the disc herniation. Vertical lines were drawn through these points to define the right and left central quadrants (Zone A) and the right and left lateral quadrants (Zone B). Zone C was identified at the level of the foramen, extending beyond the medial margin of any facet joint into the lateral quadrants.

In addition to MRI scans, all patients completed a questionnaire regarding their subjective pain experience and functional status, allowing for the calculation of ODI and VAS scores. VAS scores were reported on a scale from 0 to 10, where 0 indicates no pain, 5 indicates moderate pain, and 10 signifies unbearable pain. The total ODI points were divided by 50 and multiplied by 100 to yield a percentage of disability, categorized as follows: 0-20% (minimal disability), 21-40% (moderate disability), 41-60% (severe disability), 61-80% (disabled), and 81-100% (immobile or exaggerating symptoms).

Statistical Analysis

All collected data were statistically analyzed using SPSS software, version 16. Descriptive statistics were calculated, including arithmetic means, medians, standard deviations, and standard errors. The degree of correlation was assessed using the Pearson or Spearman correlation coefficients, with a significance level set at $p < 0.05$.

RESULTS

The most significant disc herniations among the patients examined were observed at the L4–L5 (47%) and L5–S1 (39%) levels, with only 3% of patients having no hernia (Figure 1). The most common type of herniation was protrusion (73%), while arch tension and extrusion were somewhat less frequent; sequestration was not detected in the analyzed group.

The study results indicated a significant correlation between the severity of disc herniation (classification) and the intensity of spinal pain (p = 0.010), as well as the disability index (p = 0.003). Patients with extrusion reported the highest pain levels (mean VAS = 8; ODI = 50%), while those with arch tension reported the least pain (mean VAS = 6; ODI = 32%) (Figure 2).

Nerve compression was confirmed in 48% of the patients, with no significant gender difference (p = 0.678). Patients with observed compression on MRI reported greater pain levels. Compression was more frequently noted on the left side (33.3%), followed by the right side (38.6%), bilate-

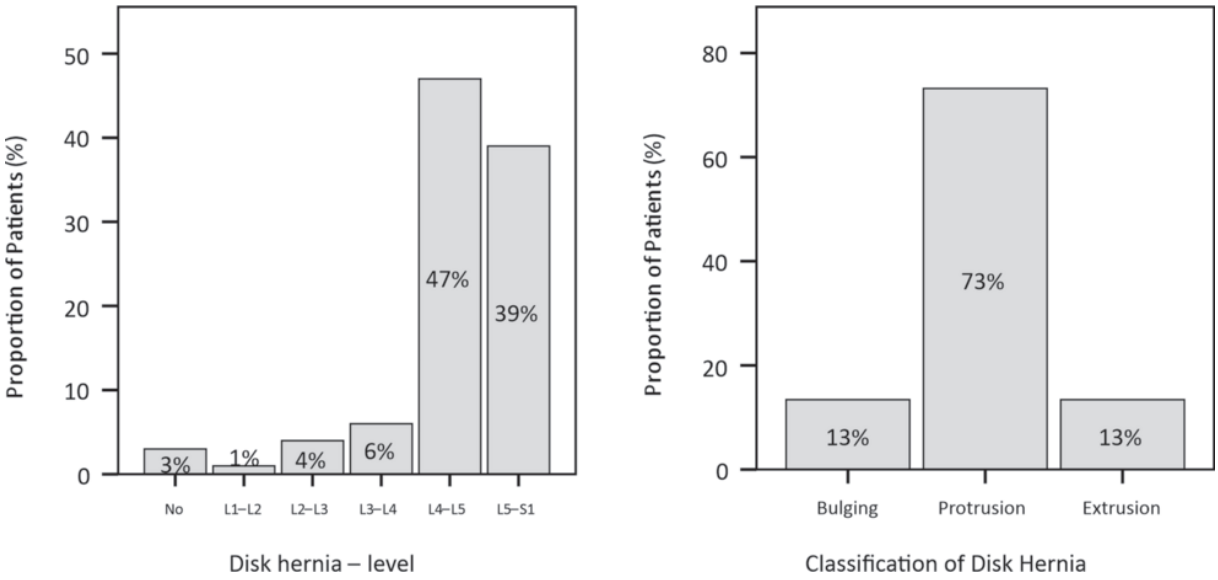

Figure 1. Proportion in the total number of patients: (left) location of disc herniation; (right) classification of herniated disc

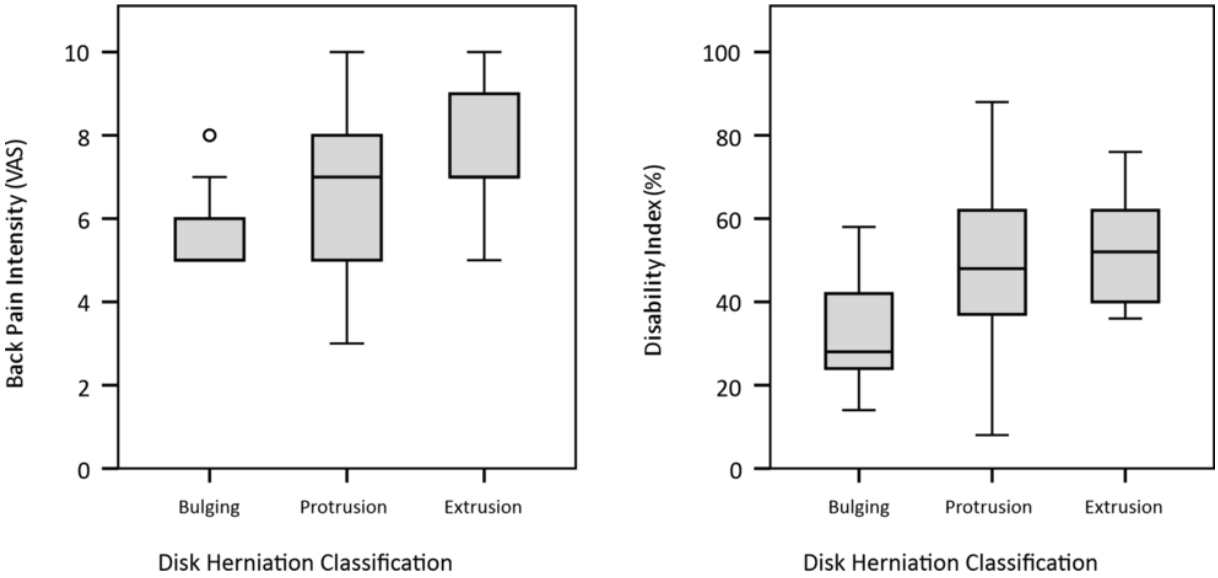

Figure 2. (left) Back Pain Intensity (VAS) and (right) Disability Index (ODI) depending on disc herniation classification

rally (14.0%), and somewhat less often on the dural sac (14.0%). There were no significant differences in VAS and ODI scores based on the sites of compression (Figure 3). However, there was a significant difference in spinal pain intensity (p = 0.006) and disability index (p = 0.001) between patients with nerve compression and those without.

No significant differences were found in spinal pain intensity (p = 0.957) and disability index (p = 0.358) concerning the location of foraminal stenosis (Figure 4).

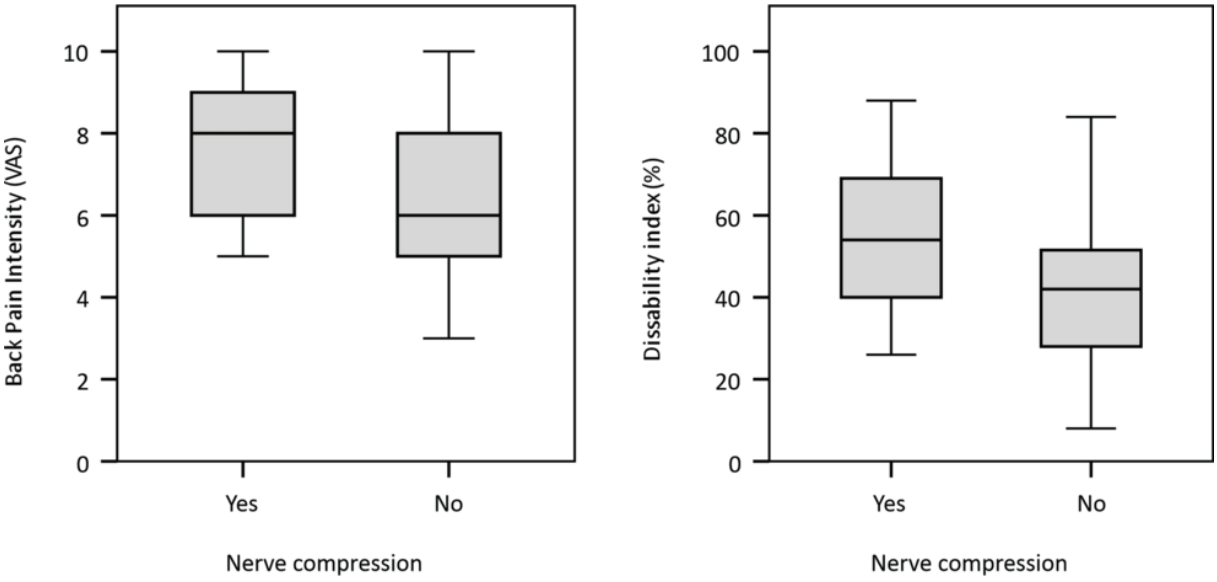

Figure 3. (left) Back Pain Intensity (VAS) and (right) Disability Index (ODI) depending on the presence of nerve compression.

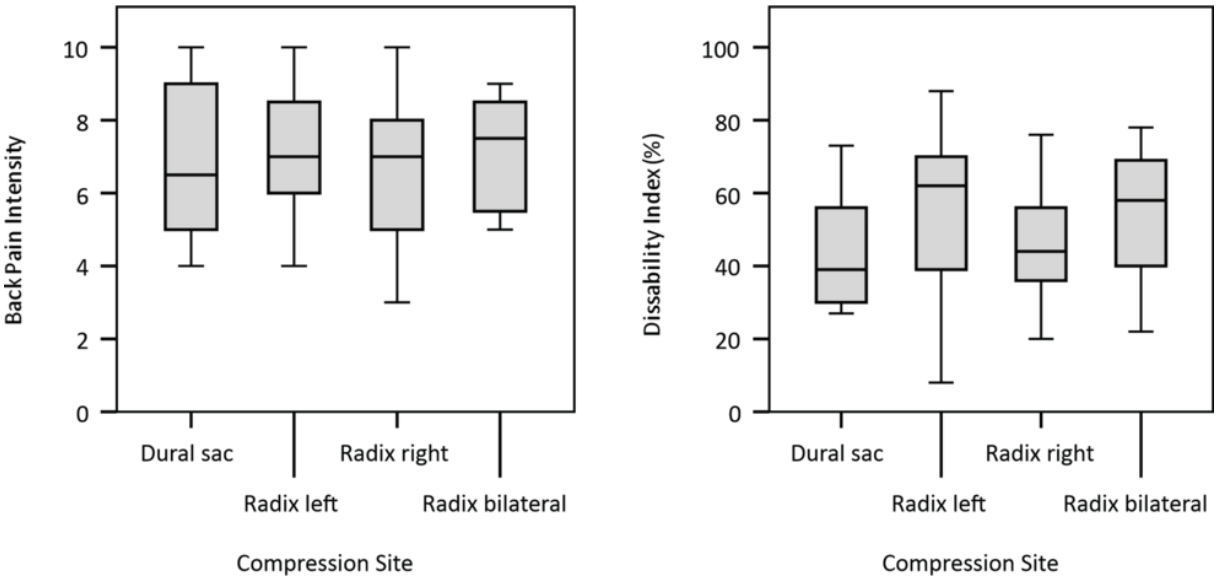

Figure 4. (left) Back Pain Intensity (VAS) and (right) Disability Index (ODI) depending on the compression site.

The most common MSU grade among patients (Figure 5) was 2-AB (34.3%), indicating a size 2 hernia that extends both centrally (A) and laterally (B). Older patients exhibited higher MSU grades (p = 0.002), as shown in the quantile plot (Figure 5).

VAS and ODI scores correlated positively with the MSU grade and severity of herniation (ranging from mildest 1-A to most pronounced 3-AB). The quantile plots illustrated a clear positive correlation between these variables (Figure 6), with significant findings for both VAS (p = 0.006) and ODI (p = 0.001)

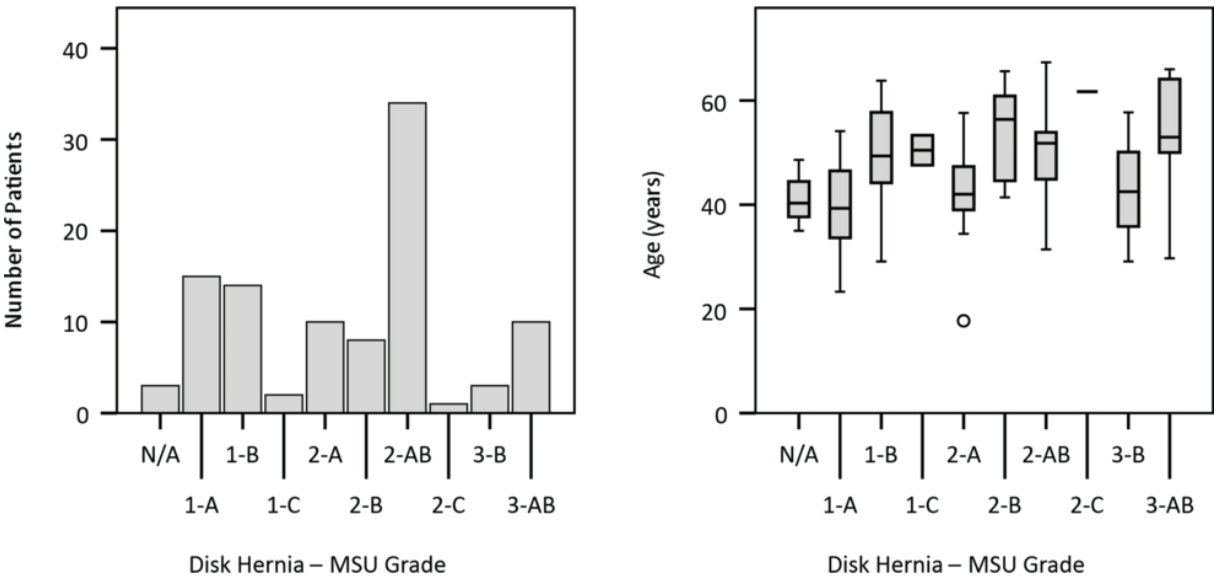

Figure 5. (left) Frequency of different MSU grades in the examined group of patients and (right) dependence of age on MSU grade.

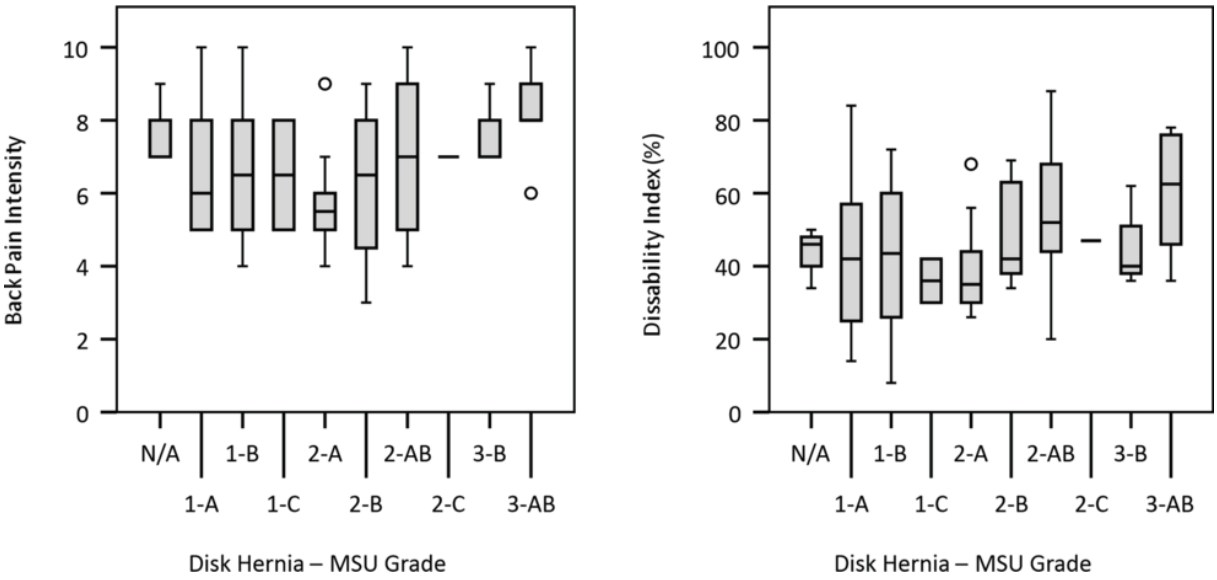

Figure 6. (left) Back Pain Intensity (VAS) and (right) Disability Index (ODI) depending on MSU grade of disc herniation.

DISCUSSION

Lumbar pain is among the most prevalent musculoskeletal disorders encountered in clinical practice, affecting an estimated 25% to 60% of individuals, making it a leading cause of disability and work inability in those under 50. Nearly 80% of people globally experience this condition at least once in their lifetime, with intervertebral disc changes, particularly herniation, being the most common source of lower back pain (15, 16). Our study aimed to investigate the relationship between MRI findings of intervertebral disc herniation in the lumbar spine and the clinical symptoms of patients, assessed using the ODI index and VAS score. Pain is a highly subjective experience that can vary significantly among patients, regardless of MRI results. Various factors can influence the perception of pain in individuals with lumboschialgia. Herniated intervertebral discs are frequently implicated in lumbar pain, with the L4-5 level showing the highest incidence of degenerative changes (47%), followed by L5-S1 (39%), and only 3% of patients lacking disc herniation. These findings align with previous studies (17, 18, 19). Bajpai et al. reported that

36% of patients had L4/L5 intervertebral discs involved in herniation, while only 3% were affected at the L1/L2 level (18). These figures are consistent with Modic et al.'s findings of 43% at L4/L5, echoing results from Garrido (20, 21). Protrusion was the most common type of herniation, observed in 73% of patients, while arch tension and extrusion were less frequent. Our study demonstrated a significant correlation between the severity of disc herniation (classification) and the intensity of spinal pain ($p = 0.010$), as well as the disability index ($p = 0.003$). Patients with extrusion reported the highest pain levels (mean VAS = 8; ODI = 50%), while those with arch tension reported the lowest (mean VAS = 6; ODI = 32%). These findings differ from those of Corniola et al. and Bajpai et al. (18, 22). El-Hady et al. observed protrusion in 48% of examined discs, with extrusion and sequestration occurring in 6.5% of cases, and only 13% displaying normal morphology (23). In our study, we evaluated functional disability using the ODI index, finding the highest scores among patients with extrusion (ODI = 50%) and the lowest among those with arch tension (ODI = 32%). The ODI questionnaire has been shown to be both reproducible and valid for assessing disability in lumboschialgia patients (24, 25). Dunsmuir found no significant correlation between disc prolapse size or location and patient symptoms, arguing that patient symptoms should guide therapy choices (26). El-Hady emphasized that clinicians should not rely solely on MRI findings for diagnosing lumboschialgia, noting the multifactorial nature of lower back pain and a lack of correlation between MRI findings and pain intensity, contrary to our results. While we found a relationship between the ODI index and MRI findings, El-Hady suggested the ODI primarily serves to enhance patient confidence and minimize unnecessary tests (23). We concur with Beattie et al. that disc extrusion is closely associated with symptoms, noted in 13% of our extrusion group (27).

Our results are somewhat inconsistent with existing literature. Some studies indicate that ODI scores are not significantly influenced by the level of spinal changes or the degree of stenosis. Conversely, Sigmundsson's studies found a correlation between increased MRI intervertebral changes and elevated ODI scores, suggesting potential utility in diagnosing lumbar spinal stenosis (28, 29, 30). In our cohort, 48% of patients exhibited nerve compression, more frequently on the left than the right, with 14% experiencing bilateral compression and another 14% having dural sac compression. Patients with nerve compression reported significantly greater back pain intensity ($p = 0.006$) and a higher disability index ($p = 0.001$) compared to those without. No significant differences in pain intensity or disability were observed based on the location of foraminal stenosis ($p = 0.957$; $p = 0.358$). These findings align with Bajpai et al., who noted radiculopathy in 54% of patients, distributed evenly between sides, and six with bilateral radiculopathy (18). Vroomen and colleagues reported a higher rate of nerve compression at 67% (31). Hirsch et al. found a strong association between neurological symptoms and disc herniation, with 86% of patients testing positive for the Lesegue sign (32).

Utilizing the MSU classification for herniated discs, we analyzed both the size and location of hernias. The predominant MSU grade among patients was 2-AB (34.3%), indicating a size 2 hernia extending both centrally (A) and laterally (B). We identified a correlation between the MSU grade of disc herniation and patient age ($p = 0.002$), consistent with findings from Ma et al. and Howard et al. (33, 34). Our results demonstrated that VAS and ODI scores correlate with the ordinal variable linking MSU grade and herniation severity (from mildest 1-A to most severe 3-AB). A positive correlation was found between VAS ($p = 0.006$) and ODI scores ($p = 0.001$).

Hosseini et al. sought to evaluate MSU classifications for better patient selection for ozone therapy, noting older patients exhibited higher MSU grades, which aligns with our findings. The mean initial VAS score across all patients was 7.5 ± 0.8, and the average initial ODI score was 48% ± 1%.

While all groups showed improvement post-therapy, statistically significant differences were noted in the magnitude of improvement. Group 2-AB demonstrated the least pain reduction and improvement in ODI scores, possibly due to the larger size of hernias in that cohort (35). Mysliwiec et al. found that one year post-surgery, 71 of 75 patients in MSU groups 2-A and 2-B reported excellent outcomes, while only 3 of 6 patients in group 2-C did (12).

Janardhan et al. aimed to correlate MRI abnormalities with clinical characteristics of lumbar prolapse, finding that centrolateral bulging or extrusion with significant foraminal damage closely aligned with clinical signs and symptoms, whereas central bulging and disc arc tension showed poor correlation. They concluded that foraminal damage plays a crucial role in determining clinical outcomes, while the type of herniation (bulging, extrusion, or protrusion) has a weaker association (36).

Our study has limitations. We did not account for other important independent variables that could influence our results, such as weight, height, BMI, education level, smoking habits, and lumbar spine strength and flexibility. We also did not assess patient physical activity levels, despite literature indicating a strong connection between sedentary lifestyles and back pain, with moderate physical activity linked to reduced pain (37, 38). Additionally, we did not examine whether sensory deficits correlated with lumbar disc prolapse and nerve root compression. Addressing these factors could enhance our understanding of the results.

CONCLUSION

VAS and ODI scores correlate with an ordinal variable that connects MSU grade with the severity of herniation.

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Declaration of patient consent: The authors confirm that they have obtained all necessary patient consent forms. Each patient has provided written consent to participate in this study.

Authors' Contributions: SHV, LD and LM contributed to the study design, data collection, and interpretation. SHV, LD, LM, IH, ASB, ASH and ZA were involved in writing, analyzing, and giving final approval of the manuscript. Each author participated in drafting the article and in the revision process. All authors approved the final version for publication and agree to take responsibility for all aspects of the work, ensuring that any questions regarding the accuracy or integrity of any part are properly addressed and resolved.

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Conflict of interest: The authors have nothing to disclose.

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REVIEW ARTICLE

Acetylsalicylic Acid (Aspirin): Past, Present, and Future

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Abstract

Acetylsalicylic acid is the most common antithrombotic drug, which started its pharmacological journey as a non-steroidal, anti-inflammatory drug. When used as a low-dose drug (of 75-100mg) once per day, it irreversibly inhibits prostaglandin H synthase, commonly termed cyclooxygenase 1 or COX-1 enzyme, which is acetylsalicylic acid's molecular drug target in human platelets. This mechanism of action ensures that the inhibition of the pro-aggregatory prostanoid - thromboxane A_2 synthesis is achieved permanently in platelets throughout their lifespan, which is responsible for acetylsalicylic acid's antithrombotic effect. In this literature review, we provide an overview of acetylsalicylic acid's development through history, the current understanding of the molecular mechanism of its action, as well as the resulting side effects impacting different tissues due to its control of the arachidonic acid metabolism and prostanoid synthesis in them. In an effort to begin a dialogue regarding the evidence in favor of unresponsiveness to acetylsalicylic acid's therapeutic effect in specific patients, we describe already identified molecular mechanisms of resistance to acetylsalicylic acid and list the existing biomarkers which are able to quantifiably measure the achieved degree of acetylsalicylic acid's clinical efficacy. Furthermore, we look to the future by encouraging a personalized approach to acetylsalicylic acid's use in order to maximize its therapeutic effect and its safety. Moreover, we mention the ongoing clinical trials evaluating the role of acetylsalicylic acid in prevention of colorectal and other cancers.

Keywords: Acetylsalicylic Acid, Aspirin, Cyclooxygenase Inhibitors, Prostaglandin Endoperoxide Synthase Inhibitors, Platelet Aggregation Inhibitors, Antithrombotic Agents

Introduction

Many pharmacological agents used in everyday clinical practice possess rich history, which is, firstly, associated with a plant or an animal source of their starting chemical compound and initial empirical use of it in patients. If deemed important for the treatment of patients, examinations of their molecular mechanisms and identification of their specific, molecular drug targets have taken place. Afterwards, pharmacokinetic/pharmacodynamic (PK/PD) studies would have been designed, performed and evaluated before their widespread clinical use. For many older pharmacological agents, different investigations during their drug development process have not followed this particular order, with PK/PD studies and large clinical trials being carried out without prior knowledge of drugs' molecular mechanisms, or their specific molecular drug targets. One such pharmacological agent is acetylsalicylic acid, which has become a household name through a widespread prescribing of its specific brand - Aspirin or aspirin - worldwide.

However, in 2024, acetylsalicylic acid still captures the imagination of clinicians and molecular pharmacologists alike. This interest is, in part, historical, for the purpose of teaching the next generations of medical doctors, pharmacologists and pharmacists about a timeline of the drug discovery and development process related to it. The current interest in acetylsalicylic acid is, however, largely clinical, as efforts are made towards identification of biomarkers for the quantifiable confirmation of the expected PD effect and more personalized prescribing of the low-dose acetylsalicylic acid in patients. In addition, as clinical trials evaluating efficacy of acetylsalicylic acid in the prevention of different cancers are coming to an end, acetylsalicylic acid could be entering into repurposed drug arena, all for the benefit of different patient populations.

History of acetylsalicylic acid development

The history of acetylsalicylic acid appears to have begun with the use of willow tree (of the genus *Salix*, family *Salicaceae*) for healing purposes in Mesopotamia (currently, parts of Iraq, Kuwait and Syria) several thousands of years ago, which was recorded on clay tablets in cuneiform writing (1). It also appears that a Greek physician and philosopher, the *"Father of Medicine"* - Hippocrates, had recommended the use of willow leaves for analgesia during childbirth and for the treatment of post-partum fever (2). The first, existing, written document in the English language, which describes in detail the preparation and the administration of the powdered bark of a white willow to patients suffering from *"agues and intermitting disorders"*, which were usually associated with malarial symptoms of fever and shivering, was a letter written by Reverend Edward Stone to the then president of the Royal Society in 1763 (3,4). In it, Reverend Stone stated the five year-long successful use of the described medicine towards the reduction of fever in 50 patients, *"except in a few autumual and quartan agues, with which the patients had been long and severely afflicted"*.

In the 19th century, the active ingredient of a willow bark, salicin, was extracted by several scientists (Figure 1). In addition, several scientists generated salicylic acid, either from salicin or by *de novo* chemical synthesis (Figure 1). Then, the first clinical trials using sodium salicylate or salicin took place in Germany, United Kingdom and France (5-8). In the United Kingdom, salicin was trialed for the treatment of *"acute articular rheumatism"*, which was accompanied with fever, by Dr Thomas John MacLagan, MD, in a Scottish town - Dundee, from 1874 until 1876 (7,9). Dr MacLagan's rationale for using salicin for the treatment of an acute rheumatic fever was that, if an extract of a bark of another tree, that of the cinchona tree, which is quinine, was successful in the treatment of a malarial fever, the same successful treatment could be achieved with salicin, as it is isolated from a bark of a tree found in an area where rheumatism is a prevalent disease. Reverend Stone and Dr MacLagan shared an opinion which was that the nature provides the remedies close to the areas of the disease. However, although both acute rheumatism and willow trees are predominating in damp climate, it was incorrectly assumed by both of them that cinchona tree originally grew in a malarious area, such as India, instead of in a non-malarious area, such as the Andes Mountains in South America. Dr MacLagan reported that the clinical effect of salicin, i.e., reduction in fever, was noticed 48 hours after the first administration of it, which led to his conclusion that the effect was specific to salicin (7,9).

After the publication of the positive results of the clinical trials performed by Stricker, Reiss, MacLagan and See, and development of the method for generation of synthetic salicylic acid on an industrial scale, the therapeutic application of it to achieve antipyretic, anti-rheumatic/anti-inflammatory and analgesic effects, to populations in many different countries, has started (10). During this time of worldwide administration of salicylic acid,

or its sodium salt - sodium salicylate, statements about its unpleasant taste and irritation to the gastrointestinal tract, accompanied with nausea and vomiting, have begun to emerge. In addition, patients who were prescribed high doses of either salicylic acid, or sodium salicylate, for the treatment of chronic rheumatic pain, experienced another unpleasant side effect - tinnitus (10). For these reasons, scientists started to consider developing a new compound, one which would retain the therapeutic effects of salicylic acid, but one which would be more palatable and devoid of the harmful side effects of the precursor compound. This task was given to a scientist employed at Bayer pharmaceutical company, Felix Hoffmann, in 1897. He successfully synthesized acetylated salicylic acid - acetylsalicylic acid, in chemically stable and pure form, on the 10th of August 1897, a date which is considered a birthday of acetylsalicylic acid. Bayer's trade name for acetylsalicylic acid - Aspirin, was registered in Berlin on the 1st of February 1899 and, soon after that date, widespread marketing and use of acetylsalicylic acid as Aspirin has begun (Figure 1) (10).

Mechanism of action of acetylsalicylic acid

In 1971, three seminal studies reported inhibition of prostaglandin production by acetylsalicylic acid and other non-steroidal, anti-inflammatory drugs (NSAIDs), such as indomethacin, including in human platelets,

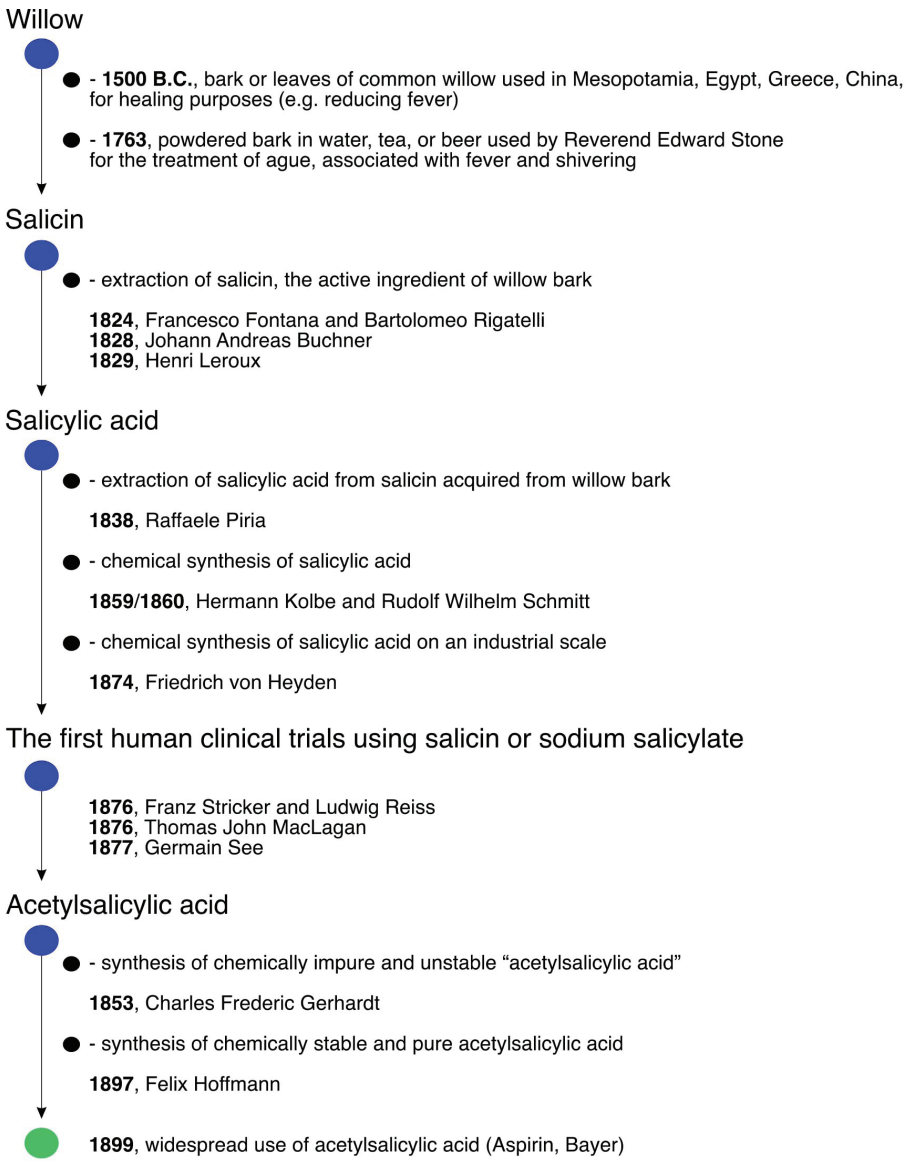


Figure 1. Historical development of acetylsalicylic acid

Development of acetylsalicylic acid is depicted as a list of key events which took place through history - from the use of bark or leaves of the common willow tree until the registration and widespread prescribing and use of acetylsalicylic acid as Aspirin by the pharmaceutical company - Bayer.

thereby describing, for the first time, the mechanism of action of acetylsalicylic acid (11-13). In addition, in 1975, another prostanoid - thromboxane (TX) A_2 (TXA_2), was identified as the major biologically active compound, which was responsible for induction of platelet aggregation. TXA_2 was shown to be derived from unstable prostaglandin endoperoxides, PGG_2 and PGH_2, respectively, generated from a fatty acid - arachidonic acid, by the enzyme prostaglandin H synthase (PGHS) (14). These studies established a mechanistic connection between the inhibition of the PGHS enzyme and inhibition of platelet aggregation by acetylsalicylic acid. In addition, it was demonstrated that acetylsalicylic acid acetylated the PGHS enzyme expressed in platelets, thus causing the inhibition of its activity (15). Furthermore, it was shown that arachidonic acid, the substrate for the PGHS enzyme, inhibited the enzyme's acetylation by acetylsalicylic acid, suggesting that acetylsalicylic acid acts at the active site of the PGHS enzyme (15). The enzyme PGHS, also known as prostaglandin endoperoxide synthase (PTGS), is a bifunctional enzyme, which incorporates two enzymes: cyclooxygenase and peroxidase. It is, at present, usually termed cyclooxygenase, or COX enzyme, even though this term leaves out the involvement of peroxidase activity in the enzyme's overall function (16). In summary, for acetylsalicylic acid, the mechanism of action was demonstrated approximately 85 years after the date of its marketing.

In humans, two cyclooxygenases, COX-1 and COX-2, are expressed (17). Although human COX-1 and COX-2 proteins share 61% identity in their amino acid sequences, there are specific differences between them, as follows: 1) the COX-1 and COX-2 proteins are encoded by two separate genes, and 2) the expression pattern of the COX-1 and COX-2 proteins, in the human organism, is different: while the COX-1 protein is continuously expressed in most tissues and cells, in a manner of a housekeeping protein, the COX-2 protein expression is largely considered to be inducible during development, or only after the release of pro-inflammatory cytokines, hormones, growth factors, etc. When the expression of the COX-2 gene/protein becomes induced, increased synthesis of the pro-inflammatory prostanoids occurs (18). The COX-1 protein/enzyme can become inducible protein/enzyme, e.g., upon increased release of endogenous bradykinin and, *vice versa*, the COX-2 protein/enzyme is a continuously expressed protein/enzyme, e.g., in the kidney (18). When acetylsalicylic acid is administered, it has the ability to acetylate both human COX enzymes. However, this occurs in a dose-dependent manner. In addition, its action is unique among NSAIDs as it covalently modifies the amino acid residues Ser-529 and Ser-516, localized within the active site of the human COX-1 and COX-2 proteins, respectively, causing an irreversible inhibition of the cyclooxygenase activities associated with both COXs (19).

The products of the COX-1 and COX-2 enzymes - prostanoids (prostaglandins and thromboxanes), mediate many physiological and pathological processes. Because of the fact that acetylsalicylic acid, as well as other NSAIDs, inhibit their generation and, consequently, limit their physiological function, knowing the expression pattern of the COX-1 and COX-2 proteins, in different organs and tissues of the human body, is important for our understanding of side effects which may develop when they are prescribed for the treatment of pathological states involving pain, fever and/or inflammation, especially for a prolonged period of time (Figure 2). Evidence suggests that both the COX-1 and COX-2 proteins are expressed in many human tissues albeit to varying degrees (20-21). Here, we list prostanoids which affect platelets, blood vessel wall, gastrointestinal tract, and kidney only, and describe effects of their reduced production, which develops upon the administration of acetylsalicylic acid, as they appear to have a significant impact in a wide population of patients.

Prostanoids in the platelets

In platelets, the COX-1 enzyme is the main enzyme for the production of TXA_2, the key prostanoid which induces platelet activa-

tion and aggregation and vascular smooth muscle cell contraction. Therefore, inhibition of the COX-1 enzyme activity by acetylsalicylic acid inhibits the production of TXA_2 and the TXA_2-induced platelet activation and aggregation and vascular smooth muscle cell contraction. In addition, it was demonstrated that platelets also express the COX-2 protein, albeit at low levels, which is capable of being induced to produce significant TXA_2 levels, especially in patients undergoing coronary artery bypass grafting (16) (22-24).

Prostanoids in the vascular system

In blood vessels, both endothelial cells and smooth muscle cells express the COX-1 protein. However, studies suggest that the COX-2 protein is expressed by endothelial cells only. Overall, it has been suggested that, under normal, healthy conditions, the vascular tissue predominantly expresses the COX-1 protein. The endothelial cells generate prostaglandin I_2 (PGI_2), or prostacyclin, which has the opposite characteristics to those of TXA_2: it inhibits the vascular smooth muscle cell contraction and prevents platelet aggregation. In addition, prostaglandin E_2 (PGE_2) contributes to the vasodilatation of blood vessels. Therefore, the administration of acetylsalicylic acid inhibits the release of vasodilatory prostanoids, i.e., PGI_2=prostacyclin and PGE_2, as well as diminishes anti-aggregation effect of PGI_2=prostacyclin on platelets (16).

Prostanoids in the gastrointestinal tract

In the gastrointestinal tract, studies suggest that both the COX-1 and COX-2 enzyme activities lead to the generation of PGE_2, especially in gastric mucosa, where PGE_2 plays a cytoprotective role against a mucosal damage by gastric acid. In addition, the release of appropriate level of PGI_2=prostacyclin maintains optimal blood flow within the gastrointestinal tract, which provides the energy for enabling stability of the gastrointestinal mucosa. Therefore, the most prominent side effect of acetylsalicylic acid, or other NSAIDS, especially in patients who have been prescribed a longer-term pharmacological therapy with these drugs, is the development of gastrointestinal injury, which is revealed by symptoms such as dyspepsia, abdominal pain, nausea, vomiting, mucosal lesions, peptic ulcers and/or gastrointestinal bleeding (16).

Prostanoids in the kidney

In the kidney, both the COX-1 and COX-2 proteins are expressed continuously under physiological conditions, i.e., without the induction by the pro-inflammatory stimuli. With regard to the expression of the COX-2 protein in the kidney in particular, it was suggested that the COX-2 expression is continuously induced by the shear stress of normal blood flow on endothelial cells of the renal arteries, rather than being constitutively expressed (16). Prostaglandins, PGE_2 and PGI_2=prostacyclin, which are generated through the activity of the COX-1 and COX-2 enzymes in the kidney, respectively, act as vasodilators, which increase renal blood flow. They also regulate sodium reabsorption, blood volume and, as a consequence, maintain blood pressure homeostasis (16,21).

In summary, different prostanoids, which act through their specific, G protein-coupled receptors specifically affect different cells and tissues. As the human body is not compartmentalized, when acetylsalicylic acid is administered, depending on its dose, all of the above cells and tissues could be affected by its mechanism of action simultaneously. Following prolonged administration of it, the resulting reduction in specific, vital prostanoids could lead to side effects or toxicity.

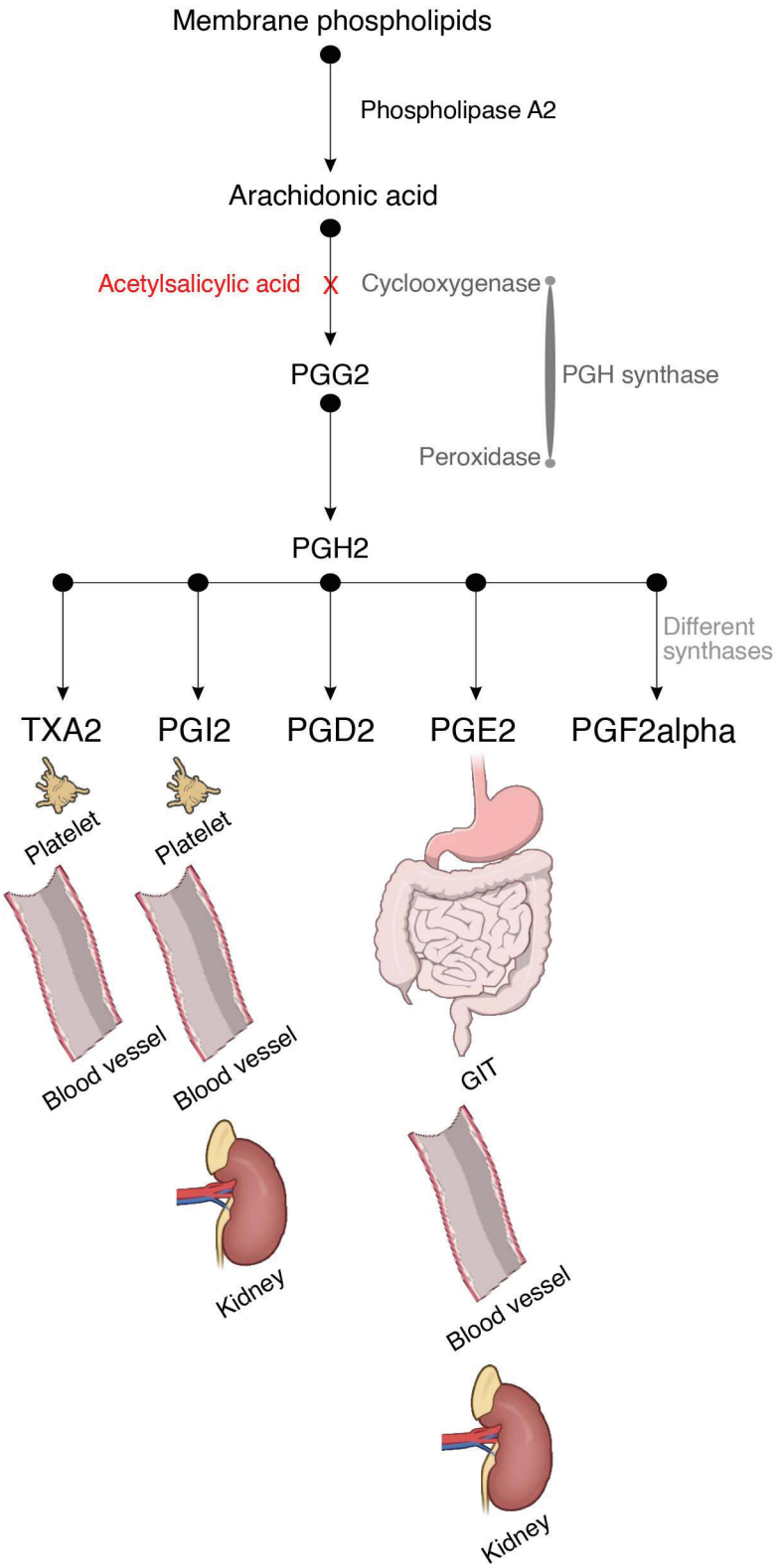
Current therapeutic use of acetylsalicylic acid as an antithrombotic drug

In 2024, acetylsalicylic acid is mainly prescribed as an antithrombotic drug. As platelets are the ultimate functional target of acetylsalicylic acid for the prevention of thrombosis, acetylsalicylic acid is often

referred to as an antiplatelet drug. Clinical trials, which started in the 1980s, were crucial in the evidence-based choice of the currently prescribed low-dose acetylsalicylic acid once per day (QD) for the prevention of cardiovascular disease (CVD) events (25-28). Doses of acetylsalicylic acid from 30-160mg/day were trialed and demonstrated effectiveness for the following CVD events: hypertension, stable angina, unstable angina, acute myocardial infarction, transient ischemic attack (TIA) and ischemic stroke,

Figure 2. Mechanism of action of acetylsalicylic acid

Acetylsalicylic acid inhibits the PGH synthase, currently termed cyclooxygenase or COX enzyme, which is its molecular drug target. When acetylsalicylic acid irreversibly acetylates the PGH synthase, the synthesis of physiologically active prostanoids, such as TXA2, PGI2, PGD2, PGE2 and PGF2alpha, is inhibited. This has implications for physiological function of different cells and tissues [e.g. platelets, blood vessels, kidney and gastrointestinal tract (GIT)]. The figure was created using illustrations from the National Institute of Allergy and Infectious Diseases, the National Institute of Health (NIAID NIH) BIOART Source: https://bioart.niaid.nih.gov/
X = inhibition; PGG2 = prostaglandin G2; PGH2 = prostaglandin H2; PGH synthase = prostaglandin H synthase; TXA2 = thromboxane A2; PGI2 = prostaglandin I2 or prostacyclin; PGD2 = prostaglandin D2; PGE2 = prostaglandin E2; PGF2alpha = prostaglandin F2α; GIT = gastrointestinal tract.



severe carotid artery stenosis, acute ischemic stroke (29).

A chosen dose of acetylsalicylic acid for the prevention of thrombosis needed to be sufficient to completely inhibit the COX-1 enzyme activity in platelets, in order to inhibit the COX-1 enzyme-dependent production of pro-aggregatory and anti-vasodilatory prostanoid - TXA_2. At the same time, the chosen dose of acetylsalicylic acid was required to spare the production of anti-aggregatory and pro-vasodilatory prostanoid - PGI_2=prostacyclin, which is produced by vascular endothelial cells, through both the COX-1 and COX-2 enzyme activities, as well as by the kidney, through the physiological activity of the continuously expressed COX-2 enzyme. A chosen dosing regimen of low-dose acetylsalicylic acid for an antithrombotic effect achieves almost complete, irreversible inhibition of the COX-1 enzyme expressed in platelets throughout their lifespan, which is approximately 9 days, as well as inhibition of the COX-1 enzyme in newly formed platelets, which are replaced every 24 hours (29). Following cessation of acetylsalicylic acid therapy, the recovery of platelets' physiological, baseline COX-1 enzyme activity and the synthesis of the pro-aggregatory TXA_2 levels, measured indirectly, through detection of the stable metabolite of TXA_2 in serum - TXB_2, occurs over a period of several days, which is consistent with platelets' turnover and the synthesis of new COX-1 protein/enzyme in them (27,30).

A summary of the latest clinical practice guidelines detailing the use of low-dose acetylsalicylic acid for primary and secondary prevention of atherosclerotic CVD events is presented:

1. The guideline by the U.S. Preventive Services Task Force (USPSTF), on the use of acetylsalicylic acid for primary prevention of CVD events, states the following: a) For a population aged 40-59 years of age, an individualized approach for low-dose acetylsalicylic acid (81mg QD) can be considered if a subject has 10% or higher 10-year CVD risk. The major concern for the use of acetylsalicylic acid in this population is the risk of bleeding, i.e., gastrointestinal bleeding; b) For a population having ≥60 years of age, due to a high risk of hemorrhage in the gastrointestinal tract and intracranial bleeding, the USPSTF does not recommend the use of acetylsalicylic acid for primary prevention of CVD events. In addition, the latest guidelines published by the USPSTF, on the use of acetylsalicylic acid for secondary prevention of CVD events, recommends the use of acetylsalicylic acid (75-100mg QD) unless contraindicated, i.e., having a high risk of hemorrhage. The individuals who belong to this group of patients usually have a diagnosis of previous CVD events, such as stroke, or myocardial infarction (31).

2. The guidelines which were published by the European Society of Cardiology (ESC) do not recommend the use of acetylsalicylic acid for primary prevention of atherosclerotic cardiovascular disease (ASCVD) due to an increased risk of hemorrhage (32).

3. The American College of Cardiology (ACC) stated that a low-dose acetylsalicylic acid (75-100mg QD) should be considered for primary prevention of ASCVD in a population aged 40-70 years, who are at higher ASCVD risk, but do not have a risk of hemorrhage. Also, the ACC does not recommend the administration of low-dose acetylsalicylic acid (75-100mg QD) for primary prevention of ASCVD in a population having >70 years of age (33).

4. The American Heart Association (AHA) does not recommend the use of low-dose acetylsalicylic acid (75-100mg QD) for primary prevention of ASCVD among populations of any age who are at an increased risk of hemorrhage (33).

5. The American Diabetes Association (ADA) recommends the use of low-dose acetylsalicylic acid (75-162mg QD) in a population having >50 years of age with diabetes mellitus and increased ASCVD risk, but without a history of vascular diseases (34, 35). The antithrombotic dose of acetylsalicylic acid does not affect the physiological, COX-2 enzyme-

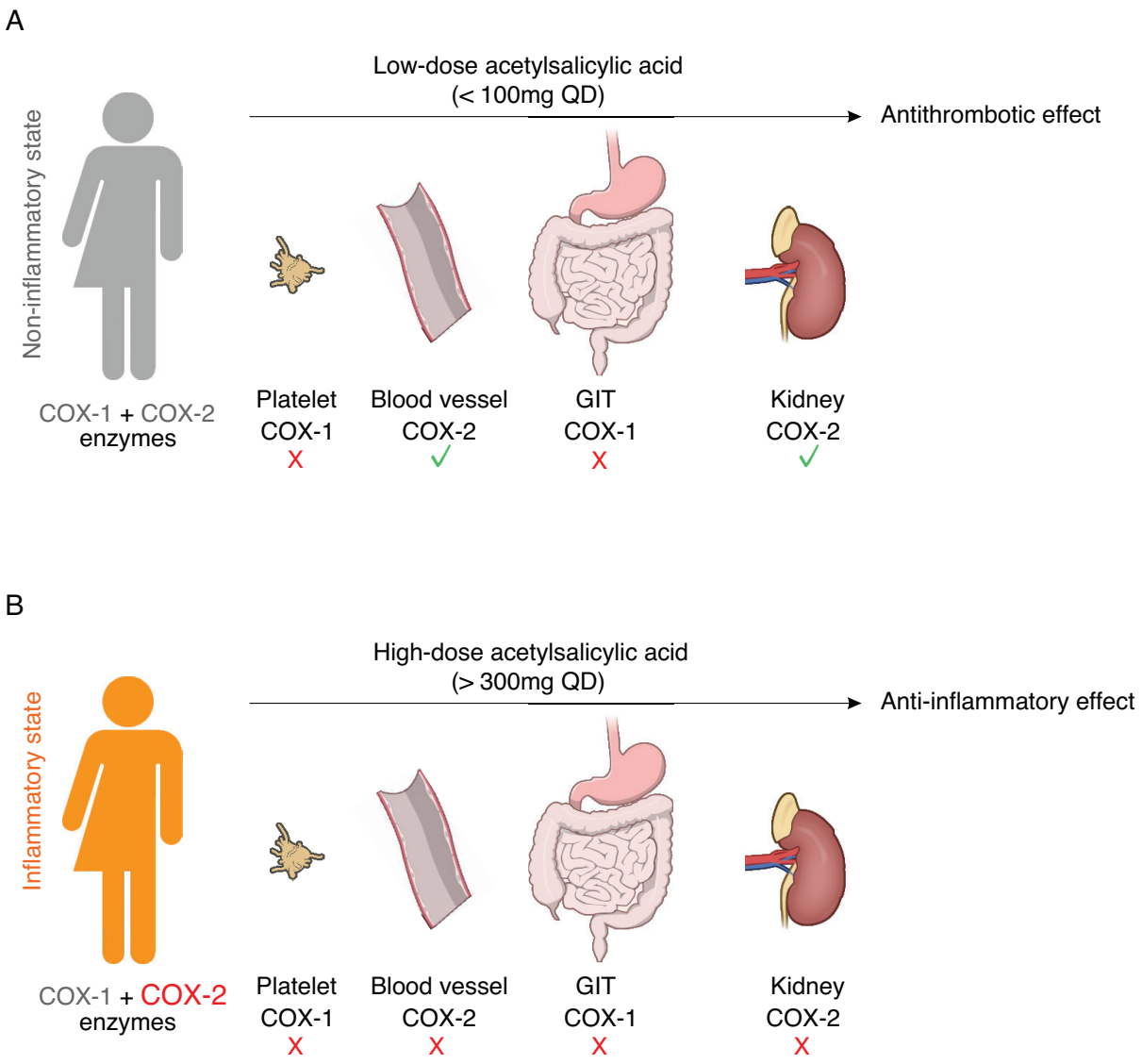


Figure 3. Pharmacological effects and side effects of low-dose versus high-dose acetylsalicylic acid

Current understanding of the pharmacological effects and cell- and tissue-specific side effects of low-dose versus high-dose acetylsalicylic acid, in individuals of both biological sexes, is presented.
A. A low-dose acetylsalicylic acid (of ≤ 100mg) is prescribed in order to achieve an antithrombotic effect. Patients who are prescribed a low-dose acetylsalicylic acid are in non-inflammatory state, which is characterised by physiological, constitutive expression of both the COX-1 and COX-2 enzymes. A low-dose acetylsalicylic acid inhibits the COX-1 enzyme in human platelets, thus inhibiting the synthesis of thromboxane A2 (TXA2), a prostanoid with a key function in platelet activation and aggregation. In addition, the COX-1 enzyme expressed in the gastrointestinal tract (GIT) is inhibited by a low-dose acetylsalicylic acid at least in part, with the resulting decrease in the levels of the prostaglandin - PGE2, causing the most common side effect of acetylsalicylic acid - a GIT upset or injury. Furthermore, as low-dose acetylsalicylic acid does not inhibit the COX-2 enzyme in blood vessels, the synthesis of the physiological levels of the PGI2=prostacyclin is maintained at an optimal level, thus providing optimal blood vessel dilatation and inhibition of platelet aggregation. Moreover, the constitutively expressed COX-2 enzyme in the kidney is also unaffected by low-dose acetylsalicylic acid, which contributes to the optimal vascular homeostasis in patients taking low-dose acetylsalicylic acid.
B. A high-dose acetylsalicylic acid (of >300mg) is prescribed in order to achieve an anti-inflammatory effect for the treatment of e.g. rheumatoid arthritis or osteoarthritis. Patients who are prescribed a high-dose acetylsalicylic acid or, either a different non-steroidal, anti-inflammatory drug (NSAID), or a COX-2 enzyme-specific inhibitor, are in an inflammatory state, which is characterised by pathological, induced expression of the COX-2 enzyme. A high-dose acetylsalicylic acid is required to inhibit the increasing levels of the COX-2 enzyme, which is 170-fold less sensitive to the inhibition by acetylsalicylic acid than COX-1 enzyme, and the resulting production of the pro-inflammatory prostanoids. As a consequence, the synthesis of physiologically active prostanoids is halted too. E.g. loss of the PGI2=prostacyclin synthesis leads to contraction of the vascular smooth muscle cells, platelet aggregation and kidney dysfunction, which clinically manifest as, e.g., pro-thrombotic and hypertensive states.
The figure was created using illustrations from the National Institute of Allergy and Infectious Diseases, the National Institute of Health (NIAID NIH) BIOART Source: https://bioart.niaid.nih.gov/

X = inhibition; ✓= intact activity; COX-1 (in black or gray color) = physiological, constitutive expression of the COX-1 enzyme; COX-2 (in black or gray color) = physiological, constitutive expression of the COX-2 enzyme; COX-2 (in red color) = induced expression of the COX-2 enzyme during an inflammatory state; GIT = gastrointestinal tract; QD = once per day.

dependent synthesis of PGI_2=prostacyclin, which takes place in tissues other than platelets, especially in the kidney. However, although the use of a higher dose of acetylsalicylic acid for the treatment of pain, fever and/or inflammation has largely been abandoned with the advent of new NSAIDs and COX-2 enzyme-specific inhibitors, it is important to remember that higher doses of acetylsalicylic acid (> 300mg) are capable of inhibiting both the COX-1 and COX-2 enzymes and, consequently, inhibit the systemic production of vasodilatory PGI_2=prostacyclin, as well as other prostanoids (27). As a result, higher doses of acetylsalicylic acid may give rise to gradual destruction of gastric mucosa barrier function, with formation of peptic ulcers, sometimes accompanied with gastrointestinal bleeding, as well as platelet aggregation, contraction of blood vessels, and kidney damage, resulting in dysregulated sodium and water homeostasis (Figure 3).

Future perspectives

The results of clinical trials using acetylsalicylic acid demonstrated that the degree of its effectiveness in the prevention of fatal and non-fatal vascular events depended on the clinical indication for which it was prescribed for, ranging from, e.g., approximately 15-50% (36). Therefore, a significant number of individuals are not protected with the drug, especially at the beginning of the treatment with it (37). This phenomenon was termed acetylsalicylic acid or aspirin resistance (38). It was demonstrated that it could develop as a result of several mechanisms, as follows: 1) changes in the expected PK characteristics of a patient; 2) presence of higher than expected platelet turnover and the resulting, significantly increased concentrations of pro-aggregatory TXA_2 in them, e.g., in patients with essential thrombocythemia; 3) induction of the COX-2 protein/enzyme expression in platelets, with consequent generation of substantial concentrations of TXA_2, e.g., in patients post coronary artery bypass grafting; 4) existence of genetic polymorphisms within genes encoding the COX enzymes expressed in platelets, or other type of, as yet undefined, protein alterations, rendering them resistant to interaction with acetylsalicylic acid; 5) overexpression of an efflux transporter protein, the multidrug resistance protein 4 (MRP4) in platelets, which was demonstrated to remove acetylsalicylic acid from cells, thus, reducing its effectiveness (23,24,39-44). In addition, studies showed that biological sex characteristics may play a role in different PK/PD effect of acetylsalicylic acid. Here, we mention the results of the placebo-controlled study by Ridker PM and colleagues, as it was a study of a significant size (about 40 thousand individuals were involved) and duration of follow up (about 10 years) (45). It was demonstrated that in individuals of female biological sex, who were ≥45 years of age and who took 100mg acetylsalicylic acid every second day for primary prevention of cardiovascular events for a minimum of 8 years, there was a statistically significant reduction in the risk of stroke. In particular, there was a reduction in ischemic stroke (while there was a non-significant increase in the risk of hemorrhagic stroke). In the treated females, there was no decrease in the risk of myocardial infarction. However, in the subgroup of females who were ≥65 years of age, the results showed a significant reduction in ischemic stroke and a reduction in myocardial infarction (45). In 2005, when the results of this study were published, the data for males indicated the opposite effect of acetylsalicylic acid, i.e., low-dose acetylsalicylic acid therapy was associated with a non-significant increase in the risk of stroke and a decrease in the risk of myocardial infarction (45).

The existing biomarkers of acetylsalicylic acid's overall pharmacological effect include serum TXB_2 and urinary 11-dehydro-thromboxane B_2 (11-dehydro-TXB_2), both physiologically inactive metabolites of physiologically active prostanoid - TXA_2. It was previously concluded that increased concentrations of urinary 11-dehydro-TXB_2 served as an indicator of an increased risk of cardiovascular events in patients to whom acetylsalicylic acid therapy was prescribed (46,47). Although the 11-dehydro-TXB_2 concentration measured in

urine does not appear to be a specific biomarker of an antithrombotic effect of acetylsalicylic acid, because it was demonstrated to be influenced by additional factors (e.g., increasing age, female sex, smoking, history of peripheral artery disease, oral hypoglycemic therapy, etc.), it does seem to serve as an indicator of the risk of stroke, myocardial infarction, and cardiovascular death in patients at risk of atherothrombotic events (47). Despite its disadvantages, urinary 11-dehydro-TXB_2 concentration will be measured as a biomarker of efficacy of acetylsalicylic acid in a clinical trial investigating the ability of acetylsalicylic acid to prevent the development of different cancers (48).

Since 1988, different studies have reported the existence of an association between regular use of acetylsalicylic acid and a reduced risk of colorectal cancer development (49). One of the key cellular mechanisms, which are responsible for colorectal cancer development and progression, includes activated platelets releasing pro-angiogenic and pro-inflammatory molecular factors, which interact with adjacent cells and drive the transformation of the normal colorectal mucosa to adenoma, carcinoma, and further on - to invasive and metastatic cancer cells, through enhanced COX-2 expression and the resulting synthesis of PGE_2. When acetylsalicylic acid is administered, PGE_2 levels are depleted through the inhibition of both COX enzymes in platelets. This, in turn, leads to increased apoptosis, decreased cellular proliferation and decreased angiogenesis, which are beneficial to cancer prevention (50). In order to establish if acetylsalicylic acid reduces the risk of development of multiple cancer types, a large placebo-controlled clinical trial titled ADD-ASPIRIN Trial was designed and approved in 2014. It will investigate if acetylsalicylic acid, of 100mg, or 300mg, affects colorectal, gastro-esophageal, breast and prostate cancers, with the primary outcome of the trial being disease-free survival, or overall survival, following a standard, primary therapy. The trial's results are expected to be published in 2025 and 2027 (48).

Overall, knowledge of the molecular mechanisms of acetylsalicylic acid's diminished pharmacological effect in specific patients, with the availability of established and emerging biomarkers, which are able to measure it precisely and quantitatively, allow for a design of studies to take place, which would establish a guideline for a personalized approach to acetylsalicylic acid's dose and dosing regimen in different patients, taking biological sex characteristics of patients into account. Considering the fact that the concentration of the main metabolite of TXA_2 synthesis, 11-dehydro-TXB_2, can be measured in an easily obtainable biological fluid - urine, it can be proposed that 11-dehydro-TXB_2 could be measured in patients in whom acetylsalicylic acid's resistance is suspected, unless very rapid effect is necessary, e.g., for the treatment of acute myocardial infarction within the first 24 hours following the onset of symptoms in patients. As it was established that almost complete inhibition of cyclooxygenase, the molecular target of acetylsalicylic acid, is achieved within 1 hour, following a single, 100mg dose of it, a delay in establishing the clinical response to acetylsalicylic acid in a patient appears minimal (30). Therefore, for a personalized approach to pharmacological therapy with acetylsalicylic acid, the existing tools allow fast determination of its initial efficacy, as well as its long-term monitoring. Alternatively, in the future, for patients who are unresponsive to acetylsalicylic acid, treatment with drugs which act at molecular targets downstream of the cyclooxygenases, COX-1 and COX-2, namely thromboxane synthase or thromboxane receptors, could become available for the inhibition of the production of, primarily, TXA_2, for a desired antithrombotic outcome (24,51).

Conclusion

This year marks the 125th anniversary of acetylsalicylic acid's registration and widespread use in different patient populations. Therefore, it is fitting that we are reminded

of the past, present, and future of acetylsalicylic acid this year. The ongoing investigations regarding the molecular mechanisms of resistance to acetylsalicylic acid's pharmacological effect, the clinical utility of the existing biomarkers, which allow measurement of its efficacy, and the clinical trials investigating the potential for re-purposing of acetylsalicylic acid towards prevention of different types of cancers, pave the way for the new era of acetylsalicylic acid's use, the one where no patient would be left behind without acetylsalicylic acid's therapeutic properties.

Authors' Contribution

NK: Investigation, Methodology, Writing - original draft, reviewing & editing.

DB: Investigation, Methodology, Writing - reviewing & editing.

MC: Conceptualization, Investigation, Methodology, Visualization, Writing - original draft, reviewing & editing.

Authors' Contribution: Nejra Kovacevic - Investigation, Methodology, Writing - original draft, reviewing & editing; Dzenan Beciragic - Investigation, Methodology, Writing - reviewing & editing; Mirsada Causevic - Conceptualization, Investigation, Methodology, Visualization, Writing - original draft, reviewing & editing.

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REVIEW ARTICLE

Red Wine and Alcoholic Beverages: Evolution of Our Knowledge Focusing on All-Cause Morbidity and Mortality

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Abstract

Medical professionals have a responsibility to inform the public about contemporary research on alcohol consumption. Earlier health recommendations focused primarily on the link between alcohol and cardiovascular diseases. Over time, these guidelines have expanded to consider the broader impact of alcohol on all-cause morbidity and mortality. Unlike the tobacco industry, which remains profitable but faces strict regulations on marketing and lobbying, the alcohol industry benefits from fewer regulations. This allows alcohol manufacturers to freely promote their products and influence both federal and state policies. Clear emphasis on the importance of ceasing alcohol consumption is crucial, particularly in primary and secondary prevention efforts.

Keywords: cardiovascular diseases, alcoholics, prevention.

INTRODUCTION

Even though the population in general, as well as medical professionals all over the world, have positive associations with red wine, imagining parties, celebrations, good times, and, of course, its health benefits for the cardiovascular system, partially due to resveratrol, the time has come to suppress the conditional reflex (1,2). Medical professionals must advise the population on contemporary research related to alcoholic beverages. That understanding has evolved (3, 4). Some time ago, on 17 September 2008, the author of this text gave an interview to "Politika", the oldest daily newspaper in the Balkans, about the global epidemic of cardiovascular diseases, with a particular focus on Serbia. The interview, prominently featured on the front page, recommended that consuming 150 ml of red wine three to seven times a week could potentially reduce the incidence of cardiovascular diseases. This suggestion was made with the caveat that such consumption posed only a small health risk, as outlined in the recommendations. In the same interview, the author also recommended including fish, fruits, vegetables, nuts, and dark chocolate in one's diet, all of which, in combination with red wine, were calculated to lower the risk of

cardiovascular diseases by up to 75%. Soon after, an anonymous reader commented, "It was inappropriate for Professor Ostojic to promote alcohol consumption at all" (the original interview can be accessed upon request from Miodrag Ostojic's file). This thoughtful comment proved to be prescient, as it accurately anticipated future developments.

OVERVIEW OF CLINICAL PRACTICE GUIDELINES

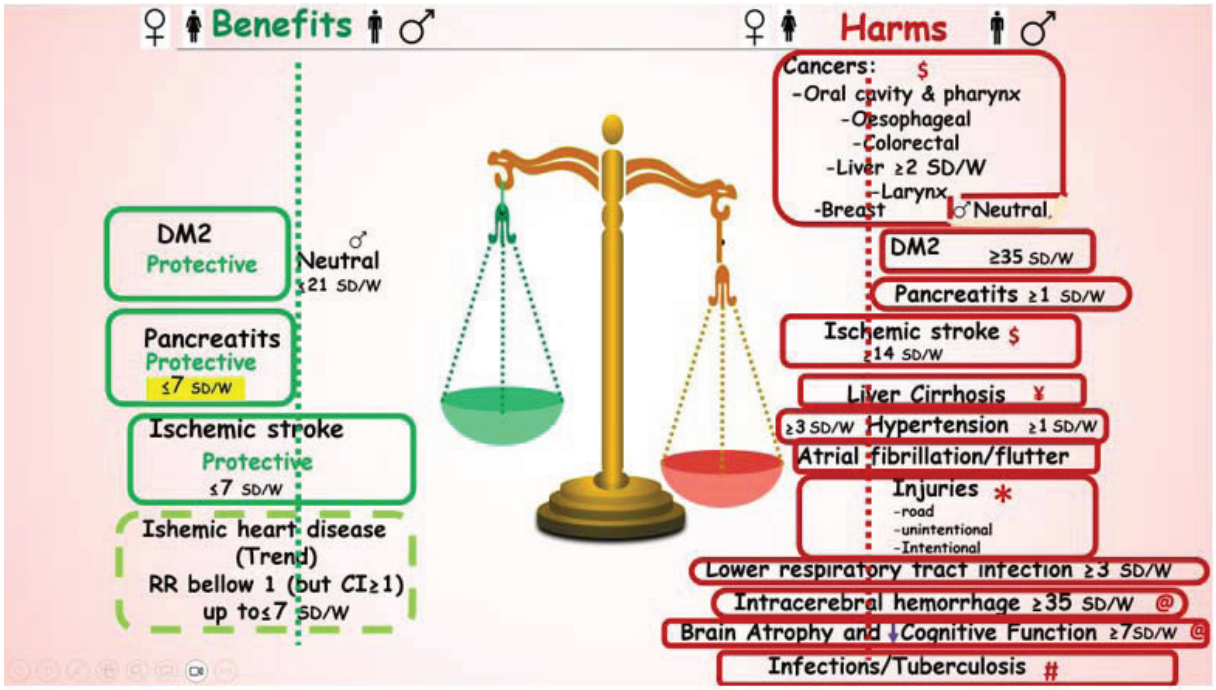
Guidelines for the prevention of cardiovascular diseases concerning alcohol use, especially red wine, were backed up by research, also saying that an increase in non-cardiovascular morbidity and mortality was not registered (4). However, new research contradicted the previous one. In retrospect, one may suspect that influences by different authorities have been involved in publishing guidelines relating to alcoholic beverages (6). In Table 1, Guidelines on alcoholic beverages from different sources in males and females regarding the amount of alcohol expressed in grams are presented in the time coordinate (7-13).

It could be appreciated that earlier recommendations were related to cardiovascular diseases, while later on all-cause morbidity and mortality were taken into account. The dose of alcohol was gradually decreased over time to come to zero dose considered to be safe. World Health Organization, as well as the Canadian Guidance on Alcohol and Health, state that the risk of alcoholic beverages starts with the first drop. Recently, the German Nutrition Society issued the same statement. Is that a brand-new position? In 2015, the Netherlands guidelines recommended zero alcohol as the only safe (14). However, prominent regional societies like ESC, AHA/ACC, etc., did not consider so. In the context of the risk of alcohol consumption on carcinogenesis, which was announced approximately 30 years ago by WHO (15), the late-breaking news is the fight to put into effect Ireland's parliamentary act of 2018 which will impose labeling alcoholic beverage containers with a range of health information as of 2026, including a warning of the direct link between alcohol and fatal cancers. Twelve countries exporting alcohol within the World Trade Organization oppose this, with the justification that it will put barriers on trading between countries (16). A similar cancer warning on alcoholic beverage packages existed in the Yukon province of Canada from 2017 until 2018. However, due to threats of legal action by the alcohol industry, it was withdrawn. The empire (industry) strikes back (16). Compiling eight scientific reports (4) and the new progress report (17), some of which reported Disability-Adjusted Life Years (DALYs – taking into account morbidity as well as mortality) and years of life lost (YLLs), the author presented the scale with benefits versus harms of consuming alcoholic beverages in Figure 1.

Table 1. Guidelines on alcoholic beverages from different sources in males and females regarding the amount of alcohol expressed in grams are presented in the time coordinate

Year of publication	Title	Safe dose	
		Females G per day or week	Males G per day or week
2024 (Aug 16)	The German Nutrition Society (DGE) (position statement)	0 (Zero) Daily	
2023 (Jan 23)	Canada's Guidance on Alcohol and Health	0 (Zero) Daily	28g Weekly Low Risk
2023 (Jan 4)	World Health Organization	0 (Zero) Daily	
2021	New Australian Treatment Guidelines for the treatment of alcohol problems: an overview of recommendations	11 Daily 80 Weekly Not>40g daily	
2021	ESC Guidelines on Cardiovascular Disease Prevention in Clinical practice	14 Daily 100 Weekly	
2020	Dietary Guidelines for Americas	14 Daily	28 Daily
2019	2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease	14 Daily	28 Daily

ESC- European Society of Cardiology; ACC/AHA - American College of Cardiology/American Heart Association



CI - Confidence Intervals; RR - Relative Risk; SD/W - Standard Alcoholic Drink per Week, 1 SD = 13.45 grams of Alcohol (Canada)

Figure 1. Alcohol effects sorted by the number of standard drinks are estimated by relative risk and confidence intervals and diagnostic criteria for different diseases. If a dashed line crosses the rectangle, it refers to both genders; if the rectangle is left or right of a dashed line, it refers to females and males, respectively. In males, alcohol consumption is neutral for breast cancer. If the number of standard alcoholic drinks per week (SD/W) is not filled in, it is ≥ 1. 1 SD equals 13.45 g of Alcohol (Canada).

The highest relative proportions of Disability-Adjusted Life Years (DALYs) for causes associated with harmful alcohol consumption were reported by Global Burden of Diseases researchers by super-region, age group, and sex in 2020 ($ Cancers: high-income countries in age group 40–64 years; ¥ liver cirrhosis: Central Europe, Eastern Europe, and Central Asia, Latin America and Caribbean, South Asia and Sub-Saharan Africa, especially males; * injuries: 15–39 years in all regions; @ intra cerebral hemorrhage and brain atrophy and decrease in cognitive function: high-income countries in age group ≥ 65 years, hypertension, high body mass index and low educational level are predisposing risk factors; # tuberculosis: low-income countries in the age group 15–40 years).

As far as ischemic heart disease is concerned, up to seven standard drinks (1 SD/W 13.45 g alcohol) per week, there was a trend toward decrease. Still, as CI is ≥1, it was not significant, but it was significant for ischemic stroke, Diabetes Mellitus type 2 in both genders. Interestingly, there was only a protective value of up to 7 SD/W for pancreatitis in women. However, the harms presented on the right side of the scale were more numerous. All cancers were more frequent (except breast in males). Alcoholic myocardiopathy is not presented in the graph, as it was assumed that it is encompassed with atrial fibrillation and hypertension. However, new findings in the small series of patients have pointed in the direction that alcoholic myocardiopathy may be a distinct disease with a genetic predisposition (18).

Although Figure 1 is self-explainatory, it accentuates brain changes and a decline in cognitive function (19, 20). As previously stated, most of our scientific knowledge in these recommendations is based on observational studies, which point out a link between alcohol consumption and different illnesses but no direct cause-consequence relation. Our calculations are usually considered correct until proven wrong. Everyone knows at least someone who has spent their life drinking alcohol daily and yet lived a very long life. To be clear, in this text we do not discuss or refer to alcoholism as an addiction but rather to the effects of consuming small or moderate doses of alcohol. In nutritional medicine, randomized controlled trials are very scarce. That is therefore the argument of the alcohol industry, to strike back. In contrast with the tobacco industry, which is still profitable, and whose manufacturers are strictly regulated in the ways they market their products or influence federal and state institutions to promote their interests, the food and alcohol manufacturing industry enjoys the lack

of regulations, which enables the alcohol manufacturing industry to promote its interests vigorously and freely by marketing their products and influencing and lobbying the federal and state governing and regulatory bodies (21-23). Very recently, in September 2024, the American Association on Cancer Research published that alcohol consumption is the third reversible cause of cancer after smoking cigarettes and obesity, appealing for the cancer warning label on alcoholic beverage packages (17). Concerning warning labeling, a similar war against the tobacco industry was won back in 1965 in the USA Senate and adopted by WHO in 2003. Genetic links and markers regarding susceptibility towards carcinogenesis elucidated by alcohol are still incomplete. However, as discovered in pharmacogenetics, hereditary factors may be crucial in substance-individual reaction response. Being aware of the fact, the industry of alcoholic beverages opted for one of the exclusion criteria to be a family history of cancer in the randomized controlled "Moderate Alcohol and Cardiovascular Health Clinical Trials (MACH)", which was prematurely terminated only after recruiting 104 of 7800 planned healthy individuals due to unclear reasons (supported by $ 100 million, but two-thirds coming from alcohol industry) (24). Of particular note is that the proportion of drinkers worldwide has remained the same since 1990; due to population growth, absolute numbers increased from 983 million to 1.34 billion in 2020. An especially worrisome fact is that 59.1% belong to the 15-to-39-year age group (25). The current controversy, with conflicting guidelines for alcoholic beverage consumption, may stimulate more fundamental investigations up to genetic ones and find the cause-effect relations in the era of next-generation evidence-based medicine (26), i.e., precision medicine. Hopefully, we may come closer to discovering the causes (etiopathogenesis) of cancers and many other diseases, enabling us to predict reactions to alcoholic beverages by each person, not just in the population. "Canada has a right to know" (8). "The risk starts with the first drop" (9). The planet should not ignore these dramatic warnings.

CONCLUSION

Alcohol consumption is linearly associated with an increased risk of all-cause morbidity and mortality. Non-pharmacological measures, particularly the reduction of alcohol consumption (similar to the approaches established for smoking cigarettes) should be integral components of primary and secondary prevention strategies that take a holistic approach. Even optimized pharmacological and other lifestyle interventions may be insufficient and ineffective without addressing these factors.

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REVIEW ARTICLE

Improving Health Care for Patients with Hepatocellular Carcinoma in the Federation of Bosnia and Herzegovina

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Abstract

Hepatocellular carcinoma (HCC) is the sixth most common cancer globally and the third leading cause of cancer-related deaths. It remains especially lethal among patients with cirrhosis and chronic liver diseases like hepatitis B and C, alcohol abuse and non-alcoholic fatty liver disease. A retrospective, multicenter study was conducted across five oncology centers in the Federation of Bosnia and Herzegovina, with the aim of gaining a better insight into the current state of healthcare for patients with HCC in this region. The study reveals several regional disparities in the etiology, treatment, and outcomes of HCC, but it also indicates that the diagnostic approach varies significantly from one city to another. One of the highlights of the study is the late-stage diagnosis of most patients, due to the limited healthcare access, diagnostic delays and, especially, lack of screening programs. Implementation of targeted screening methods, regular monitoring of high-risk patients and enhanced use of biomarkers could lead to a significant improvement in the diagnostic accuracy. The limited use of innovative treatments recommended by the global guidelines was also identified as an issue, which directly leads to limited surgical and other treatment options. This study signals the need for a standardized patient pathway in the Federation of Bosnia and Herzegovina, implementation of national registry and targeted HCC database, which could reduce mortality, improve overall care and patient outcomes.

Keywords: hepatocellular carcinoma, healthcare, standardized patient pathway.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most frequently diagnosed cancer globally, with 900,000 new cases recorded in 2020 (1). It is also the third leading cause of death among cancer patients, with over 830,000 deaths (2). With a five-year survival rate of 21%, HCC remains one of the most lethal gastrointestinal malignancies (3).

The main risk factors for HCC development are cirrhosis and chronic liver diseases, irrespective of etiology. Specific risk factors include viral infections such as hepatitis B and C, chronic alcohol abuse, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, hemochromatosis, and coinfections with HBV/HCV and HIV (4).

HEPATOCELLULAR CARCINOMA IN THE FEDERATION OF BOSNIA AND HERZEGOVINA

To analyze the current state of healthcare for patients with HCC in the Federation of Bosnia and Herzegovina (FBiH), a retrospective, multicenter collection of epidemiological, demographic, and clinical data was conducted across five oncology centers: the Clinical Center of the University of Sarajevo, University Clinical Center Tuzla, University Clinical Hospital Mostar, Cantonal Hospital Zenica, and Cantonal Hospital Bihać. The data covered patients diagnosed and/or treated for HCC between 1 January 2022 and 31 December 2023 in these centers.

The analysis revealed that Tuzla has the highest number of cases, while Zenica has the lowest. Sarajevo and Mostar fall in between, possibly reflecting differences in healthcare access, diagnostic capabilities, and demographic factors across these regions. In terms of age, Sarajevo and Mostar have older patient populations, while Zenica has a younger demographic. Zenica also has the highest proportion of male patients, potentially indicating specific regional risk factors.

Regarding etiology, HBV infection is predominant in Tuzla, while alcoholic cirrhosis is more common in Mostar, suggesting varied risk factors and habits across the country. A high percentage of undetermined causes underscores the need for enhanced diagnostics and more detailed patient monitoring.

Diagnosis in Sarajevo was largely based on biopsy, whereas non-invasive methods like ultrasound (US), CT, or MRI were more commonly used in Tuzla. This trend highlights significant disparities in diagnostic approaches and capacities between cities.

Most patients across cities are diagnosed at later stages of the disease (BCLC stage C), indicating a lack of early detection. Compared with global data, where approximately 50% of cases are diagnosed at an advanced stage, 61% of patients in FBiH receive a late-stage diagnosis, limiting surgical and other curative treatment options. Furthermore, only 10% are diagnosed in the early stage (BCLC A) compared to up to 33% globally, as observed in Italy (5). This reflects significant diagnostic delays likely due to limited healthcare access, lack of effective early screening programs, and lower health awareness among the population. Additionally, 10% of patients in FBiH are diagnosed at terminal stage (BCLC D), compared to a lower global average, indicating that patients often present with advanced disease, further highlighting the urgent need for improved early detection programs.

Innovative therapies like the Atezolizumab-Bevacizumab combination are limited in FBiH, diverging from leading global guidelines (BCLC, ESMO, NCCN), which recommend this combination as a first-line systemic therapy. Such discrepancies underscore the need for standardization in HCC treatment across Bosnia and Herzegovina to align with neighboring countries where these treatments are already standard (6-8).

Geographic disparities in diagnostic and treatment approaches across FBiH, coupled with inequalities compared to neighboring countries, signal the need for immediate healthcare system improvements focused on prevention, early diagnosis, and access to modern therapies. Comprehensive screening programs and education for both healthcare professionals and patients could significantly reduce incidence and improve HCC treatment outcomes.

According to GLOBOCAN, HCC is not among the top five cancers in Bosnia and Herzegovina. However, it ranks eighth in incidence, with 492 new cases, and sixth in mortality, with 462 deaths annually (9). These figures reflect high mortality associated with liver cancer, consistent with our analysis showing late-stage diagnoses (BCLC C) in most patients, limiting treatment options. Alarmingly, only 135 HCC patients were diagnosed/treated by oncologists in FBiH over two years, far below GLOBOCAN's expected rate. This highlights the critical need for increased awareness, early detection, and regular

monitoring of at-risk populations, as well as establishing a unified population-based and clinical registry.

OPTIMIZATION OF SCREENING AND MONITORING PROGRAMS

HCC poses a significant clinical challenge, particularly among patients with cirrhosis or chronic hepatitis B infection. Regular ultrasound and AFP screening are recommended for early detection of liver changes that may indicate HCC. For patients without nodules or with nodules less than 10 mm on ultrasound, biannual follow-ups are advised. For those with positive AFP or nodules larger than 10 mm, additional imaging (CT or MRI) is necessary to precisely define lesion characteristics (8).

Biomarkers and Diagnostic Advancements

While AFP has traditionally been used in HCC screening and diagnosis, its sensitivity and specificity limitations necessitate additional biomarkers. PIVKA-II, discovered to be elevated in HCC patients, can complement AFP, enhancing diagnostic accuracy when used together, with combined detection sensitivity reaching up to 92% compared to 52% with AFP alone (10-14).

OPTIMAL MULTIDISCIPLINARY THERAPEUTIC APPROACH

For potentially resectable or transplantable HCC patients, evaluating liver function and overall condition is critical. Resection is preferred for patients with good liver function and no portal hypertension. However, transplant remains optimal for eligible patients. Multidisciplinary team assessments should guide therapeutic decisions, incorporating ablative or arterial therapies as bridges to transplant when applicable, along with regular radiological evaluations and AFP measurement to monitor recurrence (8).

SYSTEMIC ONCOLOGICAL TREATMENT

Systemic therapy is reserved for advanced HCC patients ineligible for curative or locoregional treatments and with adequate liver function. The Atezolizumab-Bevacizumab combination is suggested for patients with good functional status, while Tremelimumab-Durvalumab is an alternative for those who cannot tolerate Bevacizumab. For patients in poor condition or post-transplant recurrence, monotherapy with Sorafenib or Lenvatinib is preferred over conventional cytotoxic chemotherapy (15).

EXPERT PANEL RECOMMENDATIONS

1. **Early Detection of HCC**: Introduce regular monitoring of high-risk patients (e.g., ultrasound and serum AFP every six months) to detect HCC in early stages, alongside patient and healthcare provider education for improved screening cooperation.
2. **Enhanced Monitoring of High-Risk Patients**: Establish routine follow-up programs for high-risk patients, supported by multidisciplinary teams for timely diagnosis.
3. **Utilization of New Biomarkers**: Introduce PIVKA II in combination with AFP and ultrasound for early HCC detection, with gastroenterologists and infectious disease specialists selecting appropriate patients.
4. **HCC Diagnosis**: Increase reliance on biochemical markers and digital radiology (CT, MRI) for early detection, reducing the need for invasive biopsy.
5. **Timely Systemic Oncological Treatment**: Ensure timely access to systemic oncological treatment with drugs established as the standard of care for HCC to improve outcomes and survival.

IMPLEMENTATION STRATEGIES

To optimize HCC care, a standardized patient pathway across FBiH is essential, covering diagnosis, multidisciplinary assessment, personalized treatment, and follow-up. This pathway should align with international guidelines, fostering equal access to healthcare and improving patient outcomes.

Developing a targeted HCC database to track clinical parameters will enhance resource planning, intervention optimization, and contribute to research initiatives. Finally, the establishment of multidisciplinary team meetings for interventional oncology procedures will ensure thorough and timely assessment of candidates for interventions such as embolization, ablation, or resection.

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REVIEW ARTICLE

Etiopathogenesis of Oral Lichen Planus: Highlighting the Role of T Cells, Mast Cells, RANTES, and Matrix Metalloproteinases

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Abstract

Oral lichen planus (OLP) is an autoimmune chronic inflammatory disease that affects the mucous membrane of the oral cavity. It is mediated by T cells, causing the basal cells of the oral epithelium to undergo apoptosis through the action of cytotoxic CD8+ T cells. A number of inflammatory mechanisms have been proposed to explain the subepithelial accumulation of CD8+ T cells as well as the death of keratinocytes that follows. This paper reviews the numerous theories on the etiopathogenesis of OLP and highlights the role of T cells, mast cells, RANTES, and matrix metalloproteinases (MMPs).

Keywords: oral lichen planus, etiology, pathogenesis, histology.

Introduction

Oral lichen planus (OLP) is a chronic inflammatory disease that affects the mucous membrane of the oral cavity. It belongs to the mucosal counterpart of cutaneous lichen planus [LP] (1, 2). Although the prevalence of cutaneous LP ranges from 0.22 to 1% and equally affects people of both sexes (3), OLP is more frequent and is reported in 2% to 5% of the general population, with a female-to-male ratio of 2:1 (4-7). Additionally, while cutaneous LP is not usually considered to have a racial predilection, some studies have suggested a higher incidence of the disease in African American, Indian and Arabian descents (8,9), and a familial component of up to 10% of first-degree relatives has been proposed (10). In terms of OLP, non-Asian populations present a greater incidence (11). LP typically appears in adults aged 30 to 60 years and occasionally involves other age groups (5).

The etiopathogenesis of OLP has been extensively investigated, and several mechanisms have been proposed to explain it. In this review, we discuss the most recent theories on the etiopathogenesis of OLP and highlight the roles of T cells, mast cells, RANTES, and matrix metalloproteinases (MMPs).

Clinical Features of LP and OLP

LP can possibly affect the skin, the lips, the oral mucosa, the esophagus, the pharynx, and the genital mucosa (the glans penis, the vulvar and vaginal mucosa, the labia majora, and the labia minora) (12). Additionally, LP may involve the scalp hair follicles (lichen planopilaris) in the form of inflammation and keratotic papules, eventually leading to scarring alopecia (13). Furthermore, the disease may affect some or all nails through longitudinal ridging, splitting, thinning, and, in the extreme cases, pterygium formation (14).

While the cutaneous disease has numerous clinical variants, it mostly presents as small, sharply demarcated, flattened, and polygonally shaped erythematous-livid papules (5). Another notable characteristic of LP is the epidermal hypergranulosis, which appears as whitish reticulate structures or Wickham's striae on the surface of the lesions (15). Typically, a classic LP manifests as a localized form affecting just the extremities, primarily the lumbar area, wrists, ankles, and dorsal surfaces of the hands and feet (15). Less frequently, it manifests as a widespread condition that affects the entire body, including the anogenital areas and the oral mucosa (5). Severe pruritus that is as intense as the affected area without apparent scratches or subsequent infections generally follows cutaneous LP (6).

OLP that occurs either associated with the classic cutaneous disease (70% of cases) or without (20 to 30% of cases) may appear in six different forms, namely reticular, papular, plaque-like, atrophic/erosive, ulcerative, and bullous; the reticular one predominates (Figure 1), followed by the erosive form, characterized by pain, a chronic, recalcitrant course, and possible malignant transformation into squamous cell carcinoma (7, 16).

Intraorally, the buccal mucosa, tongue, and gingiva are commonly involved, although other sites may be rarely affected (17).

Etiology and Pathogenesis of OLP

While the precise etiology of OLP is unknown, factors such as stress, immunity, genetics, hypersensitivity reactions, and medications including beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), thiazide diuretics, quinidine, antimalarials, and tumor necrosis factor alpha (TNFα) inhibitors may all be involved (1, 8). Additionally, many metals that are present in dental restorations, such as gold, copper, and mercury, are thought to be etiologic factors as well (18, 19).

Furthermore, over 90 controlled studies conducted worldwide, especially in the USA, Japan, and southern Europe, have found a connection between the hepatitis C virus (HCV) and the development of OLP (2, 9, 18). In fact, in OLP, HCV replication has been shown in the subepithelial band by HCV-specific CD4 and CD8 lymphocytes, as well as in the epithelial cells from the mucosa of LP lesions using reverse transcription/polymerase chain reaction or in-situ hybridi-

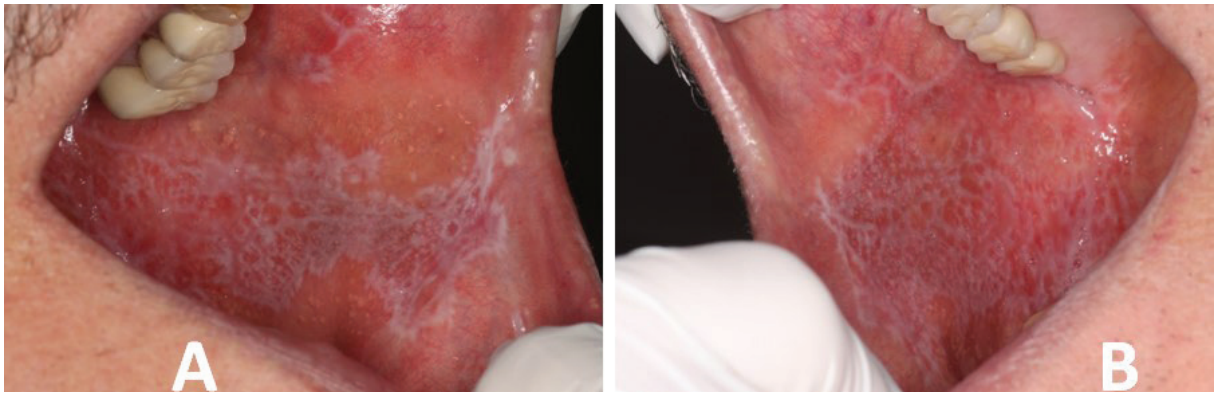

Figure 1. Intraoral photographs showing bilateral buccal reticular lesions

zation (2, 20).

Regarding the pathogenesis of OLP, numerous studies have suggested that OLP is a T cell-mediated autoimmune condition, wherein auto-cytotoxic CD8+ T cells trigger apoptosis of the basal cells of the oral epithelium (10). The early steps of the disease mechanism involve keratinocyte antigen expression or the unmasking of an antigen that may be a self-peptide or a heat shock protein (2, 21). After that, T cells (mostly CD8+ and some CD4+ cells) migrate into the epithelium as a result of either a random encounter of antigen during routine surveillance or a chemokine-mediated migration toward basal keratinocytes (2, 22). These migrated CD8+ cells are activated directly by antigen binding to major histocompatibility complex (MHC-1) on keratinocyte or throughout activated CD4+ lymphocytes (2). Additionally, the number of Langerhans cells in OLP lesions is increased along with upregulation of MHC-II expression; subsequent antigen presentation to CD4+ cells and Interleukin-12 (IL-12) activates CD4 + T helper cells which activate CD8+ T cells through receptor interaction, interferon γ (IFN- γ) and Interleukin-2 (IL-2). The activated CD8+ T cells in turn kill the basal keratinocytes through TNF-α, Fas–FasL mediated or granzyme B (GrB) activated apoptosis (2, 21, 22).

The normal integrity of the basement membrane is maintained by a living basal keratinocyte because of its secretion of both collagen 4 and laminin 5 into the epithelial basement membrane zone. Sequentially, keratinocytes require a basement membrane-derived cell survival signal to avoid the commencement of its apoptosis. Apoptotic keratinocytes are no longer able to achieve this function, which results in disruption of the basement membrane. Similarly, a disrupted basement membrane cannot send a cell survival signal. This sets in a vicious cycle which relates to the chronic nature of the disease (2, 22, 23).

On the other hand, it has been found that OLP exhibits weak expression of transforming growth factor (TGF)-β1whose deficiency may predispose to autoimmune lymphocytic inflammation. The equilibrium between TGF-β1 and IFN-γ establishes the level of immunological activity in OLP lesions. A local increase in the production of IFN-γ by CD4+ T cells attenuate the immunosuppressive effect of TGF-β1 and stimulates keratinocyte MHC class II expression and CD8+ cytotoxic T-cell activity (2, 22, 23).

Furthermore, the chemokine RANTES (Regulated on Activation, Normal T-cell Expressed and Secreted), part of the CC chemokine family which plays a significant role in the recruitment of lymphocytes and mast cells has been identified binding to cell-surface receptors CCR1, CCR3, CCR4, CCR5, CCR9, and CCR10 in OLP. The recruited mast cells undergo degranulation under the influence of RANTES and release chymase, tryptase, and TNF-α, consequently upregulating RANTES secretion. This again sets in a vicious cycle, which relates to the chronic nature of the disease (22).

Moreover, the matrix metalloproteinases (MMPs) are principally involved in tissue matrix protein degradation. MMP-9, which cleaves collagen-4, along with its activators, is upregulated in OLP lesional T cells, resulting in increased basement membrane disruption (21).

Histology of OLP

Histological features of OLP may include a thickened stratified epithelium with irregular acanthosis, hyperparakeratosis, and formation of parakeratosis foci. Additionally, a dense band-like inflammatory infiltrate consisting of mononuclear cells and a perturbation of the basement membrane integrity are observed [24].

Conclusion

OLP is an immune disease with unknown etiology. Its pathogenesis may especially involve cytotoxic CD8+ T cells that release different

cytokines, leading to the disruption of the lining epithelial basement membrane. The indirect action of mast cells, RANTES, and MMPs was identified in the pathogenesis of OLP.

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Author Contribution: Conceptualization, original draft, and review and editing were carried out by Georges Aoun.

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CASE REPORT

A Case of Calciphylaxis

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Abstract

Introduction: Calciphylaxis (calcific uremic arteriolopathy), is a condition primarily observed in patients with end-stage renal disease (ESRD).

Aim: To increase clinical awareness of calciphylaxis and to consider it a differential diagnosis in the presence of atypical skin nodules or ulcers occurring in patients with chronic kidney disease (CKD), especially in patients on hemodialysis and non-hemodialysis patients with the background of diabetes mellitus and secondary hyperparathyroidism.

Case Report: We present the case of a 77-year-old woman with CKD and diabetes mellitus as well as severely painful, firm, indurated plaques on the lower extremities. The plaques progressed to involve larger areas with associated local ulceration and necrosis. Laboratory testing revealed hyperparathyroidism and incisional skin biopsy confirmed calciphylaxis.

Conclusion: Each single CKD patient with diabetes mellitus and signs of secondary hyperparathyroidism with extremely painful ischemic cutaneous lesions or painful subcutaneous nodules without skin changes, although at times, pain may precede the development of the lesions, is a candidate for skin biopsy. Calciphylaxis is a rare but serious kidney complication.

Keywords: calciphylaxis, chronic kidney disease, prognosis, treatment.

Learning Objectives

- Identify the risk factors for calciphylaxis.
- Describe the pathophysiology of calciphylaxis.
- Present treatment and management options available for calciphylaxis.
- Explain the importance of a multidisciplinary team approach for the effective treatment of calciphylaxis.

INTRODUCTION

Calciphylaxis, also known as calcific uremic arteriolopathy, is a condition primarily observed in patients with end-stage renal disease (ESRD), though it can occasionally occur in those without ESRD (non-uremic calciphylaxis) (1). This condition is marked by the calcification of the medial layer of arterioles in the dermis and subcutaneous fat, leading to endothelial damage and microthrombi formation (1,2). These changes result in painful skin lesions, tissue ischemia, necrosis, and ulceration. Calciphylaxis has a high morbidity and mortality rate, with an estimated six-month survival rate of around 50% (2-4). A deficiency in vascular calcification inhibitors, such as fetuin-A and matrix Gla protein, may contribute to its development (5). It is more prevalent in females and is mainly linked to kidney disease, hyperparathyroidism, and diabetes mellitus, as well as conditions like obesity, liver disease, hypoalbuminemia, malignancies, and autoimmune disorders (e.g., systemic lupus erythematosus, rheumatoid arthritis) (2-5). Certain medications, including warfarin, corticosteroids, calcium-based phosphate binders, activated vitamin D, and iron therapy, are associated with calciphylaxis; for instance, warfarin reduces the vitamin K-dependent activation of matrix Gla protein (5). The aim of article is to enhance clinical awareness of calciphylaxis and consider it as a differential diagnosis when atypical skin nodules or ulcers appear in patients with kidney disease, particularly those undergoing hemodialysis and with diabetes and secondary hyperparathyroidism.

CASE PRESENTATION

A 77-year-old female patient was assessed in the outpatient nephrology clinic. She reported severe leg pain that had been ongoing for several months. During the physical examination, local erythema and necrotic ulcerations of the skin were noted (Figure 1).

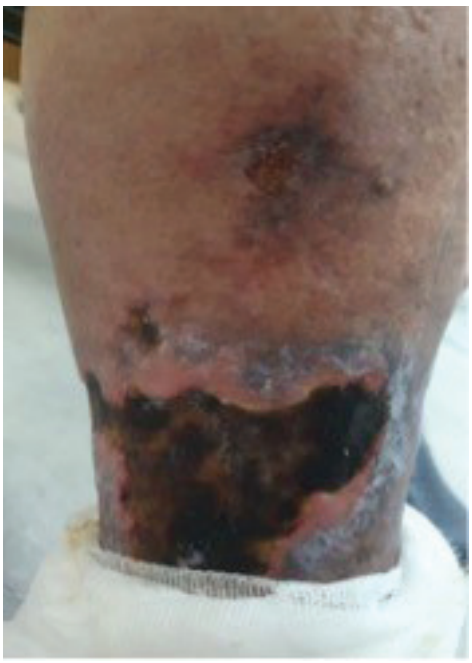

Figure 1. Necrotic ulcerations

The skin changes were initially described as diabetic ulcerations. The lesions began as red, itchy areas, but over time, necrosis and inflammation of the surrounding tissue developed, accompanied by intense pain.

Patient's medical history included hypertension, diabetes mellitus, hyperlipidemia and chronic kidney disease (CKD). In our case, laboratory investigations were consistent with chronic kidney injury as late complication of diabetic nephropathy. Within chronic kidney disease stage IV/V (eGFR13.3 mL/min/1.73m^2), electrolyte imbalance with signs of secondary hyperparathyroidism is also observed ((Ca 2.56 mmol/L - reference range 2.10-2.55 mmol/L) and PO4 1.63 mmol/L - reference range 0.81-1.59 mmol/L), PTH 50.1 pmol/L (reference range 1.6-6.9 pmol/L).

Based on the typical clinical grounds, and history of CKD with secondary hyperparathyroidism and diabetes, we suspected calciphylaxis and requested a skin lesion biopsy. Pathophysiological findings included extravascular and intravascular calcinosis of small and medium-sized blood vessels, and the appearance of erosions on the surface of the skin, which could fit into the clinical diagnosis of calciphylaxis (Figure 2).

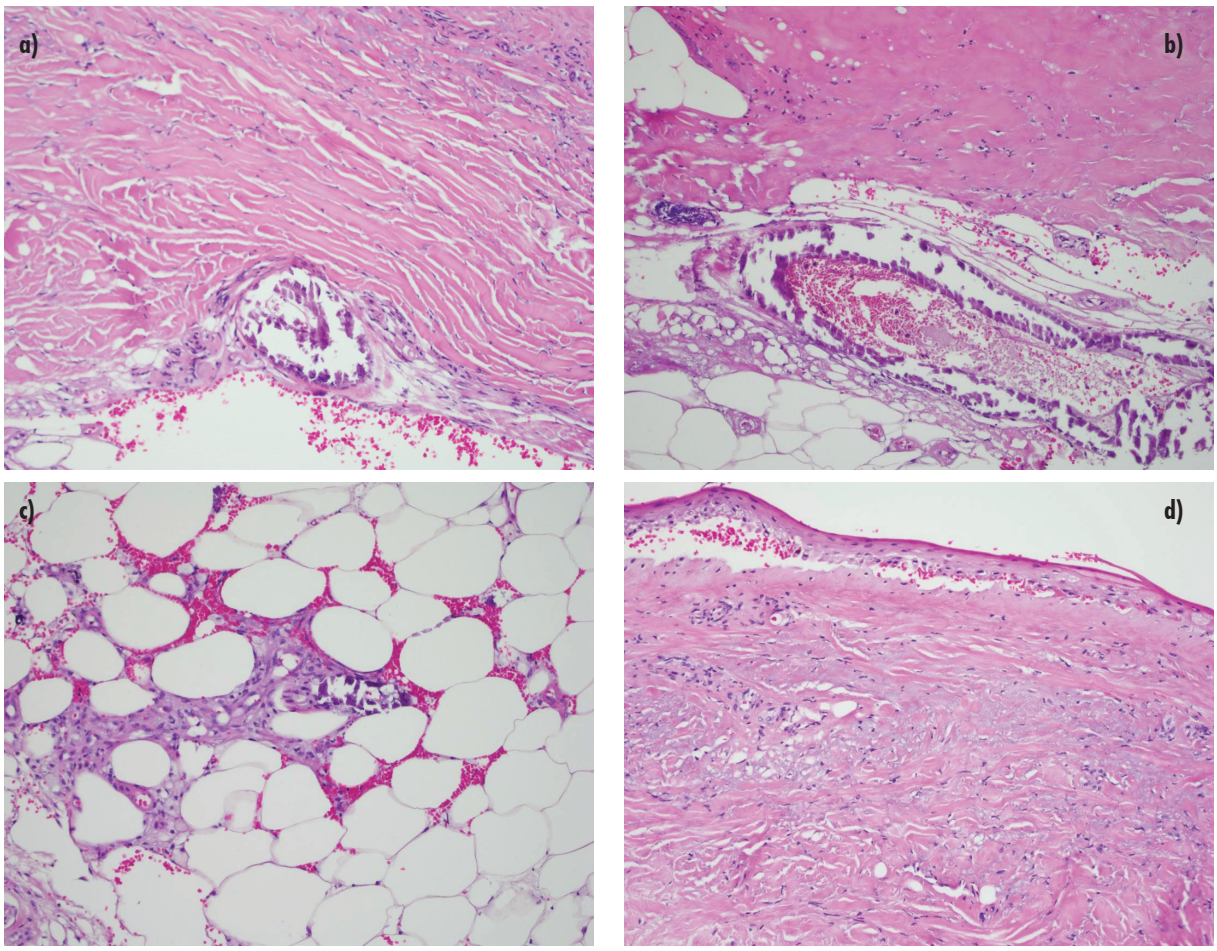

Figure 2. a) Intramural intravascular calcium deposit in the reticular layer of dermis (HE, 200 x); b) Calcium deposit in the vein wall in the subcutaneous fat tissue (HE, 400 x); c) Calcium deposit in the capillary wall in subcutaneous fat tissue (HE, 400 x); d) Skin appendages reduction and mucin deposits in superficial dermis (HE, 200x); d) Skin appendages reduction and mucin deposits in superficial dermis (HE, 200x)

DISCUSSION

In our case, laboratory investigations indicated chronic kidney injury as a late complication of diabetic nephropathy. Calciphylaxis was suspected based on clinical findings. A skin biopsy and histological evaluation showed specific inflammation and necrosis with calcification affecting small arteries and surrounding fibroadipose tissue. The laboratory workup should encompass all potential implications of CKD, with particular focus on calcium and phosphate levels, as well as any evidence of skin or systemic infection.

Treatment should prioritize local wound care and metabolic control, specifically by managing hypercalcemia, hyperphosphatemia, and hyperparathyroidism (5-9). Suggested therapies include oral anticoagulants, sevelamer carbonate, calcitriol, vitamin K, and ongoing management for diabetes mellitus and hypertension. Debridement may be necessary, although surgical debridement is controversial due to the heightened risk of sepsis and increased pain. Pain management is also critical, along with efforts to prevent both local and systemic infection (7-9).

In patients with advanced CKD, diagnosis primarily relies on physical examination, where painful, ulcerated lesions covered by black eschar are observed. The definitive diagnosis is confirmed through a biopsy of the affected skin, which is recommended if there is uncertainty. Differential diagnoses include warfarin-associated skin necrosis, antiphospholipid syndrome, cholesterol embolization, vasculitis, and cellulitis (8).

There is currently no approved treatment for calciphylaxis (5-9). A multidisciplinary approach is necessary, focusing on wound care and pain management, as well as

addressing infected wounds through surgical debridement and antimicrobial therapy to prevent sepsis, the leading cause of death in these patients. Hyperbaric oxygen therapy may also aid in wound healing for some individuals. Hyperphosphatemia and hypercalcemia should be managed, with non-calcium-containing phosphate binders recommended. Secondary hyperparathyroidism should be treated with cinacalcet. Additionally, optimizing dialysis and medication regimens is essential. For specific treatment of calciphylaxis, intravenous sodium thiosulfate (STS) may be considered.

Given that calciphylaxis is an extremely painful and debilitating condition, nutritional and psychological support, along with specialized pain management, are crucial. In our case, care goals and prognosis were discussed with the family, who chose to pursue palliative and comfort measures without further invasive surgical or medical interventions.

Early signs of calciphylaxis are extreme pain, before there are any visible signs of calciphylaxis (purple or red skin markings, sores that do not heal) with background of chronic kidney disease and diabetic nephropathy and hyperparathyroidism secondary.

In our case, at the beginning, there was extreme pain but no skin lesions. For the second control examination, the patient came with eschar, a wound covered with thick, dry, black necrotic tissue. We have missed the first skin lesion signs due to the patient's failure to come to an examination. The described lesions were the reason for our working diagnosis of calciphylaxis and the indication for skin biopsy.

CONCLUSIONS

Every CKD patient with diabetes mellitus and signs of secondary hyperparathyroidism, who presents with extremely painful ischemic skin lesions or painful subcutaneous nodules, sometimes with pain preceding the appearance of the lesions, is a candidate for a skin biopsy. Calciphylaxis is a rare but serious complication associated with CKD.

Authors' Contributions: Conceptualization: Nejra Prohic, Belma Paralija, Nejra Mlaco-Vrazalic. Formal analysis: Nejra Prohic, Nejra Mlaco-Vrazalic, Belma Paralija. Project administration: Nejra Prohic. Resources: Nejra Prohic, Svjetlana Radovic, Dragan Totic, Nejra Mlaco-Vrazalic. Software: Nejra Prohic, Svjetlana Radovic, Dragan Totic, Nejra Mlaco-Vrazalic, Belma Paralija. Supervision: Nejra Prohic, Svjetlana Radovic, Dragan Totic, Nejra Mlaco-Vrazalic, Akif Mlaco, Belma Paralija. Visualization: Nejra Prohic, Svjetlana Radovic, Dragan Totic, Nejra Mlaco-Vrazalic, Akif Mlaco, Belma Paralija. Writing – original draft: Nejra Prohic, Svjetlana Radovic, Dragan Totic, Nejra Mlaco-Vrazalic, Belma Paralija. Writing – review & editing: Nejra Prohic, Svjetlana Radovic, Dragan Totic, Nejra Mlaco-Vrazalic, Akif Mlaco, Belma Paralija.

Consent: The authors have obtained written consent from the patient to submit and publish this case report, including images and accompanying text, in accordance with COPE guidelines.

Conflict of interest: None declared.

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IMAGES IN MEDICINE

Multislice Computed Tomography Coronary Angiography Uncovers Complex Post-ASD Repair Anatomy

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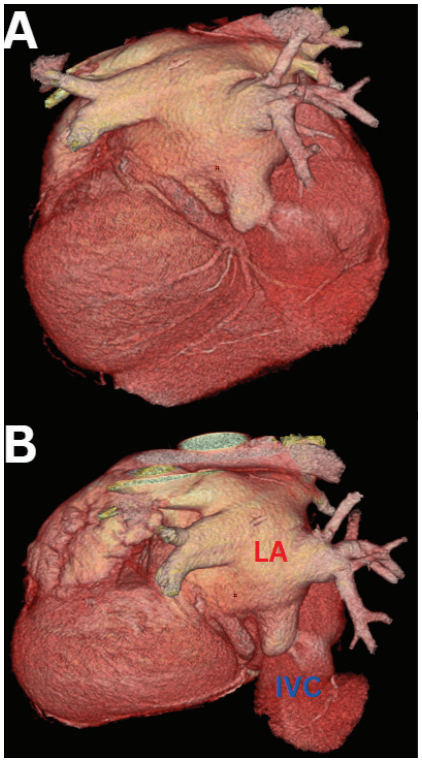

Figure 1. The inferior sinus venosus atrial septal defect (ASD), along with aneurysmal dilatation of the left atrial (LA) floor, is clearly visualized on Volume Rendering Technique (VRT) reconstructions from multislice cardiac computed tomography angiography (IVC - inferior vena cava (A) caudal-posterior-left oblique view.(B) cranial-posterior-left oblique view)

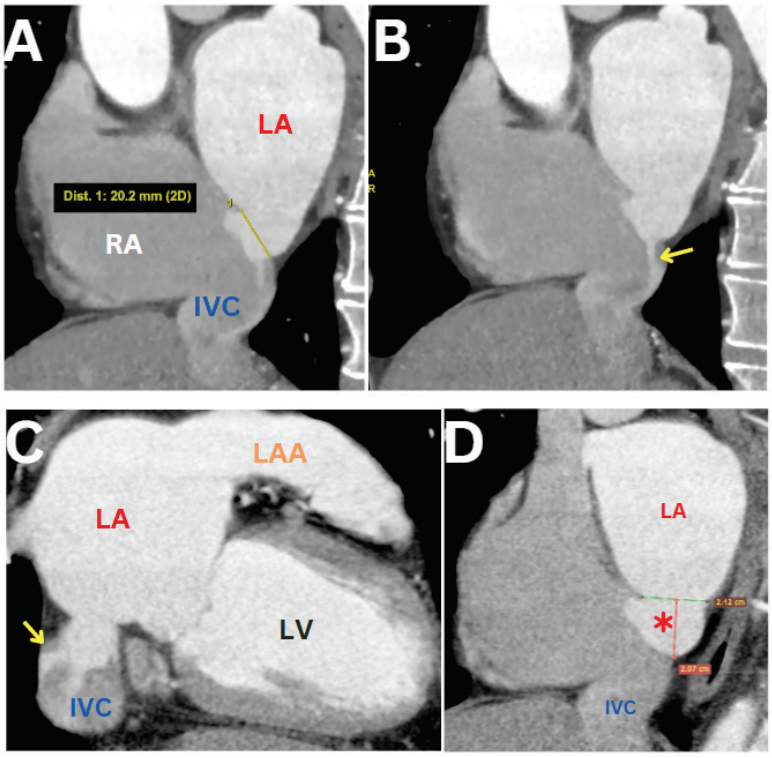

Figure 2. The inferior sinus venosus atrial septal defect (ASD) is seen in sagittal (A, B, D) and paracoronal (C) multislice cardiac computed tomography angiography images, with a defect in the interatrial septum floor near the inferior vena cava (IVC) inflow (yellow arrows in B and C). This allows contrast shunting from the left atrium (LA) to the right atrium (RA) and IVC. The left atrial appendage (LAA) is significantly dilated (C). The LA shows significant global dilatation as part of broader structural changes, including aneurysmal dilatation of its floor (asterisk in D)

A 53-year-old male with a history of heart failure with reduced ejection fraction (HFrEF) and permanent atrial fibrillation, who underwent ostium secundum atrial septal defect (ASD) repair at age 9, underwent multislice computed tomography (CT) coronary angiography to assess for significant coronary stenosis. The calcium score of 2 indicated minimal plaque burden, with the most significant lesion located at the ostium of the LCX, measuring 15.5%. This resulted in a CAD-RADS classification of 1/P1/HRP.

In addition to the coronary findings, advanced reconstruction revealed a residual sinus venosus ASD located at the inferior interatrial septum. This defect, previously assessed by transesophageal echocardiography, was described as an aneurysmally altered segment with a disruption in continuity of up to 2 mm, facilitating a left-to-right shunt from the left atrium into both the right atrium and inferior vena cava. Despite the surgical repair performed in 1980, these findings highlight the persistence of a clinically significant remnant lesion decades later. Furthermore, the left atrium exhibited enlargement, characterized by aneurysmal dilatation of its floor and marked enlargement of the left atrial appendage, though no thrombotic masses were identified (Figure 1-2). The complex anatomical features of the heart pose challenges in differentiating ASD types, although contemporary CT techniques provide clarity in evaluating such anomalies (1-3). According to the 2018 AHA/ACC guidelines, specialized management of adult congenital heart disease is essential, underscoring the importance of a multi-modality approach (2). While the primary focus of the CT was coronary assessment, the comprehensive findings offer valuable insights that inform further therapeutic decision-making in this patient with complex structural heart abnormalities.

Consent: The author have obtained written consent from the patient to submit and pu- blish this case report, including images and accompanying text, in accordance with COPE guidelines.

Authors' Contribution: Jasna Strika-Kuric was responsible for the conceptualization, methodology, formal analysis, visualization, writing of the original draft, and the review and editing of the paper.

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