



# Acta Medica Academica

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*Acta Medica Academica* is a triannual, peer-reviewed journal that publishes: (1) reports of original research, (2) original clinical observations accompanied by analysis and discussion, (3) analysis of philosophical, ethical, or social aspects of the health profession or biomedical sciences, (4) critical reviews, (5) statistical compilations, (6) descriptions of evaluation of methods or procedures, (7) case reports, and (8) images in clinical medicine. The fields covered include basic biomedical research, clinical and laboratory medicine, veterinary medicine, clinical research, epidemiology, pharmacology, public health, oral health, and medical information.

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'At Miss Doctor's. The Treatment of Muslim Women.' Source: Neuig-keitsweltblatt, 19 February 1903, s.p.

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## Acceptance of Orthodontic Therapy according to the Aesthetic Component of the Index of Orthodontic Treatment Need among Schoolchildren - a Cross-Sectional Study

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### Abstract

**Objective.** Orthodontic anomalies with impaired facial aesthetics and disturbed oral functions have a major effect on emotional and social development. It is necessary to determine the degree of acceptance of treatment. This study includes an evaluation of the Index of Orthodontic Treatment Need (IOTN) according to the Aesthetic Component (AC) of dental health in schoolchildren. **Methods.** The research included 300 schoolchildren (150 girls, 150 boys) with an age range from 12 to 15 years. An evaluation of the need for orthodontic treatment according to the AC consisted of a ten-grade scale illustrated with a sequence of ten intraoral photographs showing different degrees of acceptability of dental appearance. Results were expressed as absolute and relative frequencies. The Chi-square test (in the absence of the expected frequencies of Fisher's Exact test) was used for testing the significance of differences. Cohen's kappa statistic measure was used for measuring the agreement between the children and dentists. **Results.** There is a significant substantial agreement between children and dentists in assessing the need for orthodontic treatment. Differences in assessment of the degree of orthodontic anomalies by the doctor of dental medicine with respect to boys and girls, are negligible, and statistical analysis did not show any significant difference. Analysis of the need for orthodontic treatment with respect to the age of the children showed a significant difference. **Conclusion.** The need for orthodontic treatment is more pronounced in older children, and there is no difference between boys and girls.

**Key Words:** Orthodontic Anomalies ▪ Aesthetic Component (AC) ▪ Index of Orthodontic Treatment Need (IOTN).

### Introduction

Disturbances caused by occlusal anomalies, such as irregular teeth positions in the dental arches and an irregular proportion between the lower jaw and the skull base, are numerous. Dento-facial anomalies are conditions with deviations between the regular morphology, size and function of individual parts or the entire craniofacial complex (1). They are clinically identified as disorders of oral function: phonation, deglutition and mastication, where the greatest personal disturbance caused by these conditions is a facial aesthetics disorder in both children and adults. Abnormal arrangement of teeth in the dental arches during eruption, es-

pecially their compaction, results in the inability to eliminate food residues, even with regular oral hygiene. This is related to the development of bacterial flora, as the food gets stuck in retention spaces. Food residues and bacteria products initiate a fermentation process, where acid leads to the demineralization of the firm dental tissues, and has a pathological effect on the periodontal tissues, hence representing a direct aetiological factor for the occurrence of caries and periodontitis (2, 3). Aesthetics are one of the main reasons for undergoing orthodontic treatment, and therefore it is considered that the aesthetic component must be represented in diagnostic tools (4). It was clear

that the patients' perception of their own malocclusion needs to be taken into account.

Orthodontic anomalies, besides functional limitation, also cause psychological effects (5). Orthodontic anomalies, especially in schoolchildren, have gained epidemic proportions. Therefore, countries with well-developed oral health care are conducting active research in order to identify the need for orthodontic treatment, since early treatment significantly reduces the consequences of impaired oral health and facial aesthetics (6). Pronounced orthodontic anomalies in children, accompanied by impaired facial aesthetics and disturbed oral function (speech in particular), have a major effect on emotional and social development in children and adults alike. In children, this occurrence causes introversion, avoidance of contact with the environment, and often such children are ridiculed and taunted by their peers (7). The key to determining prevalence is diagnostics based on carefully aligned criteria, in order to set treatment priorities. Usually this is achieved by means of the Index of Orthodontic Treatment Need, using a Dental Health Component (DHC) and an Aesthetic Component to determine different levels of these needs (8, 9). In this undeveloped region of Bosnia and Herzegovina, where oral health care is inadequate, there has been no research on this topic so far. Hence, this research was oriented towards the need for orthodontic treatment using the AC. Since most schoolchildren do not readily accept orthodontic treatment, it is necessary to determine the degree of acceptance of treatment based on their own assessment and assessment by a doctor of dental medicine.

The aim of this study was to analyze the need for orthodontic treatment in schoolchildren of both genders, aged 12 to 15, based on the AC and an assessment by a dental medicine doctor. The research objectives were also to investigate the acceptance of orthodontic treatment by schoolchildren of both genders with a moderate to major IOTN.

## Materials and Methods

The research included 300 schoolchildren of both genders (150 girls and 150 boys) aged 12 to 15 years.

The study was approved by the Ethics Committee of the Rama Community Health Center, in accordance with the Helsinki Declaration. Informed consent was obtained from the parents. The children were informed about the study in an appropriate way and only those children who agreed to participate were included in the study. The sample size calculation was performed by considering the 54.3 percent prevalence of orthodontic treatment need, as measured by the DAI, with a confidence interval of 95% and 5% of level of precision. During sampling, the following exclusion criteria were applied: 1) No history of orthodontic treatment, 2) No ongoing orthodontic treatment. This study was conducted in two primary schools in the Prozor-Rama Municipality from 2015 to 2016. This is a territory where people traditionally live in an environment of similar economic, cultural and educational development, with shared financing institutions and health system organization. At this age, most permanent teeth have erupted (except for the third molar), so the research was not undertaken on individual age groups, but aggregately. Every person had their own health record, showing they had not undergone any form of orthodontic treatment before. All schoolchildren included in the study filled in a questionnaire about their assessments of orthodontic treatment need, and declared their acceptance of treatment.

For examination of the AC of the orthodontic treatment need, we used the model applied by Brock and Shaw (10) for this type of research (Figure 1). The model consists of a ten-grade scale, illustrated by a sequence of ten intraoral photographs showing different degrees of acceptable dental appearance. Considering the orthodontic treatment need, the photographs were grouped into three categories for the purposes of this research: Group 1: 1-4 "no need for treatment"; Group 2: 5-7 "moderate need for treatment"; Group 3: 8-10 "pronounced need for treatment".

According to quantification with the attached ten-grade scale, subjects with occlusal anomalies graded 1-4 do not require any or require minor orthodontic treatment, while the conditions in photographs 5-7 and 8-10 show a moderate or



Figure 1. Aesthetic Component of the Index of Orthodontic Treatment Need Scale (photographs 1–10): 1-4 "no Need for Treatment"; 5-7 "moderate Need for Treatment"; 8-10 "Pronounced Need for Treatment".

major need for treatment so they are considered as priorities. The results were formed by means of assessment by the participants and by a doctor of dental medicine. One researcher, an expert in orthodontics, previously trained in the use of the index, collected the data for each subject. All the participants with an identified moderate or major need for orthodontic treatment (photographs 5-10) were polled and asked whether they would accept the treatment. There were three possible answers: I accept orthodontic treatment. I do not have any particular opinion on the matter, and I do not accept orthodontic treatment.

### Statistical Analysis

IBM SPSS Statistics 25.0 was used for statistical analysis. Results were expressed as absolute and relative frequencies. The Chi-square test (in the

absence of the expected frequencies of Fisher's Exact test) was used for testing the significance of differences. Cohen's kappa statistic measure was used for measuring the agreement between children and dentists. The significance limit was set at  $P=0.05$ . P values less than 0.05 indicate statistical significance. P values that could not be expressed up to three decimal places were expressed as  $P<0.001$ .

### Results

There is a significant substantial agreement between children and dentists in assessing the need for orthodontic treatment (Table 1).

Significant substantial agreement in assessing the need for orthodontic treatment was also found in the analysis according to gender: boys and dentists, girls and dentists (Table 2).

Table 1. The Need for Orthodontic Treatment (AC-IOTN): Assessment by Children and Dentists

Dentist	Children			Total
	No need	Moderate need	Pronounced need	
	N (%)	N (%)	N (%)	
No need	260 (86.7)	7 (2.3)	-	267 (89.0)
Moderate need	2 (0.7)	17(5.7)	-	19 (6.3)
Pronounced need	3 (1.0)	2 (0.7)	9 (3.0)	14 (4.7)
Total	265 (88.3)	26 (8.7)	9 (3.0)	300 (100)
Cohen's Kappa = 0.774; $P<0.001$				

Table 2. The Need for Orthodontic Treatment (AC-IOTN): Assessment by Children and Dentists according to Gender

Dentist		Children			Total
		No need	Moderate need	Pronounced need	
		N (%)	N (%)	N (%)	
Boys	No need	129 (86.0)	7 (4.7)	-	136 (90.7)
	Moderate need	-	8 (5.3)	-	8 (5.3)
	Pronounced need	-	2 (1.3)	4 (2.7)	6 (4.0)
	Total	129 (86.0)	17 (11.3)	4 (2.7)	150 (100)
Cohen's Kappa = 0.774; $P<0.001$					
Girls	No need	131 (87.3)	-	-	131 (87.3)
	Moderate need	2 (1.3)	9 (6.0)	0	11 (7.3)
	Pronounced need	3 (2.0)	-	5 (3.3)	8 (5.3)
	Total	136 (90.7)	9 (6.0)	5 (3.3)	150 (100)
Cohen's Kappa = 0.835; $P<0.001$					

Significant substantial agreement in assessing the need for orthodontic treatment was also found in the analysis according to age: 12-13 year old children and dentists, 14-15 year old children and dentists (Table 3).

Comparing boys and girls, the results show a greater need for orthodontic treatment in boys, but the difference is not statistically significant (Table 4).

Analysis of the need for orthodontic treatment with respect to the age of the children showed a significant difference (Table 4). The need for orthodontic treatment is more pronounced in older children.

### **Acceptance of Orthodontic Treatment by Schoolchildren**

The objectives of this research included determination of quantification and standardization of

orthodontic treatment need, and setting priorities for orthodontic treatment based on examples of similar research studies conducted worldwide (8, 9). Assessment by the dentists showed: 14 boys and 19 girls (according to gender) and seven 12-13 year old children and twenty-six 14-15 year old children (according to age) had a moderate to major need for orthodontic treatment. No significant difference was found in the acceptance of orthodontic treatment according to gender, nor according to age (Table 5).

Regarding their negative view of the treatment, the subjects pointed out the discomfort of wearing of orthodontic appliances for a long time, and their concerns as to the positive outcome of the treatment.

Table 3. The Need for Orthodontic Treatment (AC-IOTN): Assessment by Children and Dentists according to Age

Dentist		Children			Total
		No need N (%)	Moderate need N (%)	Pronounced need N (%)	
Age: 12-13	No need	145 (96.0)	0	0	145 (96.0)
	Moderate need	-	5 (3.3)	-	5 (3.3)
	Pronounced need	-	-	1 (0.7)	1 (0.7)
	Total	145 (96.0)	5 (3.3)	1 (0.7)	151 (100)
	Cohen's Kappa = 1.000; P<0.001				
Age: 14-15	No need	115 (77.2)	7 (4.7)	-	122 (81.9)
	Moderate need	2 (1.3)	12 (8.1)	-	14 (9.4)
	Pronounced need	3 (2.0)	2 (1.3)	8 (5.4)	13 (8.7)
	Total	120 (80.5)	21 (14.1)	8 (5.4)	149 (100)
	Cohen's Kappa=0.709; P<0.001				

Table 4. The Need for Orthodontic Treatment (AC-IOTN) according to Gender and Age: Assessment by Children

Children	Need for orthodontic treatment (AC-IOTN)			Total
	No need N (%)	Moderate need N (%)	Pronounced need N (%)	
Boys	129 (86.0)	17 (11.3)	4 (2.7)	150 (100)
Girls	136 (90.7)	9 (6.0)	5 (3.3)	150 (100)
$\chi^2=2.764$ ; P=0.297; Fisher's Exact test				
Age: 12-13	145 (96.0)	5 (3.3)	1 (0.7)	151 (100)
Age: 14-15	120 (80.5)	21 (14.1)	8 (5.4)	149 (100)
$\chi^2=17.919$ ; P<0.001; Fisher's Exact test				

Table 5. Acceptance of Orthodontic Treatment According to Gender and Age

Children		Acceptance of orthodontic treatment			Total
		Would accept orthodontic treatment	Would not accept orthodontic treatment	No opinion	
		N (%)	N (%)		
Gender	Boys	10 (71.4)	1 (7.1)	3 (21.4)	14
	Girls	16 (84.2)	2 (10.5)	1 (5.3)	19
	$\chi^2=2.003$ ; $p=0.459$ ; Fisher's Exact test				
Age	12-13	6 (85.7)	1 (14.3)	0	7
	14-15	20 (76.9)	2 (7.7)	4 (15.4)	26
	$\chi^2=1.300$ ; $P=0.600$ ; Fisher's Exact test				

## Discussion

This study of the IOTN performed using the AC in two primary schools in the Prozor-Rama Municipality with respect to children aged 12-15 years, showed a very high degree of malocclusions. We also quantified the degree and priority of treatment due to the high percentage of malocclusions. The research results indicate that, out of the total number of subjects (300, 150 boys and 150 girls aged 12-15 years), 33 of them (or 11%) had a moderate or major need for orthodontic treatment. Similar studies performed in this region verified the existence of malocclusions, but did not determine their degree in order to ascertain treatment priorities (11). Using the IOTN, in different countries, different rates of these needs have been determined. In India, Tak M et al. showed that malocclusion and orthodontic treatment need was reported among 33.3% of the study subjects (12). In Europe, in primary school children in Italy, 59.5% had a need for orthodontic treatment (8), whereas 15-26% children aged 12-14 in Great Britain had this need (13), and 28.9% of children aged 8-16 years in Scotland (14). Linder-Aronson et al. conducted a study in Scotland and showed that the prevailing objective and subjective need for treatment varied in the areas studied (14). The highest prevalence of treatment need was found in areas with a large immigrant population. The prevalence of objective need for treatment varied between 23.8% and 28.9%. The subjective need for treatment ranged from 21.6% to 30.3%. A similar study performed in Germany showed that 26.2% of the examined

children had a need for orthodontic treatment (15). Many studies have shown a major discrepancy between the orthodontic treatment need assessed using the Aesthetic Component (AC), due to the fact that a dento-facial anomaly, such as a lack of teeth in the lateral area, does not always have an effect on aesthetics (16, 17, 18). Cai et al. showed that a positive relationship ( $P < 0.001$ ) existed between the young adults' AC and the orthodontist's AC ( $r=0.275$ ) (19). Taibah et al. showed a statistically significant but fair agreement between the clinician's AC and students' AC assessments in different age groups (20). It is noteworthy that no significant differences in the need for orthodontic treatment between males and females were observed in the present study. The differences in assessment of the degree of occlusal anomalies by a doctor of dental medicine are negligible with respect to both boys and girls, and they do not show statistical significance. The negative view of treatment is explained by the discomfort of long-term use of orthodontic appliances, and concerns regarding its positive outcome. In regions without an adequate preventive programme there are a large number of malocclusions in children caused by early loss of either primary or permanent teeth.

In addition, the demand for orthodontic treatment has increased due to increasing awareness and perception, resulting in extensive waiting lists. It is essential, therefore, that orthodontists should carefully prioritize and plan the provision of orthodontic treatment. In comparison to other studies, the results obtained in this study are very similar, although our country ranks quite low in socio-

economic terms. The availability of preventive programs and programs related to oral health care are still not satisfactory. Preventive programmes for early childhood caries are lacking, so this is a direct aetiological factor related to the higher prevalence of orthodontic anomalies (21).

### **Limitations of the Study**

It is important to point out some limitations of this study. The IOTN is basically an epidemiological index that has limitations in assessing the treatment needs of individual patients. The studied indices are epidemiological tools that aim to assess the degree of need for treatment, not to make diagnoses or assist in orthodontic planning.

### **Conclusions**

The IOTN may be adequate for public health planning and epidemiological purposes. On the basis of the results of this research, it may be concluded that there is still high prevalence of occlusal anomalies in the examined region, especially those with a moderate or major need for orthodontic treatment. The need for orthodontic treatment is more pronounced in older children, and there is no difference between boys and girls.

#### **What Is Already Known on this Topic:**

*Professional specialist assessment of malocclusion involves assessing both objective and subjective factors, but the patient's self-perception and aesthetic perceptions cannot be underestimated. Many occlusal indexes have been established to perform such estimations and categorize treatment need severity, such as the occlusal index, treatment priority index, and dental aesthetic index.*

#### **What this Study Adds:**

*A better understanding of patients' perception of their malocclusion severity is an essential step in orthodontic treatment planning. It is necessary to measure their aesthetic self-perception and the degree of acceptance of the treatment. This would give the orthodontist information about the patient's expectations and improve cooperation with patients.*

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### **References**

1. Ciuffolo F, Manzoli L, Attilo M. Prevalence and distribution by gender of occlusal characteristics in a sample of Italia secondary school students: a cross sectional study. *Eur J Orthod.* 2005;27(6):601-6.
2. Warren J, Bishara E. Duration of nutritive and non-nutritive sucking behaviours and their effects on the dental arches in the primary dentition. *Am J Orthod.* 2002;121(4):347-56.
3. Chew T, Aw L. Appropriateness of orthodontic referrals: self-perceived and normative treatment needs of patients referred for orthodontic consultation. *Community Dent Oral Epidemiol.* 2002;30(6):449-50.
4. Alkhatib MN, Bedi R, Foster C, Jopanputra P, Allan S. Ethnic variations in orthodontic treatment need in London schoolchildren. *BMC Oral Health.* 2005;5:8.
5. Reshitaj A, Reshitaj K, Bytyqi B. Assessment of Orthodontic Treatment Need in Kosovar Children. *The Open Public Health Journal.* 2019;12:321-4.
6. Triassi M, Viola P, Angelillo F. The prevalence of malocclusions in schoolchildren in Naples. [in Italian] *Med Prev.* 2003;26:200-8.
7. Trulsson U, Strandmark M, Mohlin B. A qualitative study of teenagers' decisions to undergo orthodontic treatment with fixed appliance. *J Orthod.* 2002;29(3):197-204.
8. Nobile C, Pavia M, Fortunato L, Angelillo F. Prevalence and factors related to malocclusion and orthodontic treatment need in children in Italy. *Eur J Public Health.* 2007;17(6):631-41.
9. Tickle M, Kay J, Bearn D. Socio economic status and orthodontic treatment need. *Community Dent Oral Epidemiol.* 1999;27(6):413-8.
10. Brock H, Shaw W. The development of an index of orthodontic treatment priority. *Eur J Orthod.* 1989;11(3):309-20.
11. Topić B. Primary dental care for children in Bosnia and Herzegovina. [in Croatian] In: Rajić Z, editor. Primary dental care. [in Croatian] Zagreb: JUMENA;1989. p. 109-15.
12. Tak M, Nagarajappa R, Sharda AJ, Asawa K, Tak A, Jalihal S, et al. Prevalence of malocclusion and orthodontic treatment needs among 12-15 years old school children of Udaipur, India. *Eur J Dent.* 2013;7(Suppl 1):S045-53.
13. Tickle M. Improving the oral health of young children through an evidence-based approach. *Community Dent Oral Epidemiol.* 2006;23(1):2-4.
14. Linder S, Bjeehorn K, Forsberg M. Objective and subjective need for orthodontic treatment in Stockholm County. *Swed Dental J.* 2002;26(1):31-40.

15. Tausche L, Luck O, Harzer W. Prevalence of malocclusions in the early mixed dentition and orthodontic treatment need. *Eur J Orthod.* 2004;26(3):237-44.
16. Adullah B, Rock P. Assessment of orthodontic treatment need in 5. 112 Malaysian children using the IOTN and DAI indices. *Community Dent Health.* 2001;18(4):242-8.
17. Gosney MB. An investigation into some of the factors influencing the desire for orthodontic treatment. *Br J Orthod.* 1986;13(2):87-94.
18. Souames M, Bassigny F, Zenati N, Riordan PJ, Boy-Lefevre ML. Orthodontic treatment need in French schoolchildren: an epidemiological study using the Index of Orthodontic Treatment Need. *Eur J Orthod.* 2006;28(6):605-9.
19. Cai Y, Du W, Lin F, Ye S, Ye Y. Agreement of young adults and orthodontists on dental aesthetics & influencing factors of self-perceived aesthetics. *BMC Oral Health.* 2018;18(1):113.
20. Taibah SM, Al-Hummayani FM. Agreement and association between normative and subjective orthodontic treatment need using the Index of Orthodontic Treatment Need. *J Orthod Sci.* 2019;8:1.
21. Zovko R, Cvitanović S, Mabić M, Ćorić A, Vukojević K, Goršeta K, et al. The prevalence of orthodontic treatment needs of school children in northern Herzegovina. *Acta Med Acad.* 2017;46(1):27-33.

## Stereotactic Body Radiation Therapy (SBRT) for Liver Oligometastases: Outcomes and Safety

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### Abstract

**Objective.** The aim of this study was to investigate adverse effects, progression free survival (PFS), one-year local control (LC) and one-year overall survival (OS) of patients with liver oligometastases treated with stereotactic body radiotherapy (SBRT), and whether there was a significant difference in these parameters in patients with primary colorectal cancer compared to other tumor localizations. **Patients and Methods.** Patients were simulated using four-dimensional computed tomography (4DCT). Using volumetric modulated arc therapy (VMAT) technique, SBRT was performed on 16 patients with <3 liver metastases. The prescribed dose was 60 Gy in 8 fractions (BED 105 Gy). Cone beam CT (CBCT) was used for image guidance before each fraction with online correction. **Results.** There were no adverse effects. Median PFS for all patients, patients with primary colorectal cancer, and patients with primary non-colorectal cancer was 11 months (SE 2.1), 16 months (SE 2.8), 6 months (SE 2.4), respectively. There was no significant difference in the PFS for these two observed groups (P=0.09). The one-year LC was 62.5%. Patients with primary colorectal cancer had one-year LC of 87.5%, while the group of patients with primary non-colorectal cancer had one-year LC of 37.5% (P=0.063). The total one-year OS was 87.5%. In the group of patients with primary colorectal cancer, the one-year OS was 100%, while in the group of patients with primary non-colorectal cancer, the one-year OS was 75% (P=0.317). **Conclusion.** SBRT with 8 × 7.5 Gy can be safely delivered and is effective method of treating liver oligometastases.

**Key Words:** SBRT ▪ Liver ▪ Oligometastases.

### Introduction

Metastases in the liver cause significant morbidity, causing pain and anorexia, among others, while significant liver dysfunction worsens general condition of the patient and is one of significant causes of mortality in patients with malignant diseases (1). Liver is one of the most common sites for metastatic spread. The largest number of liver metastases are of colorectal cancer origin (2, 3). Although it is a metastatic disease, if it is limited in number and localization only to the liver, these patients are candidates for local therapy (4, 5). Surgery is the first option for local treatment, with long-term good results in the control of oligometastatic liver disease (6-8). Unfortunately,

only 10-20% of metastases in the liver are resectable, which is why most patients are treated with systemic therapy. Although new combinations of chemotherapeutic agents and targeted drugs lead to better results, they do not do so without significant toxicity. Other methods of local ablative therapies that have shown benefit are stereotactic body radiotherapy (SBRT), radiofrequency and microwave ablation, transarterial chemoembolization, cryoablation and alcohol injection (9-11). Radiotherapy is a proven palliative treatment method, and in patients with painful metastases in the liver, even one fraction of irradiation of the whole liver could achieve a significant reduction in symptoms and lead to improved quality of life in most patients (12, 13).

Due to the low tolerance of the liver parenchyma to radiation and high risk of damage to the healthy liver parenchyma, the standard form of external radiotherapy to a larger volume of liver tissue is not an option for treating liver metastases (RILD, Radiation Induced Liver Damage) (14-16). Technological advances have improved planning systems and imaging methods which made it possible to apply high doses of radiation in a smaller number of fractions to a limited volume in the liver parenchyma while maximally sparing the surrounding healthy parenchyma (17-21). By increasing the dose that can be safely applied to the tumor, the ability to control the tumor also increases. Numerous studies have been investigating the possibilities of application, efficiency and safety of stereotactic radiation of liver metastases.

The aim of this study is to investigate adverse effects, period up to disease progression (PFS, Progression Free Survival), one-year local control (LC) and one-year overall survival (OS) of patients with liver oligometastases treated with SBRT, as well as whether there is a significant difference in these parameters in patients with primary colorectal cancer compared to other tumor localizations.

## Patients and Methods

### Patients

This retrospective study included patients who were treated consecutively in the period from August 2016 to June 2019. Sample size was formed in the way that patients were censored at the time of analysis (June 2020), so each patient had a follow-up time of at least one year. Inclusion factors for SBRT of liver metastases were: liver metastases that were unresectable or medically inoperable due to comorbidities and which were verified by biopsy or CT / MR / PET imaging with an increase in tumor markers, <3 size metastases, size  $\leq 6$  cm, stable primary tumor, good liver function, in good general condition (ECOG 0-2). Exclusion factors were observed and later confirmed, through diagnostic tests, disease progression at the time of CT simulation and crossing the dose constraints on healthy tissues.

### Methods

Patients were simulated using four-dimensional computed tomography (4DCT, GE LightSpeed, 16 slice, slice thickness 1.25 mm) in supine position using abdominal compression (Macromedics), with or without intravenous contrast (22). For more accurate visualization and delineation, available pre-therapeutic diagnostic tests were registered (contrast-enhanced CT, MR, PET/CT). The target volume was contoured at the following phases of 4DCT: fb (free breathing), 0, 50, 90 and Min-IP (Minimal Intensity Projection) in the ARIA radiotherapy system (Varian Medical Systems Inc, Palo Alto, CA, USA), with target volume position check on all available diagnostic and 4DCT simulation images. By combining the contours in the mentioned phases, ITV (Internal Tumor Volume) was defined, which was named iGTV, and then PTV with a margin of 3-5 mm. Organs at risk were contoured according to the RTOG atlas and included: liver (liver contoured on fb series and Avg (Average) series, oesophagus, small intestine, large intestine, stomach, kidneys, spinal cord, spinal cord PRV, ribs and skin.

The prescribed dose was 60 Gy in 8 fractions (7.5 Gy daily; BED 105 Gy,  $\alpha/\beta=10$ ), every other day. Planning was done using the Eclipse planning system, and the Acuros XB algorithm was used to calculate the dose. The two half-arc volumetric modulated arc therapy (VMAT) technique with a treatment couch rotation of  $\pm 10^\circ$  was used (Figure 1). The treatment was performed on a Varian Clinac DHX linear accelerator. Before each fraction, cone beam CT (CBCT) and online verification and correction of the patient's position and metastasis or metastases were performed. Checking the position of the target volume was controlled so that liver contour on the obtained CBCT image overlapped with the liver contour obtained on the Avg series of simulation 4DCT, which was considered a surrogate for the liver position during treatment if metastases were not clearly visible (23, 24).

Patients were monitored prospectively with control laboratory tests (blood count, liver biochemical tests) and radiological imaging. First control laboratory tests were 2 weeks after treat-

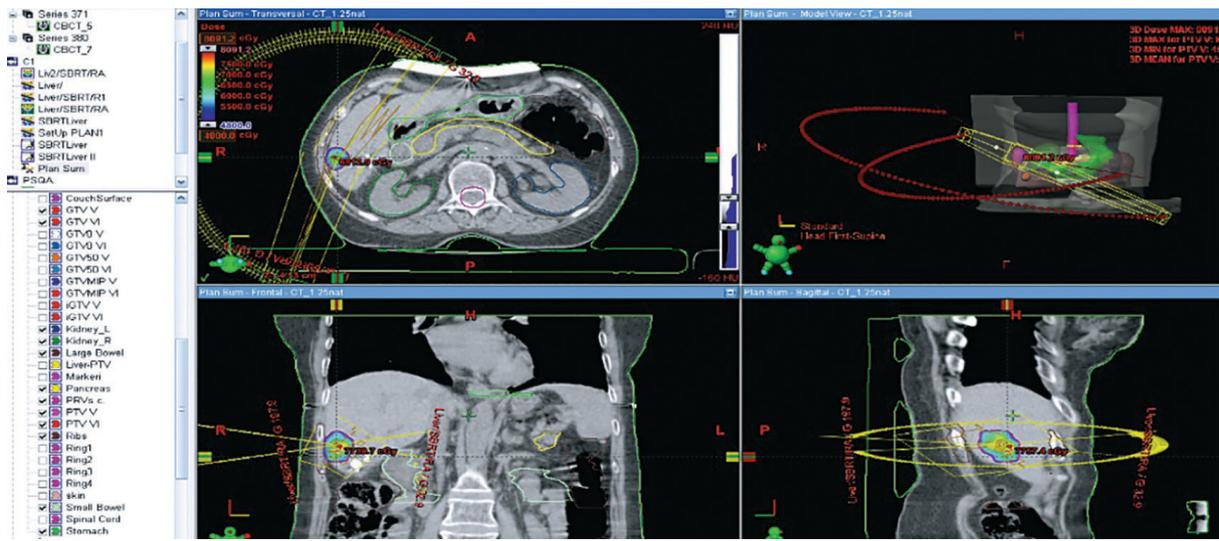


Figure 1. SBRT Plan for Liver Metastasis.

ment and then at quarterly intervals. Radiographic response assessment was performed quarterly according to RECIST 1.1 criteria and was classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). CR is defined as the total radiographic disappearance of all lesions. PR is defined as at least a 30% reduction in the amount of diameter of the target lesions. PD is defined as at least a 20% increase in the diameter of the target lesions. In addition to a relative increase of 20%, the lesion also had to show an absolute increase of at least 5 mm. The appearance of one or more new lesions was also considered progression. SD is defined as neither a sufficient decrease to qualify for PR, nor a sufficient increase to qualify for PD (25).

Progression of the disease is considered to be the progression of the treated lesion, appearance of new metastases in the liver, distant organs and/or in the lymph nodes. One-year local control is met if the treated lesion is without signs of disease progression. Patients were followed for local control for up to a year in case of disease progression which was not a consequence of the progression of the treated lesion. In case the patient dies within one year from the beginning of the treatment, it was considered that the local control was not met. One-year overall survival was measured from the day of commencement of the stereotactic radiotherapy treatment.

### Statistical Analysis

Standard descriptive methods (arithmetic mean with standard deviation, median with standard error, range of numerical feature from minimum to maximum value) were used in statistical data analysis. Survival analysis was performed using the Kaplan-Meier method. Survival curves were compared using the Log Rank test. The difference was considered significant if  $P < 0.05$ . IBM SPSS statistics software (ver. 1.0.0.1406) was used for statistical analysis.

### Results

There were no treatment side effects or changes in blood counts and liver biochemical parameters. Number of eligible patients was 16 (6 male and 10 female patients), none met the criteria for exclusion. The mean age for the 16 patients analysed (Table 1) was 63 years (standard deviation 15.64, minimum 17, maximum 78). The most numerous were the patients with primary colorectal cancer (8 patients). Four patients had primary breast cancer, 2 had primary cancer of the hepatobiliary tract, 1 had primary lung cancer and 1 had hepatocellular carcinoma. The total number of treated metastases was 21. Ten patients received chemotherapy due to liver metastases before treatment with SBRT, while

Table 1. Patients Characteristics

Characteristic	All patients N (%)	Male N (%)	Female N (%)
Number of patients	16	6 (37.5)	10 (62.5)
Age (years)			
<65	7 (43.7)	1 (6.3)	6 (37.5)
≥ 65	9 (56.3)	5 (31.2)	4 (25)
Median age	63 (range 18-78)	73 (range 62–78)	56 (range 18-76)
Primary tumor			
Colorectal cancer	8 (50)	5 (31.2)	3 (18.8)
Breast cancer	4 (25)	-	4 (25)
Lung cancer	1 (6.3)	1 (6.3)	-
Hepatobiliary tract cancer	2 (12.5)	-	2 (12.5)
Primary liver cancer	1 (6.3)	-	1 (6.3)
Number of liver metastases per patient			
One	11 (68.8)	3 (18.8)	8 (50)
Two	5 (31.3)	3 (18.8)	2 (12.5)
Size of the metastases (cm)			
<2	7	-	-
2-4	8	-	-
4-6	6	-	-

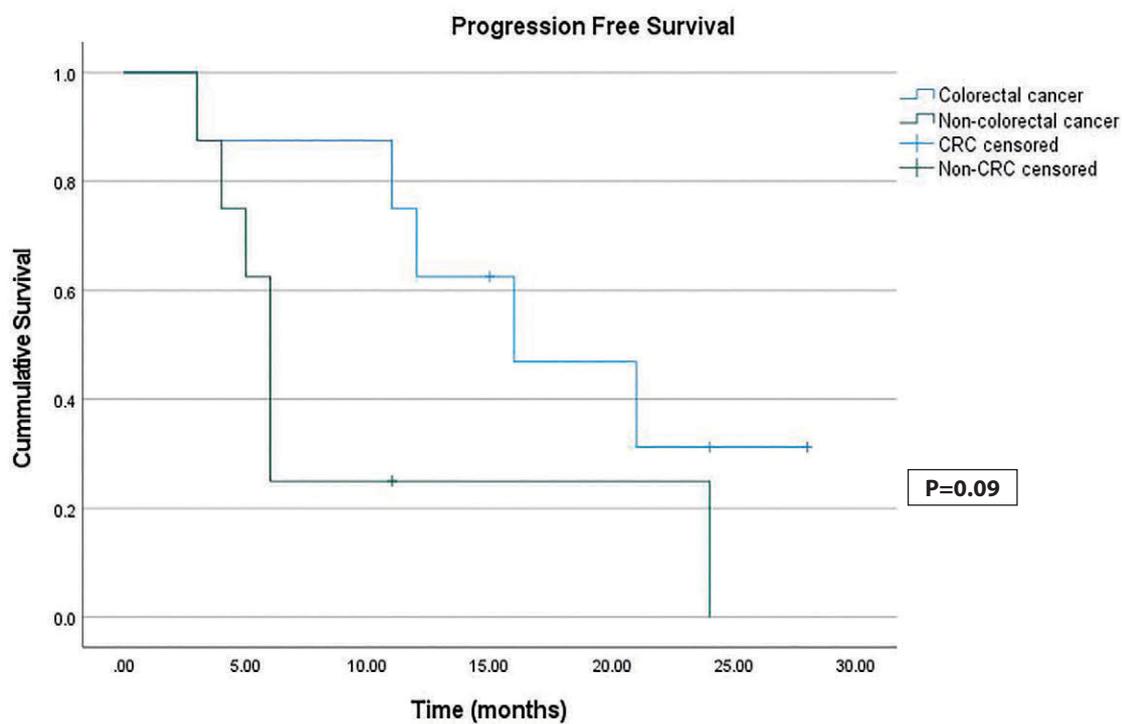


Figure 2. Progression Free Survival (PFS) Plot.

in 6 patients SBRT was the first therapy for oligometastatic liver disease.

The median PFS for all patients was 11 months (standard error 2.1, minimum 3 months, maximum 28 months). In the group of patients with primary colorectal cancer, the median PFS was 16 months (standard error 2.8, minimum 3 months, maximum 28 months). In the group of patients with primary non-colorectal cancer, the median PFS was 6 months (standard error 2.4, minimum 3 months, maximum 24 months). There was no significant difference in the disease progression free survival for these two observed groups ( $P=0.09$ ) (Figure 2). Sample mean follow-up time was 12.2 months (standard deviation 8.3).

The one-year LC was 62.5%. In the group of patients with primary colorectal cancer, the one-year LC was 87.5%, while in the group of patients with primary non-colorectal cancer, the one-year LC was 37.5%. There is no significant difference in one-year LC for patients with colorectal cancer compared to patients with primary tumor of other localizations ( $P=0.063$ ). The total one-year OS was 87.5% (14 of 16 patients). In the group of patients with primary colorectal cancer, the one-year OS was 100%, while in the group of patients with primary non-colorectal cancer, the one-year OS was 75%. There was no significant difference in the one-year OS for these two observed groups ( $P=0.317$ ).

## Discussion

This study investigates the safety and efficacy of SBRT in the treatment of patients with oligometastatic liver disease and it examines whether there is a difference in prognosis if the patient has primary colorectal cancer compared to other primary tumors. Compared to other studies (Rusthoven et al. PFS 6.1 months; Lee et al. PFS 3.9 months, Nicosia et al. PFS 7 months), an enviable median progression free survival has been achieved, especially for the group of patients with colorectal cancer (26-28). Despite not having statistically significant difference in PFS for patients with colorectal cancer compared to other primary tumors ( $P=0.09$ ), dif-

ference in median time until disease progression is clinically significant (16 months vs. 6 months), in favour of patients with primary colorectal cancer.

The achieved one-year LC of 62.5% is slightly lower, while the one-year LC of 87.5% for patients with colorectal cancer is in line with the results of LC from other studies, ranging from 71% to 95% (26, 27, 29-31). This study shows that there is no significant difference in LC in patients with colorectal cancer compared to other histologies (87.5% vs 37.5%,  $P=0.063$ ). An explanation of the results of one-year LC can be found in the prescribed dose and size of treated metastases. The higher the dose, the greater the possibility of LC, as the study by Rule et al. shows that there is a significant difference in the two-year control between 30 Gy in 3 fractions and 60 Gy in 5 fractions (56% vs 100%,  $P=0.009$ ) (32). One-year LC is 94% and 95% for the prescribed doses of 75 Gy in 3 fractions and 60 Gy in 3 fractions (26, 31). Dose escalation in these studies is safe in terms of tolerance and toxicity, if dose volume limits and liver volume are to be spared. According to the study by Rusthoven et al. 100% two-year control was achieved for metastases of size <3 cm, while for metastases >3 cm it was 77% ( $P=0.015$ ) (26). In the group of patients this study analysed, only one third of patients had metastases <2 cm, while other metastases were >2 cm, which potentially affected somewhat lower total LC.

The one-year OS for all patients, patients with colorectal cancer, and patients with other primary tumors is 87.5%, 100%, and 75%, respectively. No significant difference in one-year survival is achieved between the observed groups ( $P=0.317$ ). The results of other studies range from 68.6% to 83.5% (28-31). Rusthoven et al. showed that there was a group of favorable histologies, which included colorectal cancer, breast and kidney cancer, carcinoids, GIST and sarcomas, which had a significantly longer median survival of 32 months compared to other adverse histologies with a median survival of 12 months ( $P=0.001$ ) (26). The difference in PFS and one-year LC shows that in patients with oligometastatic liver disease, primary colorectal cancer has a good prognosis, which is confirmed by the study of Andratschke et al. (29).

The disadvantage of this study is the relatively small number of patients, which led to the formation of a group with combined patients with primary tumors other than colorectal cancer. That prevented individual comparison of outcomes between different primary tumors. The small sample also affected the result of PFS and one-year OS, i.e. the inability to obtain a significant difference between the observed groups.

## Conclusion

In conclusion, patients treated with  $8 \times 7.5$  Gy SBRT experienced no treatment-related adverse effects. This dose-fractionation regime can be effective as a local ablative treatment of oligometastatic liver disease.

### What Is Already Known on this Topic:

*Liver metastases are significant cause of morbidity and mortality in patients with malignant diseases. Most patients are treated with systemic therapy. When these patients are candidates for local therapy, surgery is the first option. Stereotactic body radiotherapy (SBRT) shows benefit in patients who are not surgical candidates.*

### What this Study Adds:

*This study showed that SBRT ( $8 \times 7.5$  Gy) can be safely delivered and have positive effect in the treatment of liver metastases. We evaluated adverse effects, PFS, one-year local control and one-year overall survival of patients with liver oligometastases treated with SBRT. In addition, better prognosis for patients with colorectal cancer is observed.*

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**Conflict of Interest:** The authors declare that they have no conflict of interest.

## References

- Costi R, Leonardi F, Zanoni D, Violi V, Roncoroni L. Palliative care and endstage colorectal cancer management: the surgeon meets the oncologist. *World J Gastroenterol.* 2014;20(24):7602-1. doi:10.3748/wjg.v20.i24.7602
- Kemeny NE, Ron IG. Liver Metastases. *Curr Treat Options Gastroenterol.* 1999;2(1):49-57. doi:10.1007/s11938-999-0018-1
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin.* 2017;67(1):7-30. doi:10.3322/caac.21387
- Weiss L, Grundmann E, Torhorst J, Hartveit F, Moberg I, Eder M, et al. Haematogenous metastatic patterns in colonic carcinoma: an analysis of 1541 necropsies. *J Pathol.* 1986;150(3):195-203. doi:10.1002/path.1711500308
- Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol.* 1995;13(1):8-10. doi:10.1200/JCO.1995.13.1.8
- Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol.* 2013;14(12):1208-15. doi:10.1016/S1470-2045(13)70447-9
- Smith JJ, Angelica D MI. Surgical management of hepatic metastases of colorectal cancer. *Hematol Oncol Clin North Am.* 2015;29(1):61-84. doi:10.1200/JOP.2015.009407
- Tomlinson JS, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol Off J Am Soc Clin Oncol.* 2007;25(29):4575-80. doi:10.1200/JCO.2007.11.0833
- Bekaii-Saab T, Wu C. Seeing the forest through the trees: a systematic review of the safety and efficacy of combination chemotherapies used in the treatment of metastatic colorectal cancer. *Crit Rev Oncol Hematol.* 2014;91(1):9-34. doi:10.1016/j.critrevonc.2014.01.001
- Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg.* 2004;240(4):644-58. doi:10.1097/01.sla.0000141198.92114.f6
- Hellman S, Weichselbaum RR. Importance of local control in an era of systemic therapy. *Nat Clin Pract Oncol.* 2005;2(2):60-1. doi:10.1038/ncponc0075
- Borgelt BB, Gelber R, Brady LW, Griffin T, Hendrickson FR. The palliation of hepatic metastases: results of the radiation therapy oncology group pilot study. *Int J Radiat Oncol Biol Phys.* 1981;7(5):587-91. doi:10.1016/0360-3016(81)90370-9
- Soliman H, Ringash J, Jiang H, Singh K, Kim J, Dinniwell R, et al. Phase II trial of palliative radiotherapy for hepatocellular carcinoma and liver metastases. *J Clin Oncol Off J Am Soc Clin Oncol.* 2013;31(31):3980-6. doi:10.1200/JCO.2013.49.9202
- Pan CC, Kavanagh BD, Dawson LA, Li XA, Das SK, Miften M, et al. Radiation associated liver injury. *Int J Radiat Oncol Biol Phys.* 2010;76(3 Suppl):S94-100. doi:10.1016/j.ijrobp.2009.06.092

15. Lawrence TS, Robertson JM, Anscher MS, Jirtle RL, Ensminger WD, Fajardo LF. Hepatic toxicity resulting from cancer treatment. *Int J Radiat Oncol Biol Phys.* 1995;31(5):1237-48. doi:10.1016/0360-3016(94)00418-K
16. Dawson LA, Normolle D, Balter JM, McGinn CJ, Lawrence TS, Ten Haken RK. Analysis of radiation-induced liver disease using the Lyman NTCP model. *Int J Radiat Oncol Biol Phys.* 2002;53(4):810-21. doi:10.1016/s0360-3016(02)02846-8
17. Kini VR, Vedam SS, Keall PJ, Patil S, Chen C, Mohan R. Patient training in respiratory-gated radiotherapy. *Med Dosim off J am Assoc. Med Dosim.* 2003;28(1):7-11. doi:10.1016/S0958-3947(02)00136-X
18. Brock KK, McShan DL, Ten Haken RK, Hollister SJ, Dawson LA, Balter JM. Inclusion of organ deformation in dose calculations. *Med Phys.* 2003;30(3):290-5. doi:10.1118/1.1539039
19. Dawson LA, Balter JM. Interventions to reduce organ motion effects in radiation delivery. *Semin Radiat Oncol.* 2004;14(1):76-80. doi:10.1053/j.semradonc.2003.10.010
20. Dawson LA, Brock KK, Kazanjian S, Fitch D, McGinn CJ, Lawrence TS, et al. The reproducibility of organ position using active breathing control (ABC) during liver radiotherapy. *Int J Radiat Oncol Biol Phys.* 2001;51(5):1410-21. doi:10.1016/s0360-3016(01)02653-0
21. Hara W, Soltys SG, Gibbs IC. CyberKnife robotic radio-surgery system for tumor treatment. *Expert Rev Anticancer Ther.* 2007;7(11):1507-15. doi:10.1586/14737140.7.11.1507
22. Wunderink W, Méndez Romero A, de Kruijf W, de Boer H, Levendag P, Heijmen B. Reduction of respiratory liver tumor motion by abdominal compression in stereotactic body frame, analyzed by tracking fiducial markers implanted in liver. *Int J Radiat Oncol Biol Phys.* 2008;71(3):907-15. doi:10.1016/j.ijrobp.2008.03.010
23. Case RB, Sonke JJ, Moseley DJ, Kim J, Brock KK, Dawson LA. Inter- and intrafraction variability in liver position in non-breath-hold stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys.* 2009;75(1):302-8. doi:10.1016/j.ijrobp.2009.03.058
24. Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. *Med Phys.* 2010;37(8):4078-101. [published correction appears in *Med Phys* 2012;39(1):563. Dosage error in article text] doi:10.1118/1.3438081
25. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009; 45(2):228-47. doi:10.1016/j.ejca.2008.10.026
26. Rusthoven KE, Kavanagh BD, Cardenas H, Stieber VW, Burri SH, Feigenberg SJ, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J Clin Oncol.* 2009;27(10):1572-8. doi:10.1200/JCO.2008.19.6329
27. Lee MT, Kim JJ, Dinniwell R, Brierley J, Lockwood G, Wong R, et al. Phase I study of individualized stereotactic body radiotherapy of liver metastases. *J Clin Oncol.* 2009;27(10):1585-91. doi:10.1200/JCO.2008.20.0600
28. Nicosia L, Cuccia F, Mazzola R, Figlia V, Giaj-Levra N, Ricchetti F, et al. Stereotactic Body Radiotherapy (SBRT) Can Delay Polymetastatic Conversion in Patients Affected by Liver Oligometastases. *J Cancer Res Clin Oncol.* 2020;10.1007/s00432-020-03223-9. [Online, ahead of print].
29. Andratschke N, Alheid H, Allgäuer M, Becker G, Blanck O, Boda-Heggemann J, et al. The SBRT database initiative of the German Society for Radiation Oncology (DEGRO): patterns of care and outcome analysis of stereotactic body radiotherapy (SBRT) for liver oligometastases in 474 patients with 623 metastases. *BMC Cancer.* 2018;18(1):283. doi:10.1186/s12885-018-4191-2
30. Mahadevan A, Blanck O, Lanciano R, Peddada A, Sundararaman S, D'Ambrosio D, et al. Stereotactic Body Radiotherapy (SBRT) for liver metastasis - clinical outcomes from the international multi-institutional RSSearch® Patient Registry. *Radiat Oncol.* 2018;13(1):26. doi:10.1186/s13014-018-0969-2
31. Scorsetti M, Arcangeli S, Tozzi A, Comito T, Alongi F, Navarra P, et al. Is stereotactic body radiation therapy an attractive option for unresectable liver metastases? A preliminary report from a phase 2 trial. *Int J Radiat Oncol Biol Phys.* 2013;86(2):336-42. doi:10.1016/j.ijrobp.2012.12.021
32. Rule W, Timmerman R, Tong L, Abdulrahman R, Meyer J, Boike T, et al. Phase I dose-escalation study of stereotactic body radiotherapy in patients with hepatic metastases. *Ann Surg Oncol.* 2011;18(4):1081-7. doi:10.1245/s10434-010-1405-5

## Sealing Ability of Mineral Trioxide Aggregate, Biodentine and Glass Ionomer as Root-End Materials: A Question of Choice

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### Abstract

**Objectives.** The goal of this study was to determine the sealing ability of MTA, Biodentine, and Fuji IX as root-end materials after ultrasonic retrograde preparation using a dye penetration method. **Materials and Methods.** Seventy permanent anterior teeth were used in this study. Root canals were prepared using rotary endodontic files, and obturated using the lateral condensation technique. The resection of the root apices was performed perpendicularly to the long axis, and 3 mm deep retrocavities were made by ultrasonic tips. The samples were randomly divided into three experimental groups (N=20) and two control groups (N=5). The root-end cavities were filled with mineral-trioxide aggregate (Rootdent MTA, TehnoDent, Russia) in Group 1, Biodentine (Septodont, Saint Maur des Fossés, France) in Group 2 and Fuji IX GP (GC Corporation, Tokyo, Japan) in Group 3. The retrocavities of the positive control group were left unfilled, while retrocavities in the negative control group were sealed using a flowable composite material. The samples were made transparent, and dye penetration was assessed under a stereomicroscope (x10). The data were analyzed with the Kruskal-Wallis test and the Mann-Whitney U-test. **Results.** The Biodentine group had a lower mean leakage value than the MTA and Fuji IX groups, and the difference was statistically significant ( $P < 0.01$ ). No statistical difference in apical microleakage was found between the MTA and Fuji IX groups ( $P > 0.05$ ). **Conclusion.** Within the limitations of this study, it was concluded that Biodentine provides better sealing ability as a root-end material than MTA and Fuji IX. There was no statistically significant difference between the sealing ability of MTA and Fuji IX as root-end materials.

**Key Words:** Sealing Ability ▪ Root-End Material ▪ MTA, Biodentine ▪ Fuji IX.

### Introduction

Elimination of inflamed and necrotic pulp tissue, and cleaning and shaping root canals with proper obturation are the main purposes of conventional endodontic treatment. Conventional root canal treatment is the first therapeutic choice, since this approach results in a high success rate of up to 86-98% (1). In the case of initial treatment failure, retreatment is indicated. Endodontic surgery becomes the next therapeutic option to save the tooth's biological function (2) only if non-surgical retreatment is impossible or would not achieve a better result (3). Surgical endodontic treatment involves resectioning the root apex, preparation

of the root-end cavity, and forming an apical plug with adequate root-end filling materials.

The choice of the proper material for the retrograde cavity is still an open question in endodontic surgery. The sealing ability of root-end materials is the ability to make intimate contact with the surrounding tissue (4). Microleakage is the constant passage of irritants from the root canal into periapical tissue (and vice versa) through gaps and cracks in the material, or attachment with the surrounding tissues (5). According to Tang et al. (6) sealing ability is a key characteristic of root-end materials that determines the success of periapical surgery.

Mineral Trioxide Aggregate (MTA) has become the gold standard material (7) for retrograde obturation due to its desirable sealing ability, biocompatibility, and potential to stimulate apical tissue regeneration (8). Biodentine (Septodont, Saint Maur des Fossés, France) is a modified formulation of tricalcium silicate cement with similar desirable characteristics as MTA and simplified application (9). The glass ionomer cement Fuji IX (GC Corporation, Tokyo, Japan) has been used as a restorative material because of its ability to form a chemical bond with hard dental tissues, biocompatibility, and antibacterial effects (10). As already mentioned, Fuji IX is restorative material and the manufacturer does not suggest its application as root-end material in the instructions for use. However, findings from previous studies (3, 4, 11), as well as the desirable properties of Fuji IX, initiated interest in evaluating its application in endodontic surgery.

The retrograde cavity preparation technique significantly affects the sealing ability of root-end materials (12). The introduction of ultrasonically driven micro tips to apical surgery improved accessibility to the resected apical part of the root, and enables the preparation of a small, deep, and centrally placed retrocavity (12). This retrograde cavity design favors the marginal adaptation of the root-end filling materials and prevents leakage (13).

This *in vitro* study aimed to determine the sealing ability of MTA, Biodentine, and Fuji IX as root-end materials after ultrasonic retrograde preparation, using a dye penetration method. We hypothesized that there would be no statistical differences in sealing ability between these three root-end materials.

## Materials and Methods

### *Sample Selection*

Seventy extracted single-rooted teeth (maxillary/mandibular incisors and canine), with a fully developed apex, were selected for this study. The teeth were collected from patients of the Department of Oral Surgery, Faculty of Dental Medicine in Sarajevo. Previously endodontically treated teeth, teeth with incomplete root development, and teeth with

obvious fractures, multiple and obliterated canals and root resorption were excluded from the study.

### **Sample Preparation**

After extraction, the samples were immersed in 3% sodium hypochlorite for disinfection and stored until the beginning of the experiment. All debris and deposits were scraped from the sample surface, the samples were sectioned at the gingival part of the root, and the root length was standardized to 18 mm. The three phases of the experimental part were: 1) Root canal instrumentation with obturation; 2) Ultrasonic retropreparation, the application of root-end materials with sample grouping; 3) Clearing technique procedure.

### ***Root Canal Instrumentation with Obturation***

Reamer #15 (VDW GmbH, Munich, Germany) was introduced into the canal for patency determination. The working length was estimated by reamer #15, subtracting one mm from the major apical foramen. According to the manufacturers' instructions, the root canals were instrumented using Mtwo® rotary endodontic files (VDW GmbH, Munich, Germany) with 1.5% sodium hypochlorite irrigation and EDTA lubrication (FileCare® EDTA, VDW GmbH, Munich, Germany). The apical parts of the samples were uniformly enlarged (ISO #40/.04) at 1 mm from the tooth apex. Gutta-percha cones (ISO #40/.04) were coated with AH Plus sealer (Dentsply De Trey GmbH, Germany), fitted to the working length, and the root canals were obturated using the lateral condensation technique. Subsequently, composite resin material (Herculite XRV, Kerr, Germany) was used to seal the coronal surface of the root canals. The samples were stored in saline for one week at room temperature until the sealer setting time had passed.

### ***Ultrasonic Retropreparation and the Application of Root-End Materials***

The apical part of the specimens was resected perpendicular to the longitudinal axis of the tooth, taking care that the resected part was not longer

than 3 mm. Retropreparation was performed using an NSK Variosurg (Ultrasonic Bone Surgery System) with an ultrasonic microtip (MODEL: E32D-S for anterior teeth/90°). The depth of intracanal preparation was also 3mm. A small 0.9 mm diameter round filling condenser was used to check the width of the retropreparation.

### **Sample Grouping**

The samples (N=70) were randomly divided into 3 experimental groups, and two control groups (positive and negative). Twenty samples were used in each experimental group, while the positive and negative groups consisted of 5 samples each.

**Retrograde Cavities in Group 1** were filled with Rootdent MTA (TehnoDent, Belgorod region, Russia). The root-end material was mixed according to the manufacturer's instructions (1 dose-0.25 g of powder with two drops of distilled water), and a paste suitable for manipulation was obtained after 30 to 40 seconds of mixing. The paste was applied into the retrograde cavities with a plastic instrument, and compacted with a ball-ended burnisher (diameter of 0.9 mm). A wet cotton ball was applied to the retrocavity surface to provide a moist environment for the material to set sufficiently.

**The Retrograde Cavities in Group 2** were filled with Biodentine (Septodont, Saint Maur des Fossés, France). The material was mixed according to the manufacturer's instructions: 5 drops of liquid from a single-dose container were added to the powder capsule and mixed mechanically for 30 s at 4500 rpm using an amalgamator. The material was inserted into the retrocavities using a plastic instrument and compacted with a ball-ended burnisher (0.9 mm diameter).

**The Retrograde Cavities in Group 3** were filled with GC Fuji IX (GC Corporation, Tokyo, Japan). The material was mixed according to the manufacturer's instructions: 1 scoop of powder and 1 drop of liquid were mixed until a creamy paste was obtained. Twenty retrograde cavities were filled with this paste using a plastic instrument and a 0.9 mm diameter ball-ended burnisher.

**Positive and Negative Control Groups** The retrocavities of the positive control group were left unfilled. After adhesive procedures were completed, the retrocavities of the negative control group were sealed using a flowable composite material (Tetric® EvoFlow, Ivoclar Vivadent).

### **Clearing Technique Procedure**

The external surface of the samples in the experimental groups and the positive control group were coated with two layers of nail varnish, except apical 3 mm. The samples of the negative control group were wholly isolated, with two layers of nail varnish. After one week of immersion in Indian ink, the nail varnish was scraped from the sample's surfaces. To achieve demineralization, the samples were stored in 5% nitric acid solution for 5 days at room temperature, with daily changes of acid. Increasing concentrations of ethyl alcohol (70%, 95%, 99%) were used for a period of 12 hours to achieve dehydration. The dehydrated samples were placed in methyl salicylate for a period of 24 h to enhance translucency.

### **Evaluation of Apical Microleakage**

The specimens in the experimental groups were analyzed under a stereomicroscope (Novex RZ-series, Euromex microscopes BV, Netherlands) at x10 magnification. Measurement of apical dye leakage was performed with calipers on images captured by a digital camera (Euromex 5.0 Mpx CCD digital camera). The extend of linear dye penetration measured in millimeters was assessed from the root apex to the most prominent coronal point of dye penetration (Figure 1). One sample from each experimental Group 2 (Biodentine) and Group 3 (Fuji IX) was excluded from further analyzes due to extensive leakage and complete dye penetration along the interface of the root canal filling and the root canal walls. In subsequent evaluations, these two experimental groups (Biodentine and Fuji IX) included 19 samples each.

### Ethics Statement

The Ethics Committee at the Faculty of Dentistry with Clinics in Sarajevo approved this research (Approval letter No: 02-3-4-189-10/2014).

### Statistical Analysis

Data were analyzed using the SPSS (Statistical Package for the Social Sciences) version 23. Preliminary analyses were conducted to specify the distribution of the dependent variables. Apical leakage data showed non-parametric distribution. In further analysis, the Kruskal-Wallis test and the Mann-Whitney U-test were used to determine the statistical differences in microleakage between the three experimental groups, at a significance level of 5%.

### Results

All the samples in the positive control group showed maximum values of apical microleakage, but no apical leakage was observed in the negative control group (Figure 1).

The descriptive values of apical microleakage are shown in Table 1. The positive asymmetry of the distributions was confirmed statistically: the values of Skewness and Kurtosis exceeded the values of the corresponding standard errors more than 3 times in each distribution (Table 1). The highest median value of microleakage was determined in the MTA group (Mdn=0.39 mm; value range: 0-2.60 mm), while median values in the Biodentine and Fuji IX groups were zero (Table 1). The Kruskal-Wallis test revealed a statistically

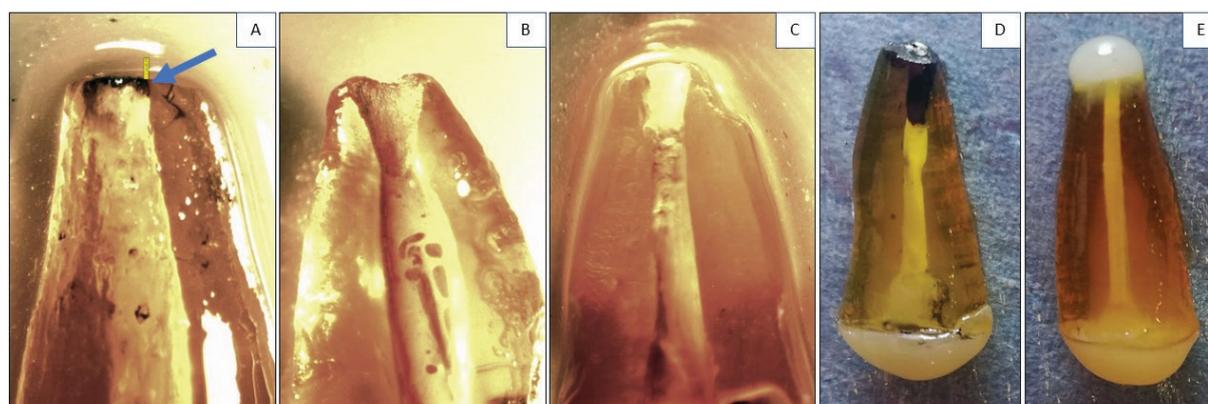


Figure 1. (A) The sample of the MTA group. The arrow shows apical dye leakage on the interface of the root-end materials and the walls of the retrograde cavity. (B) The samples of the Biodentine group and (C) the Fuji IX group, show a complete apical plug where no apical leakage was found. (D) The positive control group revealed maximum leakage, while the negative control group (E) was completely clear, without the evidence of dye penetration.

Table 1. Descriptive Values of Apical Microleakage (mm) for Three Different Types of Root-End Material

Root-end material	N	M	sd	Min	Q1	Med	Q3	Max	Skewness (SE)	Kurtosis (SE)
MTA	20	0.55	0.64	0.00	0.06	0.39	0.70	2.60	2.11 (0.51)	5.15 (0.99)
Biodentin	19	0.08	0.33	0.00	0.00	0.00	0.00	1.46	4.36 (0.52)	19.00 (1.01)
Fuji IX	19	0.41	0.67	0.00	0.00	0.00	0.68	2.34	2.03 (0.52)	3.83 (1.01)

MTA=Mineral trioxide aggregate; N=Sample size; M=Arithmetic mean; SD=Standard deviation; Min=Minimal value in distribution; Q1=First quartile, i.e. 25th percentile of the data; Med=Median, i.e. 50th percentile of the data; Q3=Third quartile, i.e. 75th percentile of the data; Max=Maximal value in distribution; SE=Standard error.

Table 2. Mann-Whitney Test Statistics for Differences in Apical Microleakage Values (mm) between Different Types of Root-Ending Material

Root-end material	Mean range	Mann-Whitney U	Z	P	r
MTA	26.35	63.00	-4.00	0.0001	-0.89
Biodentine	13.32				
MTA	22.08	148.50	-1.21	0.2269	-0.27
Fuji IX	17.82				
Biodentine	16.11	116.00	-2.53	0.0115	-0.58
Fuji IX	22.89				

MTA= Mineral trioxide aggregate.

significant difference in microleakage between the experimental groups  $X^2(2)=14.83$ ,  $P<0.01$ . Additional post hoc analysis (Table 2) showed statistically significant differences in microleakage between Biodentine and MTA (Mann-Whitney  $U=63.00$ ,  $Z=-4.00$ ,  $P<0.01$ ,  $r=-0.89$ ) and Biodentine and Fuji IX (Mann-Whitney  $U=116.00$ ,  $Z=-2.53$ ,  $P=0.01$ ,  $r=-0.58$ ). No statistically significant difference in microleakage was found between MTA and Fuji IX (Mann-Whitney  $U=148.50$ ,  $Z=-1.21$ ,  $P>0.05$ ,  $r=-0.27$ ).

## Discussion

The results of apical microleakage are affected by several factors. Besides the properties of root-end materials and their sealing ability, the methodology of assessment, root canal morphology and the diameter of the root canal may have an influence on the sealing ability results.

Various methods of microleakage evaluation have been used, such as dye penetration, fluid filtration method, bacterial leakage, radioactive isotopes, scanning electron microscopy and others. It is important to emphasize that no standard method of microleakage assessments exists, and there is a lack of technical standardization even when the same methodology is used (14-16). The lack of standardization is probably the main reason why there are so many different methods to study the same phenomenon.

Dye penetration methods are commonly used in the detection of apical leakage. In our research,

the clearing technique was used, primarily due to the possibility of three-dimensional observation of the apical microleakage. It is a simple, inexpensive procedure, on a biological substrate that is not destroyed by the evaluation method itself (14). The application of the clearing technique is based on the possibility of a dye to penetrate voids and cracks formed on the interface between the material and dental tissue. At the end of the clearing procedure, the tooth becomes completely transparent, allowing the precise measurement of the dye penetration inside the root canal in tenths of millimeters (17). The high-resolution images can be acquired and the specimen can be preserved for a long time at different study periods.

Also, the clearing technique has the limitations. When the clearing procedure is not performed correctly (e.g. reduction of demineralization period), the samples are opaque and dye penetration readings are not possible. The entrapped air could block the dye penetration, and applications of different types of dye may change the result (18). This method has been criticized because of its limited clinical relevance, but it is also a proven and efficient method to diagnose and visualize cracks and voids inside root canals (11).

Complete debridement of the root canals with complex root canal morphology is difficult to obtain, and most previous studies have comprised the evaluation of sealing ability on single root canals (19). Maxillary incisors and canines were selected as they have a simple root canal morphology. CBCT evaluations of root canal morphology revealed that 97-100% of maxillary incisors and canines have one root and one canal (20). Compared to maxillary incisors, mandibular incisors have one root (99.92-100%), and more frequently two canals (14.4-20.2%) (20). The mandibular canine has one root (98.57% of samples) and one canal (92.4% of samples) (20).

More interesting is research related to the diameter of the root canal. Wu et al. (21) analyzed root canal diameters at a different distance from the apex, and found that the occurrence of the long oval canal was  $>50\%$  in some tooth groups at 5 mm from the apex. In particular the mandibular

incisors are considerably broader buccolingually than mesiodistally (20), and oval-shaped canals in the apical third were not uncommon (22, 23). NiTi rotary files are less effective in the instrumentation of oval-shaped canals (24) and some root canal surfaces may remain untreated. These are favorable conditions for the accumulation of debris and microorganisms (25), are difficult to clean and shape, and become obturated. Extensive leakage was seen in two samples from the Biodentine and Fuji IX groups. This result might be attributed to the inability of the lateral condensation technique to fill the untreated surfaces of the samples with oval-shaped root canals.

Apical microleakage was observed in all the experimental groups, however the results of this study show the advantage of Biodentine over MTA and Fuji IX in terms of their sealing ability. The results of this study are in agreement with previous studies (26-29). Khandelwal et al. compared the effects of ultrasonic and conventional techniques of retropreparation on the sealing ability of Biodentine and MTA under a confocal laser scanning microscope (26). Biodentine and ultrasonic preparation showed significantly less microleakage than MTA. Naik et al. evaluated the apical seal of mineral trioxide aggregate (MTA) and Biodentine as root-end materials after irrigation with MTAD (a mixture of doxycycline, citric acid and a detergent). Compared to MTA, the apical seal obtained with Biodentine was superior (27). Chakmakchi et al. evaluated the sealing ability of Biodentine, MTA and glass ionomer cement (GIC) using a dye penetration model on longitudinal sections. The results of their study indicated that Biodentine provides a better seal as a retro filling material than MTA and GIC. In agreement with our results, no statistically significant difference in sealing ability was found between MTA and GIC (28). Pathak et al. analyzed the sealing ability of MTA, Biodentine, GIC and IRM using a scanning electron microscope and a stereomicroscope on longitudinal sections (29). It was concluded that Biodentine exhibited better sealing ability compared to MTA, GIC and IRM. In that study, no statistically significant difference between the materials was found,

probably because of the smaller sample size than in the present study.

The better sealing ability of Biodentine may be related to its smaller particle size and low porosity. According to Camilleri et al., Biodentine exhibited a low average pore diameter in a range of 0.01–0.05  $\mu\text{m}$ , and low porosity (30). During hydration reactions, the hydration products fill the gaps between the un-hydrated cement grains (30). These physical properties contribute to better marginal adaptation to the cavity walls and decrease the chances of leakage. The small pore volume of the material allows better penetration into the dentine tubules. The lower sealing ability of MTA may be attributed to its greater particle size (27). This is supported by the findings of Ravichandra et al., who reported that Biodentine showed better marginal adaptation as root-end material than MTA and Glass ionomer cement (31).

In our study, the pre-dose capsule formulation of Biodentine was used. Consequently, variations in water/powder ratio were reduced to a minimum, and a homogeneous consistency was obtained by mixing the material in an amalgamator. However, MTA was mixed manually and, according to the manufacturer's instructions, it was permitted to add more liquid to obtain paste consistency. In this way, the liquid/powder ratio varies in each preparation. Excess water leads to void formation, increases the porosity of the root-end material (30), and affects the sealing ability results. The results of this study may be attributed to the formation of tag-like structures at the material-dentin interface. Biodentine and MTA generated uptake of calcium and silicate ions in the adjacent root canal dentine in the presence of phosphate-buffered saline (32). Formation of tag-like structures alongside an interfacial layer was more prominent in Biodentine than MTA (32, 33). This crystal formation has the potential to increase the sealing ability of Biodentine (34), because apatite crystals fill the gaps along with the interface of the tricalcium silicate cement and root dentin.

Dimensional changes in root-end materials in different environments may affect apical microleakage. In dry conditions, MTA did not show any

dimensional changes, while Biodentine demonstrated shrinkage and crack formation. In wet conditions, Biodentine and MTA showed expansion, but in blood, both materials presented shrinkage through time. Dimensional changes of root-end materials disrupt marginal adaptation and lead to microleakage (35).

At the end of the clearing procedure, it was evident that some root-end materials were lost and missing from the retrograde cavity. Washout is the tendency of freshly prepared cement paste to disintegrate in contact with blood or other fluids. It has been reported that Biodentine has a very high washout tendency (36) and solubility (37). The clearing technique used in this study implies the application of different solutions for several days. This may explain the most frequent loss of retrograde filling from the Biodentine group in our study.

### Limitations of the Study

The limitation of the present study was the evaluation of apical microleakage in *in vitro* conditions for a relatively short period. Nabeel et al. (2019) showed a difference in the leakage values at different time intervals between MTA and Biodentine (38).

### Conclusion

Within the limitation of this study, it was concluded that Biodentine provides better sealing ability as a root-end material, than MTA and Fuji IX. There were no statistically significant differences between the sealing ability of MTA and Fuji IX as root-end materials.

#### What Is Already Known on this Topic:

*The success of endodontic surgery is closely related to the selection of appropriate root-end filling materials. These materials should hermetically seal the retrograde cavity and prevent the passage of microorganisms and/or their toxins through the apical foramen into the periapical tissues, and vice versa. Currently, no root-end filling material has achieved a fluid-tight seal. Therefore, the search for the root-end material of good sealing ability continues.*

#### What this Study Adds:

*Evaluation of the sealing ability of MTA, Biodentine and Fuji IX as root-end materials by the clearing technique was not found in any previous study. The results of this study contribute to knowledge about optimal root-end material in daily practice.*

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**Conflict of Interests:** The authors declare that they have no conflict of interests.

### Reference

1. Tabassum S, Khan FR. Failure of endodontic treatment: The usual suspects. *Eur J Dent.* 2016;10(1):144-7.
2. von Arx T. Apical surgery: A review of current techniques and outcome. *Saudi Dent J.* 2011;23(1):9-15.
3. Siqueira JF Jr, Rôças IN, Abad EC, Castro AJ, Gahyva SM, Favieri A. Ability of three root-end filling materials to prevent bacterial leakage. *J Endod.* 2001;27(11):673-5.
4. De Bruyne MA, De Moor RJ. SEM analysis of the integrity of resected root apices of cadaver and extracted teeth after ultrasonic root-end preparation at different intensities. *Int Endod J.* 2005;38(5):310-9.
5. Mulyar S, Shameem KA, Thankachan RP, Francis PG, Jayapalan CS, Hafiz KA. Microleakage in endodontics. *J Int Oral Health.* 2014;6(6):99-104.
6. Tang JJ, Shen ZS, Qin W, Lin Z. A comparison of the sealing abilities between Biodentine and MTA as root-end filling materials and their effects on bone healing in dogs after periradicular surgery. *J Appl Oral Sci.* 2019;27:e20180693.
7. Solanki NP, Venkappa KK, Shah NC. Biocompatibility and sealing ability of mineral trioxide aggregate and biodentine as root-end filling material: A systematic review. *J Conserv Dent.* 2018;21(1):10-5.
8. Tawil PZ, Duggan DJ, Galicia JC. Mineral trioxide aggregate (MTA): its history, composition, and clinical applications. *Compend Contin Educ Dent.* 2015;36(4):247-52.
9. Kaur M, Singh H, Dhillon JS, Batra M, Saini M. MTA versus Biodentine: Review of Literature with a Comparative Analysis. *J Clin Diagn Res.* 2017;11(8):ZG01-5.
10. Sidhu SK, Nicholson JW. A Review of Glass-Ionomer Cements for Clinical Dentistry. *J Funct Biomater.* 2016;7(3):16.
11. De Bruyne MA, De Moor RJ. Influence of cracks on leakage and obturation efficiency of root-end filling materials after ultrasonic preparation: an *in vitro* evaluation. *Quintessence Int.* 2008;39(8):685-92.

12. Premjith, Shetty D, Kailar A, Pare S, Kumar P, Ragher M. The effect of root end cavity preparation using Er,Cr:YSGG laser, ultrasonic retrotip, and bur on the apical microleakage of retrograde cavity filled with MTA Plus. *J Pharm Bioall Sci.* 2020;12(Suppl 1):299-303.
13. Kadić S, Baraba A, Miletić I, Ionescu A, Brambilla E, Ivanišević Malčić A, et al. Push-out bond strength of three different calcium silicate-based root-end filling materials after ultrasonic retrograde cavity preparation. *Clin Oral Investig.* 2018;22(3):1559-65.
14. Jafari F, Jafari S. Importance and methodologies of endodontic microleakage studies: A systematic review. *J Clin Exp Dent.* 2017;1;9(6):e812-9.
15. Celikten B, Uzuntas CF, Orhan AI, Tufenkci P, Misirli M, Demiralp KO, et al. Micro-CT assessment of the sealing ability of three root canal filling techniques. *J Oral Sci.* 2015;57(4):361-6.
16. Veríssimo DM, do Vale MS. Methodologies for assessment of apical and coronal leakage of endodontic filling materials: a critical review. *J Oral Sci.* 2006;48(3):93-8.
17. Reddy A, Garg G, Janardhanan S, Uthappa R, Arora S, Singh NK. An In Vitro Evaluation of Apical Leakage in Gutta-percha/ AH Plus and Resilon/Epiphany-filled Root Canals Using Two Dye Penetration Techniques. *J Contemp Dent Pract.* 2019;1;20(2):152-7.
18. Schäfer E, Olthoff G. Effect of three different sealers on the sealing ability of both thermafil obturators and cold laterally compacted Gutta-Percha. *J Endod.* 2002;28(9):638-42.
19. Long W, Li J, Liu Y, Jiang H. Effect of obturation technique with immediate and delayed post space preparation on apical voids and bond strength of apical gutta-percha. *J Int Med Res.* 2019;47(1):470-80.
20. Versiani MA, Basrani B, Sousa-Neto MD, editors. *The Root Canal Anatomy in Permanent Dentition.* 1st ed. Cham: Springer International Publishing; 2019.
21. Wu MK, Rörös A, Barkis D, Wesselink PR. Prevalence and extent of long oval canals in the apical third. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2000;89(6):739-43.
22. Almeida MM, Bernardineli N, Ordinola-Zapata R, Villas-Boas MH, Amoroso-Silva PA, Brandão CG, et al. Micro-computed tomography analysis of the root canal anatomy and prevalence of oval canals in mandibular incisors. *J Endod.* 2013;39(12):1529-33.
23. Shemesh A, Kavalerchik E, Levin A, Ben Itzhak J, Levinson O, Lvovsky A, et al. Root Canal Morphology Evaluation of Central and Lateral Mandibular Incisors Using Cone-beam Computed Tomography in an Israeli Population. *J Endod.* 2018;44(1):51-5.
24. Helvacioğlu-Yigit D, Orucoglu H, Yavuz T, Yavuz CI, Yılmaz A, Kaba YN, et al. An evaluation of the apical seal in oval-shaped root canals prepared with either self-adjusting files or protaper files. *Cumhuriyet Dent J.* 2014;17(2):109-16.
25. Espir CG, Nascimento-Mendes CA, Guerreiro-Tanomaru JM, Cavenago BC, Hungaro Duarte MA, Tanomaru-Filho M. Shaping ability of rotary or reciprocating systems for oval root canal preparation: a micro-computed tomography study. *Clin Oral Investig.* 2018;22(9):3189-94.
26. Khandelwal A, Karthik J, Nadig RR, Jain A. Sealing ability of mineral trioxide aggregate and Biodentine as root end filling material, using two different retro preparation techniques-An in vitro study. *Int J Contemp Dent Med Rev.* 2015;2015:150115.
27. Naik MM, de Ataide Ide N, Fernandes M, Lambor R. Assessment of apical seal obtained after irrigation of root end cavity with MTAD followed by subsequent retrofilling with MTA and Biodentine: An in vitro study. *J Conserv Dent.* 2015;18(2):132-5.
28. Chakmakchi MN, Yahya MM, AL-Ashou WM. Sealing Ability of Biodentine as a Retrograde Filling Materials (A Comparative in vitro study). *Al-Rafidain Dent J.* 2013;14(3):357-61.
29. Pathak S. Comparative Evaluation of Sealing Ability of Root End Filling Materials: An In-Vitro Study. *Int J Dent Med Res.* 2015;1(5):48-52.
30. Camilleri J, Grech L, Galea K, Keir D, Fenech M, Formosa L et al. Porosity and root dentine to material interface assessment of calcium silicate-based root-end filling materials. *Clin Oral Investig.* 2014;18(5):1437-46.
31. Ravichandra P V, Vemisetty H, Deepthi K, Reddy JS, Remkiran D, Krishna JNM, et al. Comparative Evaluation of Marginal Adaptation of Biodentine™ and Other Commonly Used Root End Filling Materials-An Invitro Study. *J Clin Diagn Res.* 2014;8(3):243-5.
32. Han L, Okiji T. Uptake of calcium and silicon released from calcium silicate-based endodontic materials into root canal dentine. *Int Endod J.* 2011;44(12):1081-7.
33. Atmeh AR, Chong EZ, Richard G, Festy F, Watson TF. Dentine-cement interfacial interaction: calcium silicates and polyalkenoates. *J Dent Res.* 2012;91(5):454-59.
34. Malkondu Ö, Karapinar Kazandağ M, Kazazoğlu E. A review on biodentine, a contemporary dentine replacement and repair material. *Biomed Res Int.* 2014;2014:160951.
35. Aksel H, Küçükkaya Eren S, Askerbeyli Örs S, Karaismailoğlu E. Surface and vertical dimensional changes of mineral trioxide aggregate and biodentine in different environmental conditions. *J Appl Oral Sci.* 2018;27:e20180093.
36. Grech L, Mallia B, Camilleri J. Investigation of the physical properties of tricalcium silicate cement-based root-end filling materials. *Dent Mater.* 2013;29(2):e20-8.
37. Singh S, Podar R, Dadu S, Kulkarni G, Purba R. Solubility of a new calcium silicate-based root-end filling material. *J Conserv Dent.* 2015;18(2):149-53.
38. Nabeel M, Tawfik HM, Abu-Seida AMA, Elgendy AA. Sealing ability of Biodentine versus ProRoot mineral trioxide aggregate as root-end filling materials. *Saudi Dent J.* 2019;31(1):16-22.

## Complementary and Alternative Medicine Use Among Croatian Health Studies Students – A Single Center Cross-Sectional Study

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### Abstract

**Objective.** The use of complementary and alternative medicine (CAM) among healthy population and in patients with certain health conditions has been investigated in Croatia; however, no studies have been carried out among health studies students and professionals. The aim of the study was to measure the extent of CAM use among health studies students. **Materials and Methods.** An online survey was used to question students enrolled at the Faculty of Health Studies, University of Rijeka, Croatia. The questionnaire entailed several parts, including sociodemographic data, frequency of use of 31 CAM methods, the source of obtaining CAM information, as well as the main reason for using CAM. **Results.** Seven hundred and twenty-three students were invited to take part in the survey, of whom 207 (29%) responded, mostly females (N=172; 83.1%). The median age of the respondents was 22 years. More than half of the respondents (N=113; 54.6%) were employed. The most used CAM methods were natural products, such as vitamins and minerals (93.2%), probiotics (80.7%) and herbs (78.3%). The most used mind and body practices were massages (76.3%), deep breathing (61.4%), and spirituality and prayer (56%). The main source of information on CAM was the Internet (N=151; 72.9%). Maintenance/improvement of health was the most common reason for using CAM (49.3%). **Conclusion.** The findings in this study suggest that the most used CAM methods among students were similar to general population; moreover, information about CAM is mostly derived from the Internet.

**Key Words:** Complementary Therapies ▪ Students ▪ Health Occupations ▪ Usage.

### Introduction

Complementary and alternative medicine (CAM) is not easy to define, as it implements a wide spectrum of therapies and medication (1-6). CAM includes two terms: “complementary medicine”, which refers to the treatment procedures used in addition to conventional medicine, and “alternative medicine”, which refers to treatments used instead of conventional medical treatments (2, 6). The use of CAM is becoming increasingly popular all around the world, both in developed and developing countries (3-6). The National Center

for Complementary and Integrative Health (NCCIH) is the leading agency in the USA for scientific research on the variety of medical and health systems, practices and products that are not part of conventional medicine. According to the NCCIH, the term “alternative health approaches” should be used instead of the term “alternative medicine”, and “complementary health approaches” instead of “complementary medicine”. However, the definition of the two terms remains the same: using unconventional products or practices with, or instead of conventional medicine products or practices (1, 3).

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According to the NCCIH, CAM, or complementary health approaches, are classified into three groups (1, 4): (a) natural products: herbs (also known as botanicals), vitamins and minerals, probiotics, special diets, other nutritional supplements; (b) mind and body practices such as guided imagery, hypnotherapy, meditation, deep breathing exercises, progressive muscle relaxation, acupuncture, Tai Chi, Reiki, Qi Gong, Yoga, chiropractic manipulation, osteopathy, massage, reflexology, movement therapies, etc. and (c) other complementary health approaches: traditional healers, Ayurvedic medicine, traditional Chinese medicine, naturopathy, homeopathy and functional medicine (1, 4).

According to Clarke et al. (7) more than 30% of adults in the USA used some sort of complementary health approach in 2012; furthermore, Kempainen et al. found that 25.9% of the general population in Europe used some sort of CAM methods during a 12-month period (8). Most research on the knowledge, attitude, and the use of CAM among medical and health studies students has been conducted in Asia, Africa, and the USA (3-5, 9-12). The results of these studies showed that the use of herbal medicine/supplements (9-11), meditation/Yoga/relaxation/imagery, massage (10), spirituality and prayer (4, 10) have been found to be very popular. In their study Saha et al. (3) reported that homeopathy was mostly used by pharmacy students. *Kampo* (Japanese traditional medicine) was most practised among Japanese dental students (12). The most common sources of information on CAM among many students are the Internet (3, 10, 11), the media (TV, journals) (4, 9, 10, 11), books (3, 4, 9, 10) along with faculty (9), family and friends (3, 5, 9, 11).

Croatia's health care insurance is mandatory for all employed citizens. Retired and people with low income are also insured. Most of CAM practices are not covered by in the standard insurance. However, acupuncture treatment and biofeedback are covered by the Croatian basic health insurance and may only be performed by licensed physicians (13). According to the WHO, 103 member states have authorised acupuncture treatment, out of which 18 of them have included it in their health care insurance system (14).

The use of CAM in healthy population and in patients with certain health conditions has been investigated in Croatia (15-17). The attitudes of 325 Croatian health workers were investigated and physicians had a more negative attitude towards CAM than nurses, technicians, and physical therapists (18). However, to our knowledge, the use of CAM has not been conducted with health studies students and practitioners.

The aim of this study was to examine the use of CAM among students at the Faculty of Health Studies. We investigated the frequency of use of various CAM methods, the main reasons for using CAM, and sources of information concerning CAM.

## Materials and Methods

### *Study Design and Setting*

A cross-sectional study was conducted with students from the Faculty of Health Studies (FZSRI) at the University of Rijeka, Croatia. Participation in the survey was voluntary and anonymous. All research participants were informed about the research purpose, voluntary consent, confidentiality of the data insurance, as well as the protection of the participants' identity and information use. Informed consent was given by the participants.

### *Participants*

A total of 723 students from the Faculty of Health Studies in Rijeka, Croatia were included (academic year 2018/2019). Undergraduate physiotherapy, nursing, midwifery and radiology technology students, along with graduate physiotherapy, nursing - health management and mental health promotion, clinical nutrition and physiotherapy bridging programme students were included.

### *Complementary and Alternative Medicine Use Questionnaire (CAMUQ)*

A questionnaire entitled "Complementary and Alternative Medicine Use Questionnaire" (CAMUQ) was designed, which included questions on sociodemographic data, frequency and reasons for CAM use, and sources of information on CAM.

The first part of the questionnaire (8 questions) related to participants' sociodemographic data, including gender and age of the respondents, year of study at FZSRI, employment and workplace. The second part (3 questions) examined the frequency in which 31 CAM methods had been used in the past year on a scale ranging from never (0), rarely (1-2x/year), periodically (3-4x/year), often (1-2x/month) to very often (1 or more times/week). CAM methods were divided into 3 large groups: natural products (5 methods), mind-body practices (21 methods) and other complementary approaches (5 methods). Finally, the last part of the CAMUQ examined the sources of information on CAM and the main reasons for using CAM (closed-ended questions - YES / NO).

### Procedure

The CAMUQ was distributed through the free Google Form application. The invitation to participate in the study and link to the questionnaire was distributed online via e-mail and the social network *Facebook*. Data were collected on three occasions over a period of two months (from the 28<sup>th</sup> November, 2018 until the 27<sup>th</sup> January, 2019).

### Ethics Statement

This research was conducted in accordance with the fundamental ethical and bioethical principles and in accordance with the most recent revision of the Declaration of Helsinki and was approved by the Ethical Committee at the University of Rijeka, Faculty of Health Studies (Number of approval: Class: 602-01/18-01/55; Registration number: 2170-15-18-1).

### Statistical Analysis

Categorical data is presented with frequency (N) and relative frequency (%) (19). Difference in proportions was calculated with a test of proportions ("N-1" Chi-squared test). Quantitative data is presented with appropriate mean and variability measures depending on the type of distribution (tested with the Kolmogorov-Smirnov test). All findings with a  $P < 0.05$  level were considered statistically

significant. The collected data was exported from Google Form application, recorded in spreadsheets formatted in MS Excel (Microsoft Corporation, USA), and statistically processed in MedCalc 19.17.7 (MedCalc Software, Ostend, Belgium).

## Results

### Response Rate

A total of 207 students participated in this research, which represents an average response rate of 29% (Supplement 1). The highest response rates were recorded from physiotherapy graduate students (44.1%) and undergraduate midwifery students (37.5%). The lowest response was observed among nursing - health management graduate students (12.7%).

Table 1. Participants' Characteristics

Variable	N (%)
<b>Gender</b>	
Females	172 (83.1)
Males	34 (16.4)
Missing	1 (0.5)
Total	207 (100)
<b>Year of study</b>	
1 <sup>st</sup> year of Undergraduate Study	63 (30.4)
2 <sup>nd</sup> year of Undergraduate Study	38 (18.4)
3 <sup>rd</sup> year of Undergraduate Study	42 (20.3)
1 <sup>st</sup> year of Graduate Study	31 (15.0)
2 <sup>nd</sup> year of Graduate Study	25 (12.1)
Bridging programme	8 (3.9)
Total	207(100)
<b>Working place</b>	
Primary health care	12 (10.6)
General / County Hospital	8 (7.1)
Special hospital	13 (11.5)
Clinical Hospital Centre	34 (30.1)
Private practice	13 (11.5)
Other	33 (29.2)
Total	113 (100)

### Participants' Characteristics

Out of 207 respondents, 172 were female (83.1%), 34 were male (16.4%), while one participant failed to complete this category (0.5%). The average

mean age of the respondents was 22 years (ranging from 18-58 years of age). Most of the respondents (N=63, 30.4%) were first year students of an undergraduate study programme, and the smallest number of respondents (N=8; 3.9%) attended the bridging programme (Supplement 1).

More than half (N=113; 54.6%) of the respondents were employed (Table 1). Of those employed, 100 (88.5%) of them worked in their field of expertise. Most of them were employed in clinical hospital centers (N=34; 30.1%); the fewest number worked in general/county hospitals.

### Complementary and Alternative Medicine Use

The results of the use of natural products are presented in Table 2. The most used natural products were vitamins and minerals (N=48; 23.2%). More than half of the respondents (N=128; 61.8%) had never used special diet methods. Herbs were occasionally used by a quarter of the respondents (N=54; 26.1%).

Concerning mind and body practices, 5 (2.4%) respondents stated that they had used the Qi Gong method. Furthermore, 35 (16.9%) respondents revealed that they used spirituality and prayer very often, 26 (12.6%) did deep breathing exercises very often, and 39 of them (18.8%) often got massages (Table 3).

Table 2. Frequency of Use of Natural Products

Natural products	Frequency of use N (%)				
	Never	Rarely*	Periodically <sup>†</sup>	Often <sup>‡</sup>	Very often <sup>§</sup>
Herbs	45 (21.7)	63 (30.4)	54 (26.1)	28 (13.5)	17 (8.2)
Vitamins and minerals	14 (6.8)	64 (30.9)	43 (20.8)	38 (18.4)	48 (23.2)
Probiotics	40 (19.3)	67 (32.4)	49 (23.7)	33 (15.9)	18 (8.7)
Other nutritional supplements	62 (30)	70 (33.8)	37 (17.9)	16 (7.7)	22 (10.6)
Special diets	128 (61.8)	53 (25.6)	13 (6.3)	4 (1.9)	9 (4.3)

\*1-2x/year; <sup>†</sup>3-4x/year; <sup>‡</sup>1-2x/month; <sup>§</sup>1 or more times/week.

Table 3. Frequency of Use of Mind and Body Practices

Mind and body practices	Frequency of use N (%)				
	Never	Rarely*	Periodically <sup>†</sup>	Often <sup>‡</sup>	Very often <sup>§</sup>
Biofeedback	169 (81.6)	22 (10.6)	8 (3.9)	4 (1.9)	4 (1.9)
Guided imagery	179 (86.5)	14 (6.8)	8 (3.9)	1 (0.5)	5 (2.4)
Hypnotherapy	200 (96.6)	5 (2.4)	2 (1.0)	0	0
Meditation	140 (67.6)	32 (15.5)	15 (7.2)	11 (5.3)	9 (4.3)
Deep breathing exercises	80 (38.6)	53 (25.6)	36 (17.4)	12 (5.8)	26 (12.6)
Spirituality and prayer	91 (44)	43 (20.8)	14 (6.8)	24 (11.6)	35 (16.9)
Expressive art therapies	174 (84.1)	21 (10.1)	6 (2.9)	4 (1.9)	2 (1)
Progressive muscle relaxation	144 (69.6)	29 (14)	20 (9.7)	10 (4.8)	4 (1.9)
Yoga	148 (71.5)	29 (14)	9 (4.3)	11 (5.3)	10 (4.8)
Tai-chi	192 (92.8)	12 (5.8)	2 (1)	1 (0.5)	0 (0)
Chiropractic	174 (84.1)	20 (9.7)	9 (4.3)	3 (1.4)	1 (0.5)
Osteopathy	192 (92.8)	7 (3.4)	3 (1.4)	2 (1)	3 (1.4)
Massage	49 (23.7)	73 (35.3)	33 (15.9)	39 (18.8)	13 (6.3)
Movement Therapies	153 (73.9)	21 (10.1)	13 (6.3)	7 (3.4)	13 (6.3)
Needle acupuncture	186 (89.9)	12 (5.8)	5 (2.4)	2 (1)	2 (1)
Reflexology	179 (86.5)	19 (9.2)	4 (1.9)	3 (1.4)	2 (1)
Reiki	199 (96.1)	6 (2.9)	1 (0.5)	0 (0)	1 (0.5)
Qi Gong	202 (97.6)	4 (1.9)	0 (0)	0 (0)	1 (0.5)
Touch healing	197 (95.2)	6 (2.9)	2 (1)	1 (0.5)	1 (0.5)
Electromagnetic therapy	175 (84.5)	21 (10.1)	6 (2.9)	2 (1)	3 (1.4)
Aromatherapy	130 (62.8)	44 (21.3)	20 (9.7)	6 (2.9)	7 (3.4)

\*1-2x/year; <sup>†</sup>3-4x/year; <sup>‡</sup>1-2x/month; <sup>§</sup>1 or more times/week.

Other complementary health approaches were generally rarely used by respondents (Supplement 2). Out of 207 respondents, 201 (97.1%) had never used traditional healers' services. Furthermore, traditional Chinese medicine and homeopathy were used very often by only two respondents (1.0%).

### Sources of Information and Reasons for Using CAM

Most of the respondents received information on CAM via the Internet (N=151; 72.9%), and a smaller proportion of respondents (N=12; 5.8%) through formal education. All differences were significant for individual sources ( $P < 0.001$ ) (Table 4).

The most common reason for using CAM (Table 5) for most participants was maintaining/improving health (N=102; 49.3%), while the least common reason (N=6; 2.9%) was relief of symp-

toms caused by allergies. Forty-six respondents (22.2%) stated that they had not used CAM.

### Discussion

The results of this study are new for the South European region and give an insight in the most used CAM methods among health sciences students. Our participants used natural products, massages, deep breathing exercises, and spirituality and prayer the most. Regarding the type of natural products used, the majority of respondents (93.2%) used vitamins and minerals, 80.7% used probiotics, while herbs were consumed by 78.3% of the respondents. In the study carried out by Ameade et al. (9), 117 (57.6%) out of 203 medical students in Ghana used CAM, and most of them used herbal medicines. Furthermore, James and Bah (4) showed that among 90 undergraduate pharmacy students from University of Sierra Leone, herbals/botanicals/supplements were the most frequently used CAM modalities (N=63; 70%). Research related to the mind and body practices varies depending on the practice itself. According to the results of National Health Survey conducted in the USA in 2012 (7), the most popular CAM methods used by adults included deep breathing exercises, Yoga, Tai Chi and Qi Gong, chiropractic or osteopathic manipulation, as well as meditation. Kemppainen et al.'s (8) study showed that the most frequently used CAM treatments among the general population in Europe were massages, homeopathy, osteopathy, herbal treatments, acupuncture, chiropractic, reflexology and spiritual healing. Kemppainen et al.'s findings indicated that CAM is commonly used for health-related problems; moreover, it was typically used in a complementary way.

This study revealed that respondents were either not familiar with, or rarely practiced most of the suggested mind and body practices. The most used practices included massages, which were used by 76.3% of the subjects, followed by deep breathing exercises (61.4%), and spirituality and prayer (56%). A study by Kanadiya et al. (10) examined the attitudes and use of CAM among

Table 4. Information Sources on Complementary and Alternative Medicine (N=207)

Sources of information about CAM	Yes; N (%)	No; N (%)	P*
The Internet	151 (72.9)	56 (27.1)	<0.001
The media (TV, radio, journals)	64 (30.9)	143 (69.1)	<0.001
Professional literature	50 (24.2)	157 (75.8)	<0.001
Health professionals	61 (29.5)	146 (70.5)	<0.001
Faculty	55 (26.6)	152 (73.4)	<0.001
Formal education beyond study	195 (94.2)	12 (5.8)	<0.001
Family/friends	73 (35.3)	134 (64.7)	<0.001
Other	34 (16.4)	173 (83.6)	<0.001

\*"N-1" Chi-squared test.

Table 5. Reasons for Using Complementary and Alternative Medicine.

Main reason for using CAM	N (%)
I do not use CAM methods	46 (22.2)
Maintaining/improving health	102 (49.3)
Mitigating psychological problems	13 (6.3)
Mitigating the side effects of conventional medicine	8 (3.9)
Other	18 (8.7)
To relieve symptoms caused by allergies	6 (2.9)
Treatment of chronic pain	14 (6.8)
Total	207 (100)

635 osteopathic medical students. The most used CAM methods were meditation/Yoga/relaxation/imagery, massages, and spirituality/prayer (10). Moreover, spirituality/prayer followed by massage therapy were often used by pharmacy students in a study by James and Bah (4).

Other complementary health approaches, such as the preference for traditional healers, traditional Chinese medicine and naturopathy were never used by most of the respondents in this study. Homeopathy was used by 14.5% of respondents, while Ayurveda by 8.2%. This result can be explained by the increasing influence of Eastern practices, methods and philosophies, along with other complementary methods among the Western society, all with the purpose of maintaining or improving mental and physical health. In a cross-sectional study by Saha et al. (3) on the knowledge, attitude, perception and use of CAM among Bangladesh pharmacy undergraduate students (N=250), researchers found that homeopathy (59%), Ayurveda (30%) and meditation were commonly practiced (29%). Given that the research by Saha et al. was conducted in a South Asian country, where these approaches are part of the culture and civilization, the difference with our European sample was expected. Homeopathy seems to be a popular complementary approach in Europe as well. Specifically, 5.7% of the respondents confirmed using this method (8).

Internet was the main source of information on CAM for the majority of our respondents (73%), while only 6% received information through formal education on CAM outside their studies. Furthermore, 73% of respondents stated that they had not received information on CAM during their studies, and among 71% of respondents, information on CAM was not provided by the healthcare professionals. These results could suggest a potential need for CAM implementation in health studies curricula. In other studies, students reported the Internet (10), media (4, 9) and family and friends (3, 5, 9, 11) as the main source of information on CAM. Certain CAM methods are part of Asian culture; however they are not widely implemented in the standard curriculum. Arai, Nakada and Izumi (20) investigated the use of and

the involvement of traditional Japanese medicine (Kampo) during and after medical residency in Japan. One fifth of the hospitals they investigated taught Kampo medicine, and this mostly referred to hospitals with 50 or more residents. Great majority of the residents (96%, N=93) believed that traditional Japanese medicine has its' place in hospitals and 73% of them considered that it should be introduced into the curricula (20). India has 57 traditional medicine universities and a number of research councils, where traditional medicine is studied and practiced (21). Then as well, the South Korea has established 12 universities, and a number of research councils in which traditional Korean medicine is studied and CAM treatment sponsored by the government (21). Along with the traditional Chinese medicine taught and practiced in medical institutions in China, western medicine and CAM are gaining more and more attention in their education curricula (14).

Maintaining or improving health was the main reason for using CAM according to nearly half (49%) of our respondents. The reasons for using CAM in other studies are diverse. For example, health care was the main reason for using CAM among osteopathy students in the study carried out by Kanadiya et al. (10), while Iranian medical students specified neuromuscular disorders and back pain as the main reason for CAM use (11). In the study conducted by Saha et al., respondents mostly used CAM to relieve cases of the common cold and flu (3).

A possible limitation of this research is a relatively small response rate. However, given that the survey questionnaire was conducted online, this response rate was expected and appropriate. Our sample was gender skewed as we had more female participants. Also, we did not test the participants' knowledge on CAM, but we believe that their usage presumes some pre-knowledge on the subject. Investigating the Internet sources on CAM should have been tested in more detail. It would be interesting to examine the stance on CAM, as well as the readiness to use it, among practitioners of various other health professions, such as medicine, dental medicine, medical biochemistry and pharmacy.

## Conclusion

Our research showed that Croatian health studies students who participated in this study used a variety of CAM methods, including natural products, massage, deep breathing exercises, and spirituality and prayer. Maintaining and improving health was the main reason for using CAM, while the main source of information on the topic was the Internet. Considering that most of the respondents had not received information on CAM at the faculty or from healthcare professionals, implementation of CAM courses in the study curriculum should be evaluated.

### What Is Already Known on this Topic:

*Complementary and alternative medicine (CAM) includes the term "complementary medicine", which refers to the treatment procedures used in addition to conventional medicine, and the term "alternative medicine", which refers to treatments used instead of conventional medical treatments. The use of CAM among healthy populations and in patients with certain health conditions was investigated extensively; however, to our knowledge, no such research had been conducted with health studies students in Croatia.*

### What this Study Adds:

*The use of 31 complementary and alternative medicine (CAM) methods among health studies students, the source of their information on CAM and the main reason for using CAM was investigated in this study. The results of this study revealed a need for additional education on CAM among health studies students.*

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**Conflict of Interest:** The authors declare that they have no conflict of interest.

**Research Data for this Article:** The data that support the findings of this study are openly available in Mendeley data at <https://data.mendeley.com/datasets/48vx4kt3nm/2>.

## References

1. National Center for Complementary and Integrative Health, Complementary, Alternative, or Integrative Health: What's In a Name?; 2015 [cited 2020 Jun 20].

- Available from: <https://nccih.nih.gov/health/integrative-health>.
2. Mayo Foundation for Medical Education and Research. Mayo Clinic- Book of Alternative Medicine. Zagreb: Medicinska naklada; 2012.
  3. Saha BL, Seam MOR, Islam MM, Das A, Ahamed SK, Karmakar P, et al. General perception and self-practice of complementary and alternative medicine (CAM) among undergraduate pharmacy students of Bangladesh. *BMC Complement Altern Med*. 2017;17(1):314. doi: 10.1186/s12906-017-1832-y.
  4. James PB, Bah AJ. Awareness, use, attitude and perceived need for Complementary and Alternative Medicine (CAM) education among undergraduate pharmacy students in Sierra Leone: a descriptive cross-sectional survey. *BMC Complement Altern Med*. 2014;14:438. doi: 10.1186/1472-6882-14-438.
  5. Rao A, Shakeel M, Trindade A, Rao G, Pearce A, Ah-See KW. The Importance of Complementary and Alternative Medicine Education in Medical School. *J Evid Based Complementary Altern Med*. 2012;17(3):191-8. doi: <https://doi.org/10.1177/2156587212451597>.
  6. Koithan M. Introducing Complementary and Alternative Therapies. *J Nurse Pract*. 2009;5(1):18-20. doi: 10.1016/j.nurpra.2008.10.012.
  7. Clarke TC, Black LI, Stussman BJ, Barnes PM, Nahin RL. Trends in the use of complementary health approaches among adults: United States, 2002-2012. *Natl Health Stat Report*. 2015;(79):1-16.
  8. Kempainen LM, Kempainen TT, Reippainen JA, Salmenniemi ST, Vuolanto PH. Use of complementary and alternative medicine in Europe: Health-related and sociodemographic determinants. *Scand J Public Health*. 2018;46(4):448-55. doi:10.1177/1403494817733869
  9. Ameade EP, Amalba A, Helegbe GK, Mohammed BS. Medical students' knowledge and attitude towards complementary and alternative medicine - A survey in Ghana. *J Tradit Complement Med*. 2015;6(3):230-6. doi:10.1016/j.jtcme.2015.03.004
  10. Kanadiya MK, Klein G, Shubrook JH Jr. Use of and attitudes toward complementary and alternative medicine among osteopathic medical students. *J Am Osteopath Assoc*. 2012;112(7):437-46.
  11. Sadeghi M, Rabiepoor S, Forough AS, Jabbari S, Shahabi S. A Survey of Medical Students' Knowledge and Attitudes Toward Complementary and Alternative Medicine in Urmia, Iran. *J Evid Based Complementary Altern Med*. 2016;21(4):306-10. doi: 10.1177/2156587215605751.
  12. Kameyama A, Toda K. Survey of Dental Students' Attitude Regarding Oriental Medicine/Complementary and Alternative Medicine: Comparison Between Two Japanese Dental Schools. *Afr J Tradit Complement Altern Med*. 2017;14(3):287-95. doi: 10.21010/ajtcam.v14i3.30
  13. Croatian Health Insurance Fond, List of health care procedures from compulsory health insurance. [cited 2020

- Nov 20]. Available from: <https://www.hzzo.hr/zdravstveni-sustav-rh/popis-ugovorenih-zdravstvenih-partnera-usluga/>.
14. Wang WY, Zhou H, Wang YF, Sang BS, Liu L. Current Policies and Measures on the Development of Traditional Chinese Medicine in China. *Pharmacol Res.* 2020;105187. doi: 10.1016/j.phrs.2020.105187. Epub ahead of print.
  15. Vitale K, Mundar R, Sović S, Bergman-Marković B, Janev Holcer N. Use of complementary and alternative medicine among family medicine patients – example of the town of Čakovec [in Croatian]. *Acta Med Croatica.* 2014;68(4-5):345-51.
  16. Vuletić I. The use of alternative and complementary medicine in children with type 1 diabetes mellitus and malignant disease [Master's thesis]. Zagreb: University of Zagreb, School of Medicine, Zagreb; 2018. Available from: <https://urn.nsk.hr/urn:nbn:hr:105:383668>.
  17. Andrašek S. Our knowledge of use of complementary and alternative medicine among patients with oncology diseases [Master's thesis]. Zagreb: University of Zagreb, School of Medicine, Zagreb; 2015. Available from: <https://urn.nsk.hr/urn:nbn:hr:105:351199>.
  18. Živčić D, Racz A, Naletilić D. Differences in attitudes towards/beliefs on complementary and alternative medicine witnessed between physiotherapists, nurses/paramedics and physicians. *African J Tradit Complement Altern Med.* 2014;11(6):57-65. doi: <http://dx.doi.org/10.4314/ajtcam.v11i6.6>
  19. Petz B, Kolesarić V, Ivanec D. Basis statistical methods for nonmathematicians. Jastrebarsko: Naklada Slap; 2012.
  20. Arai M, Nakada Y, Izumi SI. The education of traditional Japanese (Kampo) medicine: surveys of training hospitals and residents. *BMC Complement Altern Med.* 2017;17(1):134. doi:10.1186/s12906-017-1634-2.
  21. Kang YM, Komakech R, Karigar CS, Saqib A. Traditional Indian medicine (TIM) and traditional Korean medicine (TKM): a constitutional-based concept and comparison. *Integr Med Res.* 2017;6(2):105-13. doi:10.1016/j.imr.2016.12.003.

## Supplements

### Supplement 1. Participants' Response Rates at the Faculty of Health Studies in Rijeka

Study programme at the Faculty of Health Studies in Rijeka	Total number of students at FZSRI; N (%)	Participants in the study; N (%)	Response rate; %
Undergraduate Physiotherapy Study	103 (14.3)	34 (16.4)	33.0
Undergraduate Nursing Study	252 (34.6)	65 (31.4)	25.8
Undergraduate Radiology Technology Study	51 (7.1)	19 (9.2)	37.3
Undergraduate Midwifery Study	56 (7.8)	21 (10.1)	37.5
Graduate Physiotherapy Study	93 (12.9)	41 (19.8)	44.1
Graduate Nursing - Mental Health Promotion Study	43 (6)	8 (3.9)	18.6
Graduate Nursing - Health Management Study	79 (11)	10 (4.8)	12.7
Graduate Clinical Nutrition Study	31 (4.3)	5 (2.4)	16.1
Physiotherapy Bridging programme	15 (2.1)	4 (1.9)	26.7
Total	723 (100)	207 (100)	28.6

FZSRI=Faculty of Health Studies in Rijeka.

### Supplement 2. Frequency of Use of Other Complementary Health Approaches

Other complementary health approaches	Never N (%)	Rarely* N (%)	Periodically† N (%)	Often‡ N (%)	Very often§ N (%)
Tradicional healers	201 (97.1)	6 (2.9)	-	-	-
Ayurvedic medicine	190 (91.8)	10 (4.8)	5 (2.4)	2 (1.0)	0
Tradicional Chinese medicine	195 (94.2)	8 (3.9)	-	2 (1.0)	2 (1.0)
Naturopathy	197 (95.2)	8 (3.9)	2 (1)	-	-
Homeopathy	177 (85.5)	20 (9.7)	7 (3.4)	1 (0.5)	2 (1.0)

\*1-2×/year; †3-4×/year; ‡1-2×/month; §1 or more times/week.

## A Novel Test, the Sternomental Distance Ratio, Used as a Predictor of Difficult Laryngoscopy in a Normal Population and in Thyroid Tumor Surgery Patients: A Preliminary Study

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### Abstract

**Objective.** The aim of the present preliminary study was to assess whether the sternomental distance ratio (SMDR) could be suitable as a predictor of difficult laryngoscopy, in both normal surgical patients and patients scheduled to undergo thyroid tumor surgery. **Methods.** Two hundred and twenty-one consecutive adult patients (among them 122 patients with presumed normal airways and 33 patients with thyroid tumors), scheduled to undergo elective surgery under general anesthesia, were included in this study. Physical and airway characteristics, SMDR, difficult laryngoscopy (using Cormack-Lehane scale) and any kind of assisted intubation were assessed. **Results.** Decreased SMDR demonstrated a strong correlation with difficult laryngoscopy in both thyroid tumor (Kendall's tau-b  $-0.578$  ( $P=0.004$ )) and normal patients  $-0.362$  ( $P<0.001$ ). Difficult laryngoscopy was 0 at  $SMDR>1.9$  and 33% at  $SMDR<1.55$  ( $P<0.001$ ). The higher the SMDR was, the better the glottic view obtained. **Conclusions.** A  $SMDR>1.9$  indicates an easy laryngoscopy, whereas  $SMDR<1.55$  indicates a difficult one in both thyroid tumor and normal patients. SMDR is an objective test to assess difficult airway in thyroid surgery.

**Key Words:** Laryngoscopy ▪ Sternomental Distance Ratio ▪ Thyroid Surgery ▪ Thyroid Tumor.

### Introduction

Patients undergoing thyroid tumor surgery are at risk of difficult intubation and consequent increased morbidity and mortality (1-5). The rate of difficult laryngoscopy in thyroid surgery patients may range from 6% up to 9% (6, 7) and head, neck, ear, nose and throat surgeries may account for more than 20% of malpractice claims related to difficult tracheal intubation (5).

Several predictive tools for difficult laryngoscopy have been proposed, but with limited accuracy (8-10). Sternomental distance and neck extension are two of these predictive tests (11, 12). Furthermore, short neck and limited cervical spine extension are among the common (10% and 16% respectively) predictors of difficult tracheal intubation recognized in a large closed claims analysis

(5). Combined tests have been reported to be more accurate in predicting difficult laryngoscopy (8-10). However, cervical spine mobility is not easy to quantify objectively (8, 12). The ratio of the sternomental distance in neutral and full extension head positions combines the aforementioned predictors accurately and objectively.

Inadequate airway assessment can be a significant contributor to patient harm (5), especially in a setting, such as thyroid surgery that may lead to an increased incidence of difficult intubation (6). No single predictive test that identifies difficult laryngoscopy and correlates well with both "normal" subjects and thyroid surgery patients has yet been found.

The aim of the present preliminary study was to assess whether the sternomental distance ratio

(SMDR) could be a suitable predictor of difficult laryngoscopy in both normal patients and patients scheduled to undergo thyroid tumor surgery.

## Methods

This masked, preliminary study included 221 consecutive adult patients from 29/05/2013 to 02/11/2013, scheduled to undergo elective surgery under general anesthesia, and was performed in a secondary general hospital, the Thriasion General Hospital of Elefsina, Greece. Individual written informed consent was obtained, as well as institutional Ethics Committee approval (Nr 01/17-01-2013). Pregnant patients, minors, emergency cases, American Society of Anesthesiologists (ASA) status IV patients, and patients with a history of failed or difficult tracheal intubation were excluded from the study. Preoperative patient assessment was performed by a senior anesthesiologist blinded to the study interventions.

The following variables were recorded on a separate sheet for the study purposes: age, gender, body mass index (BMI), Mallampati classification (Mall), upper lip bite test (ULBT), thyromental distance (TMD), and type of surgery. Furthermore, the sternomental distance (the distance from the mentum to the sternal notch) was measured in two different positions: with the neck in full extension as classically described (10), and in a neutral position. The ratio was recorded of the full neck extension sternomental distance to the neutral position sternomental distance. This variable was named the SMDR (Figures 1 and 2).

All patients fasted preoperatively, as per the European Society of Anaesthesiology (ESA) guidelines (13). Standard monitoring, including ECG, SpO<sub>2</sub> and NIBP, was applied to all patients, and an 18G intravenous cannula was inserted. Muscle relaxation was assessed with train-of-four (TOF) monitoring using a peripheral nerve stimulator (Innervator 252, Fisher & Paykel Electronics Ltd, Auckland, New Zealand) placed in the ulnar nerve. Premedication with intravenous midazolam 1-2 mg was administered to all patients. Preoxygenation was performed with 100% O<sub>2</sub> via face

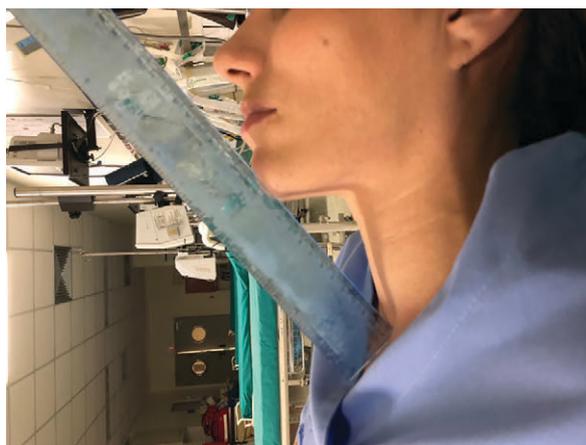


Figure 1. Sternomental Distance in Neutral Head Position.

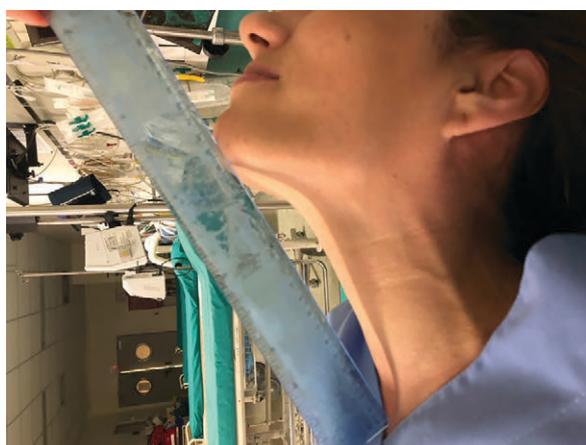


Figure 2. Sternomental Distance in Full Neck Extension.

mask; anesthesia was induced with propofol (2-3 mg.kg<sup>-1</sup>) and fentanyl (1-2 µg.kg<sup>-1</sup>). Rocuronium 0.6 mg.kg<sup>-1</sup> was administered for tracheal intubation. After adequate muscle relaxation had been achieved, as assessed by a TOF value of 0 in the nerve stimulator, laryngoscopy was attempted by a second senior anesthesiologist, blinded to the airway assessment and the study protocol. The Cormack/Lehane (C/L) scoring system was used to assess the glottic views obtained during laryngoscopy (14). Any aiding technique, such as external laryngeal pressure, backwards-upwards-rightwards manoeuvre, gum elastic bougie, change of anesthetist, 3<sup>rd</sup> attempt with a video-laryngoscope, was recorded as “assisted intubation” for the study purposes.

### Statistical Analysis

Continuous variables are presented as mean values  $\pm$  standard deviation, whereas categorical variables are presented as absolute and relative (%) frequencies. The association between normally distributed continuous variables and binary variables categories was evaluated through Student's t-test for independent samples. In the case of categorical variables with  $>2$  categories, one-way analysis of variance (ANOVA), was applied after checking for homoscedacity. Due to the multiple comparisons, the Bonferroni rule was applied to correct for the inflation of type-I error. Whether these variables were normally distributed was tested through the P-P plot and equality of variances through Levene's test. Associations between categorical variables and sample categories were tested by the use of the chi-squared test. Non-parametric tests (i.e. Spearman's  $\rho$  and Kendal's tau-b) were applied to estimate the correlations between SMDR with glottic view. Given the fact that there are no data in the international literature for this predictive factor, the values obtained were divided into 4 quadrants for initial evaluation ( $<1.55$ ,  $1.55-1.72$ ,  $1.73-1.90$ ,  $>1.90$ ) and correlation with somatometrics, indicators of difficult laryngoscopy and glottic views obtained. The receiver operating characteristic (ROC) curve identified the best sensitivity and specificity cut-off point as a SMDR value of 1.7 (Fig. 3). By using the ratio 1.7 as a cut-off point, a binary covariate of SMDR ( $<1.7$  vs.  $\geq 1.7$ )

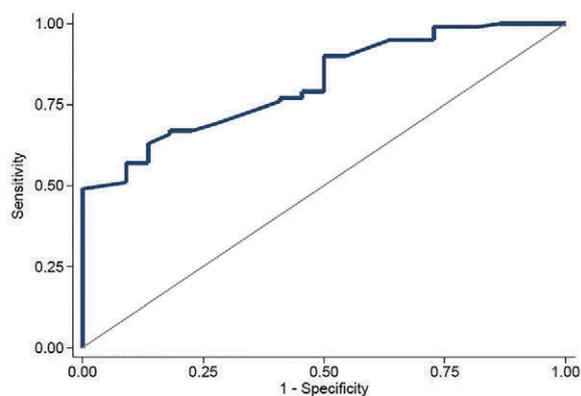


Figure 3. Receiver Operating Characteristic Curve for Sternomental Distance Ratio (SMDR).

was created. The statistical calculations were performed on the SPSS version 21 (IBM Hellas, Athens, Greece).

### Results

The study included 221 patients who were all intubated after a maximum 3 attempts and no adverse events. Of the 221 patients, 122 were considered as normal, i.e. not having any visible facial, head and neck deformity during preoperative assessment, and served as a control group for the SMDR test. Of the remaining 99 patients, the second study group comprised 33 patients with thyroid tumors (10 previously operated, and 23 to be operated). The remaining 66 patients were excluded from the present analysis, as they presented characteristics that could influence laryngoscopy (protruding teeth, prognathism and poor dentition).

The characteristics of the study population are presented in Table 1. In the three groups assessed (normal population, previous thyroid tumor surgery and scheduled thyroid tumor surgery), no significant differences were observed in the patients' somatometrics, difficult laryngoscopy indicators, laryngoscopy views, or assisted intubation rates. Furthermore, no significant differences were observed in the SMDR values between normal patients and thyroid surgery patients.

The SMDR values obtained from the patients were divided into four groups, as mentioned in the Methods section (Table 2). It appeared that the higher the SMDR was, the better the glottic view obtained (lower C/L class). A SMDR above 1.9 led to zero assisted intubations and 89% good or excellent glottic views, whereas when it fell to 1.55, the good or excellent glottic views fell to 65% and the rates of assisted intubation accounted for one in three cases (33%).

When applying a cut-off point of 1.7 for the SMDR, as assessed by ROC analysis, poor or bad glottic views accounted for 13.3% for  $SMDR > 1.7$ , compared to 48.1% for  $SMDR < 1.7$ . As depicted in Table 3, according to the Kendall rank correlation coefficient, the binary variable SMDR ( $< 1.7$  and  $> 1.7$ ) was significantly negatively correlated with

Table 1. Patients' Characteristics

Characteristics	Total (n=221)	Normal subjects (n=122)	Previous thyroid tumor surgery (n=10)	Thyroid tumor surgery (n=23)	ANOVA P-value
Age, years mean (SD)	54 (17)	45 (13)	42 (15)	51 (12)	0.086
Men number (%)	84 (38)	41 (33.6)	4 (40); P=0.68 vs normal	9 (39.1); P=0.61 vs normal	—
BMI (kg/m <sup>2</sup> )	27.1 (5.1)	26.9 (5.5)	23.8 (4.7)	29.6 (5.1)	0.159
TMD (cm)	8.5 (1.3)	8.8 (1.3)	8.4 (1.1)	8.4 (1.2)	0.281
SMDR	1.74 (0.28)	1.73 (0.26)	1.78 (0.31)	1.76 (0.22)	0.76
Upper lip bite test					
I	60%	56%	40%; P=0.33 vs normal	52%; P=0.52 vs normal	—
II	38%	41%	60%; P=0.24 vs normal	48%; P=0.53 vs normal	—
III	2%	3%	0%; P=0.58 vs normal	0%; P=0.40 vs normal	—
Mallampati score					
I	45%	46%	40%; P=0.71 vs normal	26%; P=0.076 vs normal	—
II	39%	41%	50%; P=0.58 vs normal	43%; P=0.86 vs normal	—
III	13%	12%	0%; P=0.25 vs normal	22%; P=0.20 vs normal	—
IV	3%	1%	10%; P=0.034 vs normal	9%; P=0.018 vs normal	—
Glottic view					
I	50%	43%	60%; P=0.30 vs normal	48%; P=0.65 vs normal	—
II	21%	25%	10%; P=0.28 vs normal	18%; P=0.47 vs normal	—
III	27%	30%	30%; P=1.0 vs normal	30%; P=1.0 vs normal	—
IV	2%	2%	0%; P=0.65 vs normal	4%; P=0.56 vs normal	—
Assisted intubation	16%	18%	20%; P=0.88 vs normal	17%; P=0.91 vs normal	—

SD=Standard Deviation; BMI=Body mass index; TMD=Thyromental distance; SMDR=Sternomental distance ratio.

Table 2. Patients' Characteristics according to Different SMDR Value Ranges

Patients' characteristics	>1.90	1.90-1.73	1.72-1.55	<1.55	P-value
SMDR	(N=53)	(N=56)	(N=57)	(N=55)	
Number	38	27	40	47	0.16
Mean %	38	27	40	47	0.16
BMI kg/m <sup>2</sup> mean (SD)	27.6 (4.8)	26.7 (5.3)	26.6 (5.1)	27.6 (5.3)	0.65
TMD cm, mean (SD)	8.4 (1.2)	8.4 (1.3)	8.8 (1.3)	8.5 (1.5)	0.38
Upper Lip Bite Test					
I	68(%)	68(%)	56(%)	49(%)	0.27
II	30(%)	32(%)	40(%)	49(%)	0.27
III	2(%)	0(%)	4(%)	2(%)	0.27
ASA Status					
ASA I	43(%)	48(%)	55(%)	49(%)	0.42
ASA II	49(%)	45(%)	33(%)	35(%)	0.42
ASA III	8(%)	7(%)	12(%)	16(%)	0.42
Mallampati Score					
I	55(%)	50(%)	44(%)	33(%)	0.33
II	32(%)	38(%)	35(%)	49(%)	0.33
III	9(%)	12(%)	14(%)	15(%)	0.33
IV	4(%)	0	7(%)	3(%)	0.33
Cormack/Lehane Glottic View					
I	66(%)	59(%)	47(%)	29(%)	<0.001
II	23(%)	27(%)	16(%)	18(%)	<0.001
III	11(%)	14(%)	35(%)	47(%)	<0.001
IV	0	0	2(%)	6(%)	<0.001
Assisted intubation	0	7(%)	25(%)	33(%)	<0.001

SMDR=Sternomental Distance Ratio; BMI= Body Mass Index; SD=Standard Deviation; TMD=Thyromental Distance.

Table 3. Rank Correlation between SMDR with the Cormack/Lehane Scores, in the Total Sample and in Study Subgroups

Kendall's tau-b (P-value)	Total population (N=221)	Normal subjects (N=122)	Previous thyroid surgery (N=10)	Thyroid tumor surgery (N=23)
	Sternomental distance ratio			
Cormack/Lehane (Glottic view)	-0.356 (P<0.001)	-0.362 (P<0.001)	-0.420 (P=0.19)	-0.578 (P=0.004)

the Cormack/Lehane scores (glottic views). In other terms, the higher the SMDR, the lower the C/L score, hence the better the glottic view.

Furthermore, this also seemed to apply for the patients scheduled to undergo thyroid tumor surgery. This correlation also existed for the patients who had already undergone thyroid surgery, although it was not significant, probably due to the small sample.

## Discussion

Numerous preoperative tests are continuously being proposed and assessed in order to predict difficult laryngoscopy, particularly in especially challenging settings, such as thyroid surgery (15). Sternomental distance has been proposed as a good predictor for difficult laryngoscopy, but various cut-off points have been proposed without being sufficiently accurate (16). The same applies for cervical spine movement (8-10, 12). The incidence of difficult airways in thyroid surgery varies widely (from 5.3% to 13.6%), depending on the report (17-21).

In the present study, in thyroid surgery patients there were extremely poor glottic views in 4%, and the rate of assisted intubation was 11%. However, these results are not comparable for several reasons. First of all, none of the samples in the aforementioned studies was homogenous. The patients included in these studies varied from simple thyroid nodule cases to extremely large goiters.

SMDR has the advantage of combining neck height, neck mobility and mandibular space, in an accurate and objective way. In the present sample no differences were identified in the rates of difficult laryngoscopy or assisted intubation between patients undergoing thyroid surgery and other patients. However, this was not the aim of the study,

but to assess whether the SMDR would correlate with difficult laryngoscopy in both thyroid tumor surgery and normal airway patients. In the present study, a SMDR value below 1.55 led to 53% of poor laryngoscopic views, whereas a SMDR value above 1.9 almost certainly led to an easy laryngoscopy in all types of patients, including thyroid tumor surgery patients.

An important limitation of the present study (as in all preliminary studies) is its small sample, and the fact that no sample size calculation was performed. Furthermore, regarding the methodology of the study, in order to better evaluate the prognostic performance of SMDR, a simultaneous comparison with a combination of several predictive tests could perhaps also have been undertaken. Of course, this additional set of variables would require an even larger sample, but would have provided more conclusive results.

## Conclusions

SMDR is a quick and objective test to assess a patient's airway. In this preliminary study, SMDR appeared to correlate significantly with difficult laryngoscopy in both normal and in thyroid tumor patients. However, larger studies are necessary in order to provide further data.

### What Is Already Known on this Topic:

*Patients undergoing thyroid tumor surgery are at risk of difficult intubation and consequent increased morbidity and mortality. Several predictive tools for difficult laryngoscopy have been proposed, but with limited accuracy. A recent study reported that sternomental distance difference in neutral head position and in full neck extension could be a good predictor of difficult laryngoscopy.*

### What this Study Adds:

*A cut-off point based on a distance difference is very difficult to define, whereas a cut-off point based on an analogy may be easier to assess. In the present study, a sternomental distance ratio (SMDR) >1.9 indicated*

*an easy laryngoscopy whereas a SMDR <1.55 indicated a difficult one in both thyroid tumor and normal patients. SMDR is an objective test to assess difficult airway in thyroid surgery. This is the first study assessing this novel predictor of difficult laryngoscopy in thyroid surgery patients.*

**Authors' Contributions:** Conception and design: EK, EA, TD and PS; Acquisition, analysis and interpretation of data: EK, EA and MP; Drafting the article EK and MP; Revising it critically for important intellectual content: MP and TD; Approved final version of the manuscript: TD and PS.

**Conflict of Interest:** The authors declare that they have no conflict of interest.

## References

- Bacuzzi A, Dionigi G, Del Bosco A, Cantone G, Sansone T, Di Losa E, et al. Anaesthesia for thyroid surgery: perioperative management. *Int J Surg*. 2008;6(Suppl1):S82-5.
- Dempsey GA, Snell JA, Coathup R, Jones TM. Anaesthesia for massive retrosternal thyroidectomy in a tertiary referral centre. *Br J Anaesth*. 2013;111(4):594-9.
- Peterson GN, Domino KB, Caplan RA, Posner KL, Lee LA, Cheney FW. Management of the difficult airway: a closed claims analysis. *Anesthesiology*. 2005;103(1):33-9.
- Hisham AN, Roshilla H, Amri N, Aina EN. Post-thyroidectomy Sore Throat Following Endotracheal Intubation. *ANZ J Surg*. 2001;71(11):669-71.
- Joffe AM, Aziz MF, Posner KL, Duggan LV, Mincer SL, Domino KB. Management of Difficult Tracheal Intubation: A Closed Claims Analysis. *Anesthesiology*. 2019;131(4):818-29.
- De Cassai A, Boscolo A, Rose K, Carron M, Navalesi P. Predictive Parameters of Difficult Intubation in Thyroid Surgery: A Meta-Analysis. *Minerva Anestesiol*. 2020;86(3):317-26.
- Kalezić N, Sabljak V, Stevanović K, Milčić B, Marković D, Tošković A, et al. Predictors of difficult airway management in thyroid surgery: a five-year observational single-center prospective study. *Acta Clin Croat*. 2016;55(Suppl 1):S9-18.
- Roth D, Pace NL, Lee A, Hovhannisyan K, Warenits AM, Arrich J, et al. Airway physical examination tests for detection of difficult airway management in apparently normal adult patients. *Cochrane Database Syst Rev*. 2018;5:CD008874.
- Chhina AK, Jain R, Gautam PL, Garg J, Singh N, Grewal A. Formulation of a multivariate predictive model for difficult intubation: A double blinded prospective study. *J Anaesthesiol Clin Pharmacol*. 2018;34(1):62-7.
- Detsky ME, Jivraj N, Adhikari NK, Friedrich JO, Pinto R, Simel DL, et al. Will This Patient Be Difficult to Intubate?: The Rational Clinical Examination Systematic Review. *JAMA*. 2019;321(5):493-503.
- Savva D. Prediction of difficult tracheal intubation. *Br J Anaesth*. 1994;73(2):149-53.
- Ji SM, Moon EJ, Kim TJ, Yi JW, Seo H, Lee BJ. Correlation between modified LEMON score and intubation difficulty in adult trauma patients undergoing emergency surgery. *World J Emerg Surg*. 2018;13:33.
- De Hert S, Imberger G, Carlisle J, Diemunsch P, Fritsch G, Moppett I, et al. Task Force on Preoperative Evaluation of the Adult Noncardiac Surgery Patient of the European Society of Anaesthesiology. Preoperative evaluation of the adult patient undergoing noncardiac surgery: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol*. 2011;28(10):684-722.
- Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia*. 1984;39(11):1105-11.
- De Cassai A, Papaccio F, Betteto G, Schiavolin C, Iacobone M, Carron M. Prediction of difficult tracheal intubations in thyroid surgery. Predictive value of neck circumference to thyromental distance ratio. *PLoS One*. 2019;14(2):e0212976.
- Prakash S, Mullick P, Bhandari S, Kumar A, Gogia AR, Singh R. Sternomental distance and sternomental displacement as predictors of difficult laryngoscopy and intubation in adult patients. *Saudi J Anaesth*. 2017;11(3):273-8.
- Bouaggad A, Nejmi SE, Bouderkha MA, Abbassi O. Prediction of difficult tracheal intubation in thyroid surgery. *Anesth Analg*. 2004;99(2):603-6.
- Amathieu R, Smail N, Catineau J, Poloujadoff MP, Samii K, Adnet F. Difficult intubation in thyroid surgery: myth or reality? *Anesth Analg*. 2006;103(4):965-8.
- Kalezić N, Milosavljević R, Paunović I, Zivaljević V, Diklić A, Matic D, et al. The incidence of difficult intubation in 2000 patients undergoing thyroid surgery—a single center experience. *Vojnosanit Pregl*. 2009;66(5):377-82.
- Tutuncu AC, Erbabacan E, Teksoz S, Ekici B, Koksall G, Altintas F, et al. The Assessment of Risk Factors for Difficult Intubation in Thyroid Patients. *World J Surg*. 2018;42(6):1748-53.
- Loftus PA, Ow TJ, Siegel B, Tassler AB, Smith RV, Schiff BA. Risk factors for perioperative airway difficulty and evaluation of intubation approaches among patients with benign goiter. *Ann Otol Rhinol Laryngol*. 2014;123(4):279-85.

## Epidemiological Data, Serovar Distribution and Antimicrobial Resistance Patterns of *Salmonella* Species in Children, Greece 2011-2017: A Retrospective Study

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### Abstract

**Objective.** This study aimed to describe *Salmonella* epidemiology and antimicrobial resistance in Greek children over the period of 2011-2017. **Materials and Methods.** A 7-year retrospective study (2011-2017) was performed, based on data recorded by the National Reference Centre for *Salmonella*, among children aged  $\leq 14$  years. Epidemiological data, serovar distribution and antimicrobial resistance patterns were recorded. **Results.** Overall, 2347 *Salmonella* isolates were collected (27 typhoid-paratyphoid). Salmonellosis cases increased by almost 2-fold in 2017 compared to 2011. The highest rates were reported in August, with infants being the most vulnerable group (17.9%). The majority of isolates were identified in stool samples (91%). Boys slightly outnumbered girls (~1.05:1). *Salmonella Enteritidis* was the most prevalent serovar (28.5%), followed by *Salmonella Typhimurium* (12.2%) and *Salmonella monophasic Typhimurium* (10.4%). Non-typhoid isolates displayed low resistance rates to 3<sup>rd</sup> generation cephalosporins (1%) and ciprofloxacin (0.3%), while the corresponding resistance of typhoid isolates was 10% and 5% respectively. An increasing trend of *Salmonella monophasic Typhimurium* was recorded, associated with high rates of multidrug resistance, reaching a percentage of 97.8% in 2017. **Conclusions.** Salmonellosis epidemiology in Greek children is comparable to previously published European data. Antimicrobial resistance rates to 3<sup>rd</sup>-generation cephalosporins and ciprofloxacin for non-typhoid and typhoid-paratyphoid remain low. Notably, there is an increasing prevalence of *Salmonella monophasic Typhimurium* isolates, associated with multiple antimicrobial resistance.

**Key Words:** *Salmonella* ■ Epidemiology ■ Antimicrobial Resistance ■ Serovars ■ Children.

### Introduction

*Salmonella* infection (Salmonellosis) is a global public health problem, predominantly among children, associated with significant morbidity and mortality (1). *Salmonella* species (*Salmonella spp.*) cause typhoid fever and non-typhoid salmonellosis that causes gastroenteritis, rarely associated with complications, such as reactive arthritis and bacteremia.

*Salmonella* serotype *Typhi* and *Salmonella* serotype *Paratyphi A, B, and C* (ie, typhoidal *Salmonella*) are responsible for causing typhoid fever in humans, an illness that is most burdensome in the developing

world. The World Health Organization (WHO) estimates 16 to 33 million cases of typhoid fever causing 500,000 to 600,000 deaths worldwide annually (2).

Non-typhoidal *Salmonella* (NTS) species, which are found widely in animals, are estimated to cause more than 90 million illnesses worldwide, and to account for approximately 155,000 deaths each year (2). The transmission of salmonellosis is frequently associated with the consumption of contaminated water and food of animal origin (i.e. eggs, meat, dairy products), and is facilitated by conditions characterized by poor hygiene (3). Young children and infants are at increased risk

of acquiring salmonellosis, while children with certain underlying conditions (such as hemoglobin disorders, infection with human immunodeficiency virus (HIV), malignancy, or other causes of immune suppression) have an increased risk of severe disease and death from complications (3).

*Salmonella* monitoring and control programs have been recently implemented in the European Union (EU). In contrast to the earlier declining trend of human salmonellosis (4), there have been some unfavorable changes on this trend since 2016 in Europe (5). In self-limiting gastrointestinal infections, antimicrobial treatment is not required. On the other hand, antimicrobial treatment is essential and life-saving in cases of invasive salmonellosis, mainly among children, the elderly and the immunocompromised (6).

The increasing resistance rates against traditional agents (aminopenicillins, trimethoprim-sulfamethoxazole, and chloramphenicol) have caused a shift to fluoroquinolones and 3<sup>rd</sup>-generation cephalosporins in empirical treatment of salmonellosis (7, 8). Nevertheless, under selection pressure, resistance to fluoroquinolones and extended-spectrum  $\beta$ -lactamases (ESBL) has been reported, and multi-drug resistant (MDR) *Salmonella* spp. isolates have emerged (9-11). Several factors contribute to reducing the efficiency of a targeted antimicrobial treatment, such as: subpopulations of *Salmonella* showing increased survival after exposure to antibiotics (12), the presence in the host of more than one strain with different antimicrobial susceptibility (13), the selection pressure and the possibility of transferring the resistance between bacteria through mobile genetic elements conferring resistance (14-16). Given the importance of salmonellosis in global foodborne illnesses and in childhood diarrhea, knowledge of local epidemiology and antibiotic resistance patterns is important to determine suitable therapeutic and control strategies.

This study aimed to describe the epidemiological data, serovar distribution and antimicrobial resistance of *Salmonella* spp. isolates among children aged  $\leq 14$  years old in Greece, based on data recorded by the National Reference Centre for *Salmonella* (NRCS) over the period from 2011 to 2017.

## Materials and Methods

All human salmonellosis cases diagnosed by clinical and diagnostic laboratories are mandatorily reported to the Hellenic Centre for Disease Control and Prevention (HCDCP); *Salmonella* isolates are voluntarily forwarded to the NRCS for serotyping and antimicrobial susceptibility testing. A 7-year retrospective study (2011 - 2017) was carried out, through the NRCS data, among children aged  $\leq 14$  years old. When two or more specimens corresponded to the same case-infectious episode, the latter was separately defined in the analysis to exclude duplicate surveillance data. Epidemiological data were recorded, while serotyping was performed according to the White-Kaufmann-Le Minor Scheme. Susceptibility testing was assessed using the disk diffusion method. Antimicrobial agents appropriate for monitoring the antibiotic resistance in human *Salmonella* isolates were tested, according to the relevant EU protocol (17). The antimicrobial agents were evaluated, including: ampicillin, amoxicillin-clavulanic acid, amikacin, ceftazidime, ciprofloxacin, chloramphenicol, cefotaxime, tobramycin, netilmicin, nalidixic acid, streptomycin, sulfamethoxazole (that was available only during the sub period of 2014 to 2017), tetracycline and trimethoprim. Multi-drug resistance was defined as acquired non-susceptibility to at least one agent in three or more classes of antimicrobials. The EU Antimicrobial Susceptibility Testing breakpoints (2010) were applied. Isolates that displayed intermediate susceptibility to the antimicrobial agent being tested were classified as resistant, since even if they inhibit the bacterium in vitro, they are excluded from routine clinical practice. The Local Institute Ethics Review Board approved the study protocol (35/1625/2011).

## Statistical Analysis

A descriptive statistical analysis was performed. Categorical variables (gender, age, specimen source, geographical data, antimicrobial resistance) are expressed as frequencies and percentages. Time trends in the occurrence of salmonellosis were assessed with time series analysis (ARIMA modeling procedure). Analyses were undertaken with the SPSS v. 18.0.  $P < 0.05$  was considered the criterion of significance.

## Results

### Epidemiology

In the 7-year period spanned by this study, NRCS received 2347 *Salmonella* spp. isolates from children aged  $\leq 14$  years old (Figure 1A). Overall, 117 different serovars were identified. A similar trend was observed in the total number of salmonellosis cases reported during the study period, in all age groups (children and adults) (Figure 1A) (http://www.mednet.gr/whonet/). Salmonellosis cases observed in children aged  $\leq 14$  years constantly represented a higher proportion of the total salmonellosis cases (Figure 1B).

Data on the date of collection were available for 2170 cases (92.5%). The seasonal variation of salmonellosis is shown in Figure 2, while Figure 3 shows age distribution. Gender data were available for 2302 clinical isolates (98.1%). Boys slightly outnumbered girls (overall ratio  $\sim 1.05:1$ ), and this difference remained fairly constant during the whole study period ( $P=0.44$ ,  $>0.05$ ). For all the cases included in our study, specimen source data were available. The majority of isolates were identified from stool samples (91%), followed by blood (3%) and urine (0.7%). Geographical data were available for 2321 clinical isolates (98.9%). The majority

were recorded in Athens, where rates remained almost stable over the first 5 years of the study period, ranging from 173 to 215, but significantly increased in the last two years, 2016 and 2017, (346 and 384 respectively) ( $P<0.05$ ).

All the cases were acquired in Greece, with 1 possible exception of a child with enteric fever caused by *Salmonella Typhi*, who had history of recent travel to France.

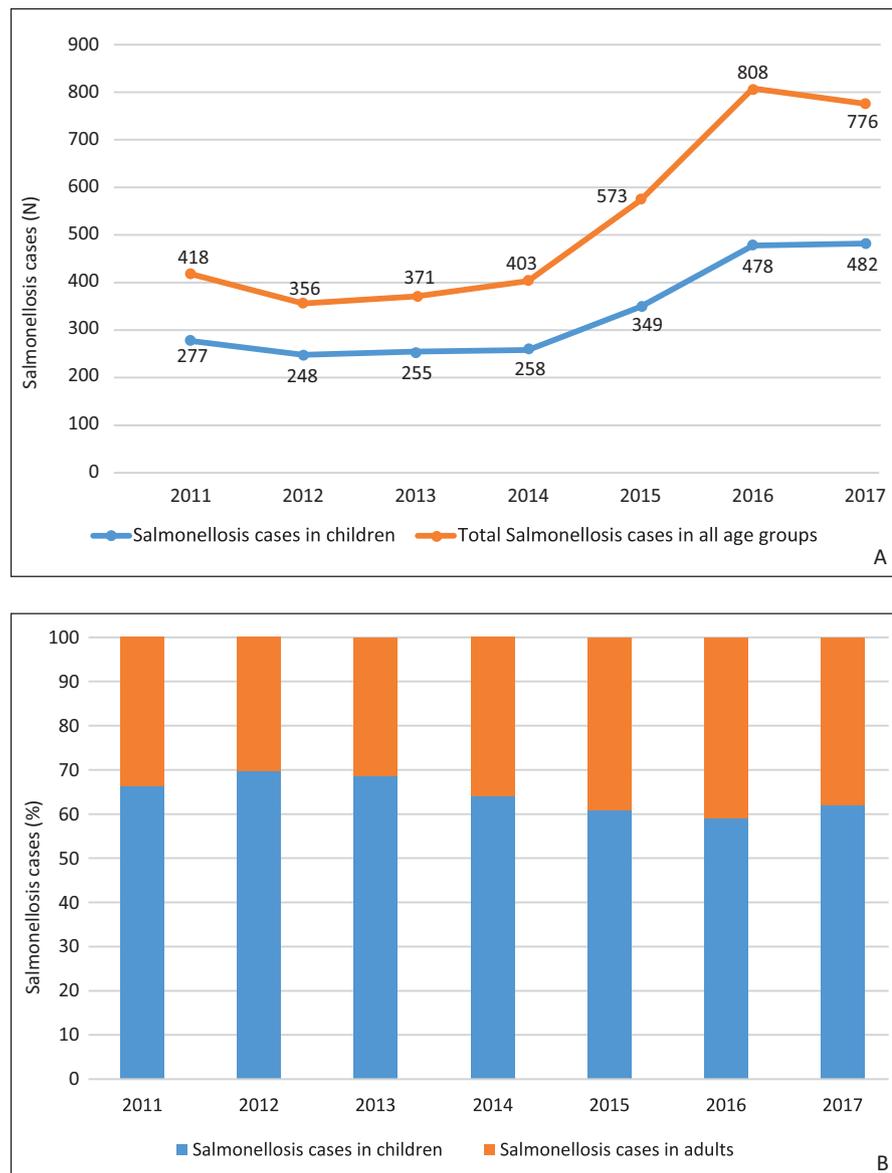


Figure 1. A: Annual rates of Salmonellosis cases in children  $\leq 14$  years old, Greece, 2011-2017; B: Percentage distribution of Salmonellosis cases in children  $\leq 14$  years old and adults by year. Greece, 2011-2017.

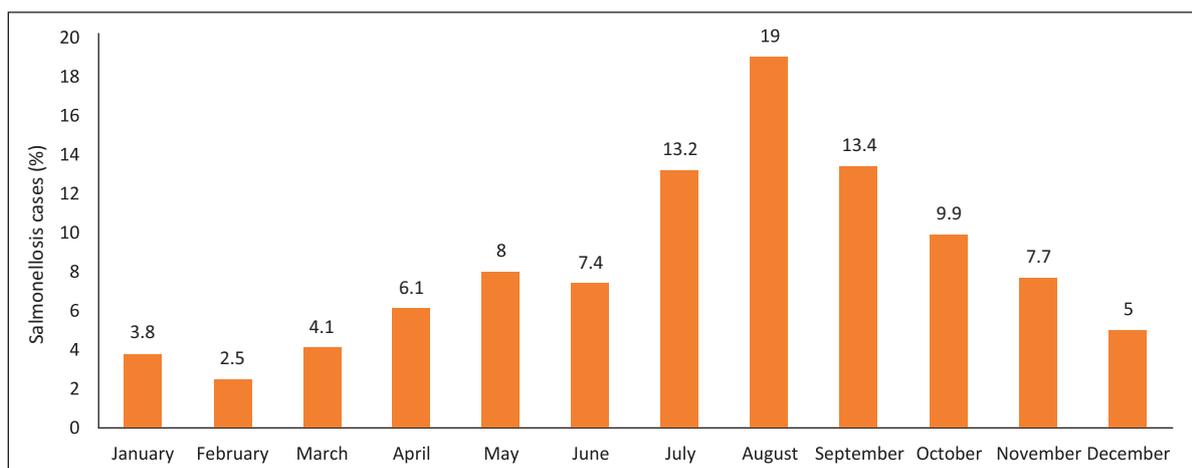


Figure 2. Seasonal percentage distribution of Salmonellosis cases in children aged  $\leq 14$  years old, Greece, 2011-2017.

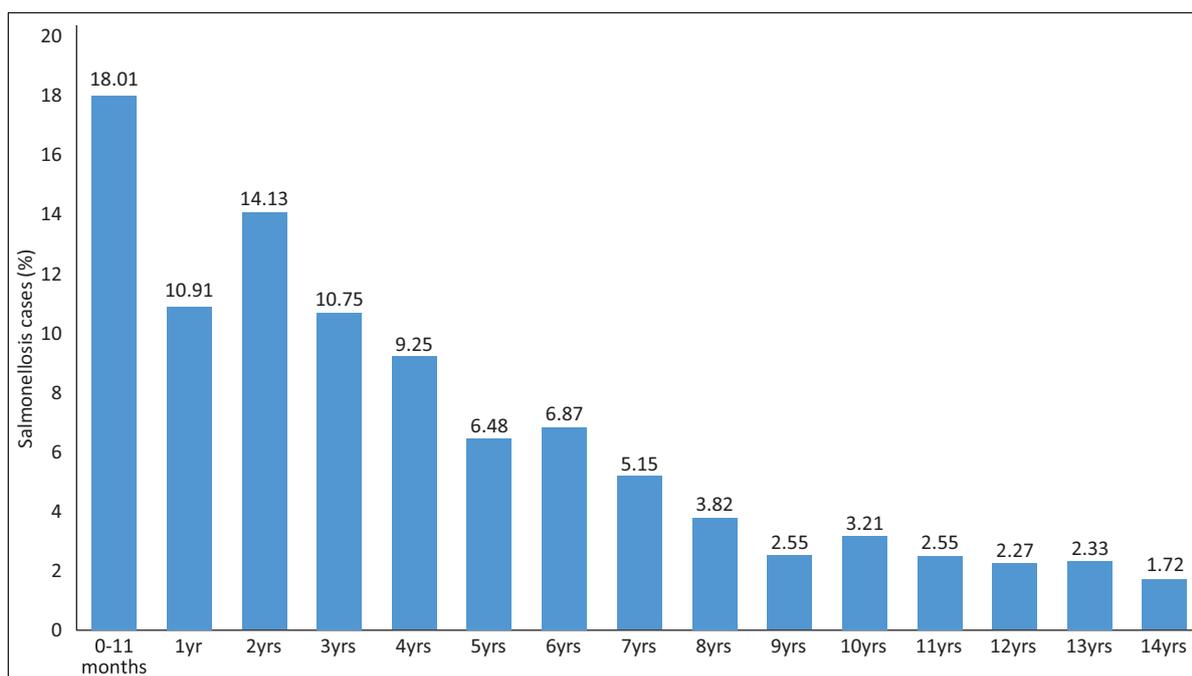


Figure 3. Percentage distribution of Salmonellosis cases in children by age, Greece, 2011-2017.

### Serovars and Antimicrobial Resistance

According to serovar distribution, shown in Figure 4, only 27 cases (1.1%) were positively identified as typhoid salmonellosis (12 cases of *Salmonella Typhi*, 44.4%, and 15 cases of *Salmonella Paratyphi B*, 55.6%). *Salmonella Enteritidis*, *Salmonella Typhimurium* and *Salmonella monophasic Typhimurium* represented 51.2% in total (Figure 5). Other *Salmonella* spp. serovars were encountered far less commonly, but accounted for 47.7% in total

(Figure 5). The increase observed in salmonellosis cases in 2015 and 2016 was predominantly due to an increase in the rates of other *Salmonella* spp. serovars, while the increase in 2017 was attributed to an increase in both the rates of other *Salmonella* spp. serovars and the rates of *Salmonella monophasic Typhimurium* isolates (Figure 5).

The antimicrobial resistance pattern was assessed for 1456 isolates (62%; 1436 non-typhoid: 20 typhoid). Table 1 presents the resistance of non-

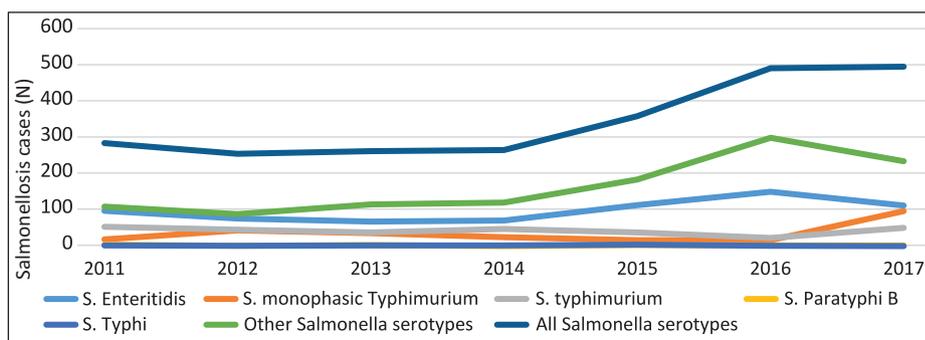


Figure 4. Distribution of *Salmonella* serovars by year in children  $\leq 14$  years old, Greece, 2011-2017.

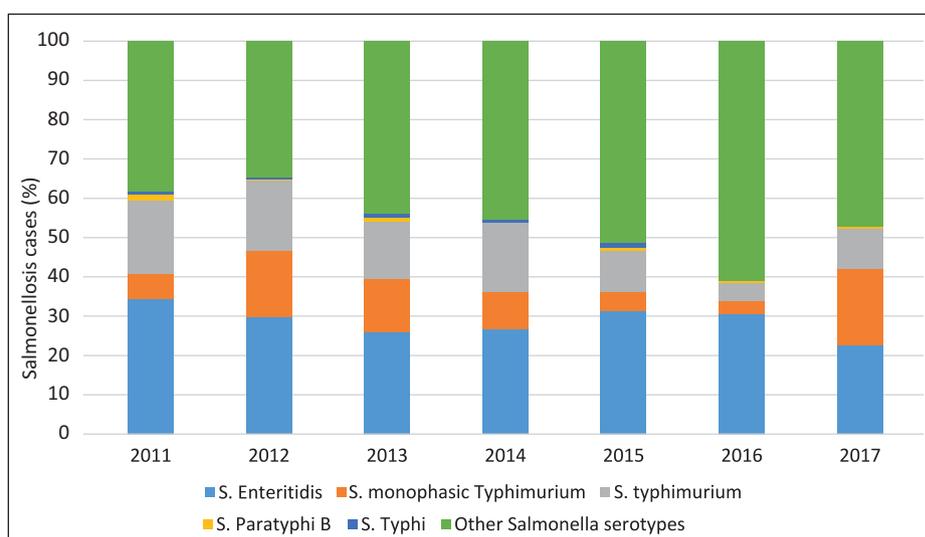


Figure 5. Percentage distribution of *Salmonella* serovars by year, in children  $\leq 14$  years old, Greece, 2011-2017.

typhoid *Salmonella spp.* isolates during the study period. Resistance to ciprofloxacin, ceftazidime and cefotaxime was low. Resistance to chloramphenicol also remained low (3.6%). Intermediate rates of resistance were observed against ampicillin and trimethoprim, (17.1% and 10.6% respectively). Sulfamethoxazole was associated with the highest resistance rates (51.4%), even though it was only available during the sub period of 2014-2017.

Antimicrobial resistance was tested for 414 *Salmonella Enteritidis* isolates (62% of the 669 that were identified during the study period). *Salmonella Enteritidis* exhibited low resistance rates to cefotaxime and ceftazidime (0.4% each), while there was no isolate that was resistant to ciprofloxacin. The percentage of the identified MDR isolates also

remained low (6/414 cases, 1.5%).

Antimicrobial resistance data was assessed for 218 *Salmonella Typhimurium* isolates (89% of the 245 that were totally isolated in the study). All *Salmonella Typhimurium* isolates were susceptible to ciprofloxacin, while resistance to cefotaxime and ceftazidime was low, 0.5% and 1% respectively. Significant resistance rates were recorded to ampicillin, streptomycin, tetracycline and sulfamethoxazole (49%, 53%, 55% and 80%, respectively). A considerable percentage of MDR isolates was also recorded (45/218 cases, 20.6%).

Regarding *Salmonella monophasic Typhimurium*, antimicrobial resistance was tested for 226 *Salmonella monophasic Typhimurium* isolates out of the 287 cases that were identified (79%). *Salmonella monophasic Typhimurium* resistance rates were low for cefotaxime, ceftazidime and ciprofloxacin. (0%, 0.7%, and 0.6% respectively). However, high rates of resistance were recorded to ampicillin, streptomycin, tetracycline, sulfamethoxazole (82%, 85%, 90% and 89% respectively). Remarkably, 72.1% of the isolates during the whole study period were MDR, reaching the percentage of 97.8% in 2017.

Antimicrobial resistance patterns were available for 20 of the 27 typhoid *Salmonella spp.* isolates (Table 1). Eight typhoid *Salmonella spp.* isolates were susceptible to all antibiotics tested. All

Table 1. Resistance of *Salmonella* Isolates to the Antimicrobial Agents Tested, among Children ≤14 Years Old, Greece, 2011-2017

Antimicrobial agent	Non-Typhi/Paratyphi isolates		Typhi/Paratyphi isolates	
	Number*	%	Number*	%
Ampicillin	245/1436	17.1	3/20	15
Amox/clav†	21/1436	1.5	0/20	0
Ceftazidime	15/1436	1	1/20	5
Cefotaxime	15/1436	1	1/20	5
Amikacin	5/1436	0.3	0/20	0
Gentamycin	8/719	1.1	0/20	0
Tobramycin	69/1436	4.8	1/20	5
Netilmicin	9/1436	0.6	0/20	0
Streptomycin	348/1436	24.2	1/20	5
Sulfamethoxazole	370/719	51.4	5/20	25
Trimethoprim	152/1436	10.6	1/20	5
Tetracycline	292/1436	20.4	1/20	5
Chloramphenicol	52/1436	3.6	2/20	10
Nalidixic acid	84/1436	5.9	6/20	30

\*Number of resistant isolates/Number of total isolates for which the corresponding resistance data was available; †Amoxicillin/Clavulanic Acid.

typhoid *Salmonella* spp. isolates were susceptible to cefotaxime and ceftazidime, but two *Salmonella Paratyphi B* isolates that were resistant (10%). All typhoid *Salmonella* spp. isolates were susceptible to ciprofloxacin, apart from one *Salmonella Typhi* isolate that was resistant (5%). It is noteworthy that typhoid *Salmonella* isolates were considerably resistant to nalidixic acid and sulfamethoxazole, (30% and 25% respectively), whereas they displayed lower resistance profiles to ampicillin and chloramphenicol (15% and 10% respectively). Two typhoid *Salmonella* isolates (one *Salmonella Typhi* and one *Salmonella Paratyphi B*) were MDR (10%).

### Bacteremia

Seventy cases of *Salmonella* bacteremia were identified during the study period. Nine of these children also yielded *Salmonella* spp. in their stool cultures (13%). Out of the twenty-seven different serovars identified in blood, the most common one was *Salmonella Enteritidis* (10 cases, 14.3%), followed by *Salmonella Oranienburg* (8 cases, 11.45%) and *Salmonella Typhi* (6 cases, 8.6%). The highest rate of *Salmonella* bacteremia was recorded

in 2017 (14 cases, 20%). The majority of cases occurred in August, and the lowest in February.

The age distribution of salmonellosis bacteremia cases is shown in Fig. 6. Boys outnumbered girls (ratio~1.8:1). Most cases were recorded in Athens (64.3%). Antimicrobial resistance was assessed for 41 salmonellosis bacteremia isolates (58.6%). The highest resistance rates were recorded to sulfamethoxazole (56%), followed by ampicillin (14.6%), streptomycin (19.5%), tetracycline (9.7%), trimethoprim (9.7%) and chloramphenicol (7.3%). Resistance rates were low for the 3<sup>rd</sup> generation cephalosporins and ciprofloxacin (2.4% each). Twenty-seven *Salmonella* bacteremia isolates (out of 41 for which antibiotic resistance pattern was available) were susceptible to all antimicrobial agents tested (65.9%), while 7 isolates were MDR (17%).

### Discussion

To our knowledge, our study is one of a few reports that have been published so far on salmonellosis epidemiology and antimicrobial resistance rates in children. Salmonellosis rates in children aged ≤14 years old remained almost unchanged during the

2011-2014 period, albeit they were significantly higher in the following years (2015-2017). A similar trend has been previously reported in salmonellosis rates in all age groups in Greece, most likely attributed to improved hospital staff compliance with reporting procedures, especially following a study highlighting salmonellosis underreporting in Greece compared to other countries (18, 19). Alternatively, a recently established weekly comparison of NRCS data with those reported to the HCDCP may have contributed to the increase in salmonellosis rates during the 2015-2017 period. Additionally, this increase was in line with an increase in the number of *Salmonella* outbreaks in other countries across Europe (19). In detail, on the basis of data of the European Centre for Disease Prevention and Control (ECDC), salmonellosis rates in Europe gradually decreased during the 2007-2013 period. The implementation of an integrated legislative approach by food business operators and policy makers in Europe, to monitor and control salmonellosis along the food chain from primary production to consumption, over the last 10 years thus brought about important progress. Nevertheless, in the years that followed, an increasing trend was observed (19). Alternatively, travel-associated cases may have contributed to this increase. However, Greece was among the countries with the highest proportion of domestic cases versus travel-associated cases, ranging from 86% to 100% (19).

In our study, the most commonly identified serovars were *Salmonella Enteritidis*, *Salmonella Typhimurium* and *Salmonella monophasic Typhimurium*. The last is a monophasic variant of *Salmonella* serovar that lacks the second-phase flagellar antigen encoded by the *fljB* gene, and its exact antigenic formula is 4,[5],12:i:1,2. *Salmonella Enteritidis* and *Salmonella Typhimurium* were also the most common serovars in previous studies conducted in Greece (20-23). Our results agree with those reported by the WHONET, *Greek System for the Surveillance of Antimicrobial Resistance*. Similar trends have been reported in other European countries (24-26). Low percentages of *Salmonella Typhi* and *Salmonella Paratyphi B* were recorded in our study,

in accordance with other studies reporting low rates of typhoid *Salmonella* cases (~1-2%) (24-26). The remaining serovars, although quite rarely reported, accounted for nearly half of all reported cases, in agreement with other European reports (24-26). Remarkably, *Salmonella monophasic Typhimurium* cases increased substantially during the study period, being the second most prevalent serovar in 2017. The first description of a monophasic *Salmonella Typhimurium* epidemic in Europe was that of a "Spanish clone," in 1997 (24-26). Since then, many European countries have reported the increased incidence of this serovar responsible for foodborne disease, particularly associated with pig herds, but later with cattle (27, 28).

The majority of salmonellosis cases were reported among infants, as previously described (29). Remarkably, salmonellosis rates in children were consistently higher compared to adults, since children often present with more severe symptoms and are more frequently admitted (24). Therefore, salmonellosis in children is more likely to be recorded, compared to adults, who most often present with mild symptoms and do not refer to a physician.

The vast majority of salmonellosis cases were reported in Athens, most likely implying better compliance with the reporting procedures. Indeed, city hospitals have easier access to diagnostic procedures compared to regional ones. Continuous monitoring and better staff training in the reporting procedures are required to overcome this problem.

Our results support recently published European data showing low resistance rates to 3<sup>rd</sup> generation cephalosporins among non-typhoid *Salmonella* serovars (19). All non-typhoid *Salmonella spp.* isolates were susceptible to ciprofloxacin, although higher resistance rates have been reported in Europe (~11%) (24-26). Resistance rates of non-typhoid *Salmonella* serovars to chloramphenicol also remained low. Non-typhoid *Salmonella spp.* isolates displayed considerable resistance rates to sulfamethoxazole, streptomycin, tetracycline and ampicillin, as previously described (24-26). No non-typhoid *Salmonella spp.* isolate was resistant to ciprofloxacin and cefotaxime. This finding agrees with European data re-

porting that combined resistance to ciprofloxacin and cefotaxime was 0.6% (24).

*Salmonella Enteritidis* isolates displayed low resistance rates to 3<sup>rd</sup> generation cephalosporins; resistance rates to ciprofloxacin were also low (0%). Other European data show that *Salmonella Enteritidis* resistance rates to 3<sup>rd</sup> generation cephalosporins were also low, whereas a higher proportion of *Salmonella Enteritidis* isolates (12.3%) were resistant to ciprofloxacin (24-26). Overall, resistance rates of *Salmonella Enteritidis* were lower compared to a previous study conducted in Greece (23). *Salmonella Typhimurium* and *monophasic Typhimurium* isolates also exhibited low resistance rates to 3<sup>rd</sup> generation cephalosporins and ciprofloxacin, as previously described in Europe (24-26).

Notably, an increasing prevalence of MDR *Salmonella monophasic Typhimurium* isolates was observed among children in our study. A similar trend has been previously described in Europe and the USA among the general population. Currently, there are no available data showing that there was also such an increase among the subpopulation of children (30-31).

The antimicrobial resistance profile of typhoid *Salmonella* isolates in our study is similar to that reported by other European countries (17). Importantly, antimicrobial resistance rates to 3<sup>rd</sup> generation cephalosporins and ciprofloxacin remain low (19). Significant resistance rates have been reported to ampicillin, chloramphenicol, nalidixic acid and sulfamethoxazole (19). Notably, 10% of isolates were MDR, while in endemic regions in Sub-Saharan Africa and South-East Asia the corresponding percentage was >33.3% (32).

*Salmonella* bacteremia most commonly affected infants and young children <5 years of age, with a slight predominance of boys, similarly to previous reports (22). *Salmonella Enteritidis* was the most common isolate associated with bacteremia, also frequently isolated in stool cultures, as previously described in Greece (22). *Salmonella Typhimurium*, *Salmonella Enteritidis* and *Salmonella Dublin* are the most frequently related with bacteremia worldwide (33). Antimicrobial resistance rates to clinically important 3<sup>rd</sup> generation

cephalosporins and ciprofloxacin for *Salmonella* isolates causing bacteremia remained low (34). In our study, almost one in five *Salmonella* bacteremia isolates (17.1%) were MDR, similarly to previous studies reporting that MDR isolates are most frequently associated with bacteremia (9-11).

Our study has several limitations, mainly associated with its retrospective design. Firstly, supplementary epidemiological data are often underreported, confounding our results. However, we assume that weekly validation of our data with the HCDCP may have minimized this possibility. Secondly, hospital staff in regional areas (apart from Athens) often do not comply with the reporting procedures, implying that continuous training is required to increase the salmonellosis reporting rates. Besides, most comparisons have been made with studies conducted among adults. Although *Salmonella* serovars that cause disease in adults and children do not differ significantly, underlying conditions or previous antibiotic use in adults may affect antimicrobial resistance patterns. Furthermore, large amounts of data on epidemiological characteristics and antimicrobial resistance were missing. To overcome this problem, we mentioned the precise number of cases for which the corresponding data were available. Besides, this study was based on data recorded by the NRCS over the period 2011 to 2017. Apart from epidemiological data i.e age, gender, specimen source, geographical data and recent travel abroad, other data regarding the clinical course are not routinely provided. Therefore, such an analysis was not feasible. The inclusion of sulfamethoxazole data for only 4 of the surveillance years is a notable limitation, but that did not preclude us from unveiling the high rates of antimicrobial resistance to this important antimicrobial during the years that it was available. Finally, resistance rates to azithromycin, that is currently an important clinical choice, were not evaluated in our study.

## Conclusion

In conclusion, we have provided a blueprint of current serovar prevalence and antimicrobial resistance of *Salmonella* isolates among children

in Greece. Salmonellosis epidemiology in Greek children is comparable to previously published European data. Antimicrobial resistance rates to 3<sup>rd</sup> generation cephalosporins and ciprofloxacin for non-typhoid and typhoid-paratyphoid remain low. Notably, there is an increasing prevalence of *Salmonella monophasic Typhimurium* isolates, associated with multiple antimicrobial resistance. Hence, continuous surveillance is mandatory, to monitor such trends.

#### What Is Already Known on this Topic:

*Salmonellosis is a major health problem worldwide. Resistance to the current 1st line antibiotics, such as ciprofloxacin and 3rd-generation cephalosporins, the higher rates of Salmonella spp. isolates resistant to fluoroquinolones, as well as the emergence of ESBL and MDR clinical isolates are important clinical concerns. This problem has become even worse among children who predominantly present with severe salmonellosis. However, hardly any studies exist describing Salmonella epidemiology and antimicrobial resistance among this vulnerable population.*

#### What this Study Adds:

*This study presents the epidemiological data, serovar distribution and antimicrobial resistance patterns of Salmonella spp. isolates among children aged ≤14 years old in Greece. This information allowed a comparison between Salmonella surveillance data in this population and European data among adults already published, encouraging clinicians to feel comfortable prescribing 3rd generation cephalosporins and fluoroquinolones as the 1st line empirical treatment of salmonellosis in children. This approach, together with control measures (i.e. avoiding unnecessary antibiotic therapy) will lead to the more judicious use of antimicrobials for the treatment of salmonellosis, with the potential to suppress antimicrobial resistance further with continuous surveillance of salmonellosis epidemiology and antimicrobial resistance.*

**Authors' Contributions:** Conception and design: GG and GM; Acquisition, analysis and interpretation of data: GG and GM; Drafting the article TL; Revising it critically for important intellectual content: GG and GM; Approved final version of the manuscript: GG, TL and GM.

**Conflict of Interest:** The authors declare that they have no conflict of interest.

#### References

- ECDC E. The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2016. EFSA J. 2018;16(2):5182. DOI: 10.2903/j.efsa.2018.5182
- Crump JA, Mintz ED. Global trends in typhoid and paratyphoid fever. Clin Infect Dis. 2010;50(2):241-6.
- Bula-Rudas FJ, Rathore MH, Maraqa NF. Salmonella Infections in Childhood. Adv Pediatr. 2015;62(1):29-58.
- O'Brien SJ. The "decline and fall" of nontyphoidal salmonella in the United Kingdom. Clin Infect Dis. 2013;56(5):705-10.
- European Food Safety Authority and European Centre for Disease Prevention and Control (EFSA and ECDC). The European Union One Health 2018 Zoonoses Report. EFSA J. 2019;17(12):e05926.
- Crump JA, Sjölund-Karlsson M, Gordon MA, Parrye CM. Epidemiology, Clinical Presentation, Laboratory Diagnosis, Antimicrobial Resistance, and Antimicrobial Management of Invasive Salmonella Infections. Clin Microbiol Rev. 2015;28(4):901-37.
- Chen HM, Wang Y, Su LH, Chiu CH. Nontyphoid Salmonella infection: Microbiology, clinical features, and antimicrobial therapy. Pediatr Neonatol. 2013;54(3):147-52.
- Kagambèga A, Lienemann T, Aulu L, Traoré AS, Barro N, Siitonen A HK. Prevalence and characterization of Salmonella enterica from the feces of cattle, poultry, swine and hedgehogs in Burkina Faso and their comparison to human Salmonella isolate. BMC Microbiol. 2013;13:253.
- Hassing RJ, Goessens WHF, van Pelt W, Mevius DJ, Stricker BH, Molhoek N, et al. Salmonella subtypes with increased MICs for azithromycin in travelers returned to the Netherlands. Emerg Infect Dis. 2014;20(4):705-8.
- Abgottsson H, Zurfluh K, Nüesch-Inderbinen M, Hächler H, Stephan R. Quinolone resistance mechanisms in salmonella enterica serovars hadar, kentucky, virchow, schwarzengrund, and 4,5,12:i:-, isolated from humans in Switzerland, and identification of a novel qnrD variant, qnrD2, in s. hadar. Antimicrob Agents Chemother. 2014;58(6):3560-3.
- Doublet B, Praud K, Nguyen-Ho-Bao T, Argudín MA, Bertrand S, Butaye P, et al. Extended-spectrum  $\beta$ -lactamase- and ampc  $\beta$ -lactamase-producing D-tartrate-positive Salmonella enterica serovar Paratyphi B from broilers and human patients in Belgium, 2008-10. J Antimicrob Chemother. 2014;69(5):1257-64.
- Arnoldini M, Vizcarra IA, Pena-Miller R, Stocker N, Diard M, Vogel V, et al. Bistable expression of virulence genes in Salmonella leads to the formation of an antibiotic-tolerant subpopulation. PLoS Biol. 2014;12:e1001928.
- Claudi B, Sprote P, Chirkova A, Personnic N, Zankl J, Schurmann N, et al. Phenotypic variation of Salmonella in host tissues delays eradication by antimicrobial chemotherapy. Cell. 2014;158(4):722-33.
- Wirth T. Massive lineage replacements and cryptic outbreaks of Salmonella Typhi in eastern and southern Africa. Nat Genet. 2015;47(6):565-7.
- Colobatiu L, Tabaran A, Flonta M, Oniga O, Mirel S, Mihaie M. First description of plasmid-mediated quinolone resistance determinants and beta-lactamase encoding genes in non-typhoidal Salmonella isolated from humans, one companion animal and food in Romania. Gut Pathog. 2015;7:16. doi:10.1186/s13099-015-0063-3.

16. Wong VK, Baker S, Pickard DJ, Parkhill J, Page AJ, Feasey NA, et al. Phylogeographical analysis of the dominant multidrug-resistant H58 clade of *Salmonella* Typhi identifies inter- and intracontinental transmission events. *Nat Genet.* 2015;47(6):632-9.
17. European Centre for Disease Prevention and Control. EU Protocol for Harmonized Monitoring of Antimicrobial Resistance in Human *Salmonella* and *Campylobacter* Isolates – June 2016. Stockholm: ECDC; 2016.
18. Mellou K, Saranti-Papasaranti E, Mandilara G, Georgakopoulou T. Laboratory capacity of Greek hospitals for diagnosis of salmonellosis and surveillance systems' performance in the years of economic crisis, 2010-2016. *Epidemiol Infect.* 2019;147:e17.
19. European Food Safety Authority. The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2017. *EFSA Journal.* 2018;16(12):5500.
20. Maraki S, Papadakis IS. Serotypes and antimicrobial resistance of human nontyphoidal isolates of *salmonella enterica* from crete, Greece. *Interdiscip Perspect Infect Dis.* 2014;2014:256181.
21. Maraki S, Mantadakis E, Nioti E, Katragkou A, Samonis G. Serotype distribution and antibiotic resistance of human gastrointestinal isolates of *salmonella enterica* from Crete, Greece. *J Chemother.* 2009;21(2):222-5.
22. Papaevangelou V, Syriopoulou V, Charissiadou A, Pangalis A, Mostrou G, Theodoridou M. *Salmonella* bacteraemia in a tertiary children's hospital. *Scand J Infect Dis.* 2004;36(8):547.
23. Tassios PT, Markogiannakis A, Vatopoulos AC, Katsanikou E, Velonakis EN, Kourea-Kremastinou J, et al. Molecular epidemiology of antibiotic resistance of *Salmonella enteritidis* during a 7-year period in Greece. *J Clin Microbiol.* 1997;35(6):1316-21.
24. European Centre for Disease Prevention and Control. Annual Epidemiological Report 2016 – Typhoid and paratyphoid fever. [Internet]. Stockholm: ECDC; 2016.
25. Collard JM, Bertrand S, Dierick K, Godard C, Wildemaue C, Vermeersch K, et al. Drastic decrease of *Salmonella* Enteritidis isolated from humans in Belgium in 2005, shift in phage types and influence on foodborne outbreaks. *Epidemiol Infect.* 2008;136(6):771-81.
26. ECDC. Disease Data from ECDC Surveillance Atlas -Salmonellosis.; 2018. Available from: <https://www.ecdc.europa.eu/en/salmonellosis/surveillance-and-disease/atlas>.
27. Animal Health and Veterinary Laboratories Agency. Department for Environment and Food and Rural Affairs. *Salmonella* in Livestock Production in Great Britain, 2013. Surrey: Animal Health and Veterinary Laboratories Agency; 2013.
28. Moreno Switt AI, Soyer Y, Warnick LD, Wiedmann M. Emergence, distribution, and molecular and phenotypic characteristics of *Salmonella enterica* serotype 4,5,12:i:-. *Foodborne Pathog Dis.* 2009;6(4):407-15.
29. Sinha A, Sazawal S, Kumar R, Sood S, Reddaiah VP, Singh B, et al. Typhoid fever in children aged less than 5 years. *Lancet.* 1999;354(9180):734-7.
30. Petrovska L, Mather AE, Abuoun M, Branchu P, Harris SR, Connor T, et al. Microevolution of monophasic *Salmonella typhimurium* during epidemic, United Kingdom, 2005–2010. *Emerg Infect Dis.* 2016;22(4):617-24.
31. Shippy DC, Bearson BL, Holman DB, Brunelle BW, Allen HK, Bearson SMD. Porcine Response to a Multidrug-Resistant *Salmonella enterica* serovar I 4,[5],12:i:- Outbreak Isolate. *Foodborne Pathog Dis.* 2018;15(5):253-61.
32. Bhan MK, Bahl R BS. Typhoid and Paratyphoid Fever. *Lancet.* 2005;366(9487):749-62.
33. Ao TT, Feasey NA, Gordon MA, Keddy KH, Angulo FJ, Crump JA. Global Burden of Invasive Nontyphoidal *Salmonella* Disease, 2010. *Emerg Infect Dis.* 2015;21(6):941-9.
34. Crump JA, Medalla FM, Joyce KW, Krueger AL, Hoekstra RM, Whichard JM, et al. Antimicrobial resistance among invasive nontyphoidal *Salmonella enterica* isolates in the United States: National Antimicrobial Resistance Monitoring System, 1996 to 2007. *Antimicrob Agents Chemother.* 2011;55(3):1148-54.

## Multivessel Disease Patients' Outcome and Second Generation Stent: Is Syntax Still a Valid Score? A Real-World Study from a Tertiary Center

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### Abstract

**Objective.** The SYNTAX trial was designed to evaluate whether multivessel disease patients could benefit from percutaneous or surgical revascularization using a paclitaxel eluting stents, but after the introduction of second generation stents, this score needs to be reevaluated. The aim of our study was to analyze the association between SYNTAX score and the prognosis of multivessel patients submitted to percutaneous coronary intervention (PCI) and second generation everolimus eluting stents (EES) implantation. **Materials and Methods.** Data on 289 patients with multivessel coronary artery disease submitted to PCI with EES were stored in a dedicated database and retrospectively analyzed. During a mean follow-up period of  $14.4 \pm 6.4$  months, major adverse cardiac and cerebrovascular events (MACCE) including death from any cause, myocardial infarction, target lesion revascularization (TLR) and stroke, were systematically assessed. **Results.** The incidence of MACCE at follow-up was 13.1%; death from any cause occurred in 19 patients (6.6%) and myocardial infarction in 9 patients (3.1%). TLR was detected in 2.7% of patients and stroke was observed in 2 patients. The SYNTAX score did not prove to be an independent predictor of overall death at multivariable analysis. **Conclusion.** At mid-term follow-up, the incidence of MACCE in multivessel disease patients submitted to PCI and EES implantation was low; no significant association was found between SYNTAX score severity and MACCE at follow-up, suggesting that it should be modified after the introduction of EES.

**Key Words:** Multivessel Disease ■ Percutaneous Coronary Intervention ■ SYNTAX Trial ■ Dual Antiplatelet Therapy ■ Outcome.

### Introduction

Revascularization treatments for patients with complex coronary lesions are continuously evolving and new scores to choose the best approach for revascularization have been investigated. Despite this, the indications for coronary revascularization continue to be debated between interventional cardiologists and surgeons, who have experience with new drug-eluting stents (DES) and percutaneous coronary intervention (PCI) techniques, as well as new coronary artery bypass graft (CABG) strategies, in their daily practice. In the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial (1) PCI with paclitaxel eluting stents (PES) was compared to CABG as the primary treatment option for patients with de novo coronary three-vessel disease,

and/or left main (LM) disease. CABG resulted in significantly more favourable outcomes for the incidence of target lesion revascularization (TLR), and major adverse cardiac and cerebrovascular events (MACCE), after twelve months in patients with a SYNTAX score  $\geq 33$  (2). The SYNTAX score is a tool to characterize coronary anatomy on the basis of nine anatomical criteria, including the number, the site and the complexity of coronary lesions, obtaining a score for each lesion and an overall score for each patient. The score obtained is divided into three classes [low ( $\leq 22$ ), intermediate (23-32) and high ( $\geq 33$ )]. Apart from patients with low SYNTAX score ( $\leq 22$ ) for whom PCI is preferred over CABG, for patients with a SYNTAX score of 23-32, the SYNTAX trial does not furnish strict recom-

recommendations, reporting only a higher, though not significantly, incidence of MACCE in PCI patients (16.7% versus 12.4% in CABG patients) (1). Recent data reporting the 5 year follow-up of this trial have shown that in patients with a SYNTAX score higher than 22, CABG with respect to PCI demonstrated clear superiority in terms of MACCE, death, MI, and repeat revascularization (3). Nevertheless, previous studies demonstrated that the introduction of everolimus eluting stents (EES) has been associated with a reduction in events with respect to PES (4-6), suggesting that the use of the anatomical SYNTAX score needs to be reevaluated. Moreover, in a wide open-label randomized trial, PCI with EES in patients with multivessel coronary artery disease was not inferior in respect to CABG, despite a similar anatomical SYNTAX score (7).

In addition to this, other SYNTAX derived scores have been developed in the last few years to better guide decision-making between CABG and PCI, that combine the anatomical SYNTAX score with other clinical variables (8, 9) and have been demonstrated superior to the purely angiographic score (10, 11).

The aim of our study was to evaluate the association between the SYNTAX score and the outcome of 289 unselected multivessel patients, consecutively submitted to PCI and EES implantation in the General Cardiology Unit of the Department of Cardiovascular and Thoracic Medicine of the Azienda Ospedaliero-Universitaria Careggi in Florence (Italy).

## Material and Methods

### *Patient Population and Study Design*

In our study we analyzed the data of 349 patients with multivessel coronary artery disease who were admitted to the General Cardiology Unit of the Department of Cardiovascular and Thoracic Medicine of the Azienda Ospedaliero-Universitaria Careggi in Florence (Italy) from January 2010 to December 2010 for stable angina (SA) (N=88), non-ST acute coronary syndrome (NST-ACS) (N=182) or ST elevation myocardial infarction (STEMI) (N=79). Among these, 289 patients (83%) underwent PCI and 60 (17%) CABG, and the latter were excluded from the analysis, which was based on PCI patients alone. The selection

of patients for CABG was based not only on the SYNTAX score (mean  $43.8 \pm 10.3$ ) but also on clinical and instrumental assessment, taking into consideration the presence of a concomitant valvulopathy, the possible contraindications to dual antiplatelet therapy (DAPT), or the presence of comorbidities. The clinical, biohumoral and angiographic data of multivessel patients submitted to PCI were collected and stored in a dedicated database and analyzed retrospectively. In particular, data on gender, age, arterial hypertension, obesity (defined as a body mass index  $>30 \text{ Kg/m}^2$ ), diabetes mellitus, dyslipidemia, smoking habit, chronic obstructive pulmonary disease, and a family history of cardiovascular disease were collected. The presence of peripheral arteriopathy was diagnosed by means of Doppler ultrasound. Renal failure was defined as an estimated glomerular filtration rate (eGFR)  $<30 \text{ ml/min}$  measured using Cockcroft-Gault equation. The EuroSCORE I was calculated as previously reported (12). Doppler echocardiography was performed in all patients to exclude the presence of severe valvulopathy, as well as to evaluate left ventricular ejection fraction. Blood chemistry included the measurement of troponin I, CK-MB, creatine phosphokinase and creatinine values.

Coronary angiography and PCI were performed as previously described according to the International Guidelines (13); in the majority of patients (92.3%) radial access was employed. In 104 patients (35.9%), PCI was staged in several sessions depending on lesion complexity, hemodynamic status or associated renal failure; exclusively Xience V everolimus stents were implanted in all patients. This kind of stents was the only second generation stent available in our hospital during the study period.

Chronic total occlusion (CTO) was defined as the complete occlusion of the vessel by heavy atherosclerotic plaque that had been present for at least 3 months. Vessels with CTO were treated with PCI only after demonstration of ischemia viability in the segment of the myocardium supplied by the index vessel, and in the presence of favourable anatomical characteristics. A revascularization was defined "complete" if all stenotic vessels  $\geq 2.5 \text{ mm}$  were revascularized (anatomic revascularization) (14).

### ***SYNTAX Score Calculation***

The SYNTAX score is a tool to characterize coronary anatomy on the basis of nine anatomical criteria, including the number, the site and the complexity of coronary lesions, obtaining a score for each lesion and an overall score for each patient (1). The score is given by the sum of the scores of each individual lesion >50% in vessels with a diameter >1.5 mm. The coronary tree is divided into 16 segments based on the AHA classification. Each segment is assigned a score of 1 or 2 which is based on the presence or absence of atherosclerotic disease, and this score is weighed on the location of the disease in the different coronary segments (from 3.5 for the proximal left anterior descending to 5.0 for the left main). Vessels less than 1.5 mm in diameter are not included in the score calculation. A multiplication factor of x 2 is used for non-occlusive and x 5 for total occlusions, reflecting the difficulty of the angioplasty revascularization procedure. The computerized algorithm calculates the total score based on 12 main questions that can be divided into two groups. The first three questions determine the coronary dominance, the total number of lesions and the coronary segments involved. The other nine questions refer to the morphological characteristics of the lesions and are repeated for each lesion. For example, one point is given for bifurcations of type A, B or C, 2 points for D, E, F, or G, and one point is given for bifurcation angles greater than 70°. The scores obtained with the SYNTAX score can be divided into 3 classes, [low ( $\leq 22$ ), intermediate (23-32) and high ( $\geq 33$ )]. A high SYNTAX score, indicating a more complex coronary picture, suggests the high risk of submitting the patient to a mechanical revascularization strategy, and is related to a poor prognosis (therefore CABG is better), while a low score favours PCI. An important feature of the score is that it is weighed exclusively on anatomical lesion criteria, and a separate score is calculated for each lesion. The total score is then calculated from the sum of the individual scores.

### ***Antiplatelet Therapy and Other Therapeutic Measures***

All patients received a loading dose of acetylsalicylic acid (ASA) 325 mg and clopidogrel 300 mg the day before the PCI in the elective procedures, and a loading dose of ASA 325 mg and clopidogrel 600 mg in the catheterization laboratory for urgent PCI. After the procedure, all patients were treated with ASA 100 mg/day and clopidogrel 75 mg/day. Moreover, in these patients platelet aggregation was evaluated with Light Transmittance Aggregometry (LTA) induced by ADP (10 micromol/L) and arachidonic acid (2 mmol/L) in platelet rich plasma, in order to estimate the Residual Platelet Activity (RPA) on antiplatelet therapy (15). Responders were identified by a RPA <70% for ADP and <20% for arachidonic acid (15). Non-responder patients were switched from clopidogrel to prasugrel (that was the only alternative P2Y<sub>12</sub> receptor inhibitor available at the time of the study), and from ASA 100 mg to a higher dose (160-325 mg), as previously reported (16).

To prevent contrast induced nephropathy (CIN), elective patients underwent hyper-hydration with saline solution and intravenous administration of N-Acetyl Cisteyn 600 mg twice/day. Patients affected by Chronic Renal Failure with eGFR <30 ml/min were submitted to continuous renal replacement therapy (CRRT) before and after contrast medium administration (13).

All patients gave their informed consent for participation in the study, and all the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation, and with the Helsinki Declaration of 1975, as revised in 1983.

### ***Follow-Up***

Clinical follow-up was scheduled at 1, 6 and 12 months, and performed in all 289 patients (100%) by independent research personnel who were unaware of the study objectives. During the scheduled visit electrocardiography and Doppler echocardiography were performed. A stress test was scheduled in all patients in the following 6-12 months,

and coronary angiography was only performed in patients with documented ischemia or those who had undergone very complex procedures, or who had unequivocal clinical symptoms of angina. In case of hospitalization, data were obtained by a systematic review of the hospital records.

The primary end-point of the study included MACCE, consisting in death from any cause, myocardial infarction, TLR and stroke as in the SYNTAX trial, and the secondary end-point included cardiovascular death, stable angina, CIN and bleedings, and their correlation with SYNTAX score.

Data regarding the primary and secondary end-points were systematically assessed during a mean follow-up period of  $14.4 \pm 6.4$  months.

Myocardial infarction was defined after the detection of a rise and/or fall in cardiac biomarker values [preferably cardiac troponin I (TnI)] with at least one value above the 99<sup>th</sup> percentile upper reference limit and with at least one of the following: 1) symptoms of ischemia; 2) new or presumed new significant ST-segment - T wave changes or new left bundle branch block; 3) development of pathological Q waves in the ECG; 4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; 5) identification of an intracoronary thrombus by angiography or autopsy (17).

TLR was defined as a PCI of the target lesion due to restenosis or re-occlusion within the stent or in an adjacent segment of 5 mm distally or proximally to the edges of the stent (18). Stroke was defined as rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin. Cardiovascular death was defined as death resulting from an acute myocardial infarction, sudden cardiac death or death due to heart failure, stroke, cardiovascular procedures, cardiovascular haemorrhage, and to other cardiovascular causes. Stable angina was defined as chest pain or discomfort occurring most often with activity or emotional stress.

CIN was defined as a 25% increase in creatinine compared to its baseline value after PCI. Major bleedings were classified according to TIMI criteria as a decrease in haemoglobin  $>5$  g/dl or at least 15%

in haematocrits; minor bleedings were classified according to TIMI criteria as a decrease in haemoglobin  $>3$  g/dl or at least 10% in hematocrits (19). Follow-up data were obtained either by hospital records or by phone by two physicians unaware of the patients' in-hospital course, and were verified by the Registry Office of the Florence Health Authority.

### **Statistical Analysis**

Data were stored in a dedicated database and analyzed with the IBM-SPSS 20.0 statistical package (SPSS Inc. Chicago, IL, USA). Continuous variables were tested for normality with the Kolmogorov-Smirnov one sample test, and reported as mean  $\pm$  SD or median and interquartile range when appropriate. Categorical variables were expressed as frequency and/or percentage. Between-group comparisons were performed with Student's t and chi-square (or Fisher's when needed) tests, respectively. A two-tailed p-value less than 5% was considered significant. Unadjusted OR and their relative 95% confidence intervals for the occurrence of MACCE were calculated either considering a one unit step increase in the SYNTAX score and different classes of SYNTAX score [class 2 (23-32) vs. class 1 ( $\leq 22$ ), class 3 ( $\geq 33$ ) vs. class 1 ( $\leq 22$ ) and class 3 ( $\geq 33$ ) vs. class 2 (23-32)] for each cardiovascular event. Outcomes which were significantly associated with SYNTAX score (one unit step increase) at univariate analysis were further adjusted at multivariable analysis for clinical, angiographic and laboratory data related to the antiplatelet response significantly associated with the outcome examined at univariate analysis. Multivariable analysis was performed to evaluate the independent association between adverse events significantly associated with the SYNTAX score at univariate analysis, and other clinical, angiographic and laboratory data significantly associated with the outcome analyzed at univariate analysis. Considering overall death as an independent variable, we adjusted the analysis for renal dysfunction, EuroSCORE I and response to ADP. Taking into account the number of events (19 overall deaths occurred at follow-up) only two predictors were added simultaneously to the

model of multivariable analysis. A ROC curve was built to evaluate the value of SYNTAX score with a higher specificity/sensitivity ratio in predicting cardiovascular events.

## Results

The baseline clinical characteristics of patients submitted to PCI and analyzed in the study are reported in Table 1.

Table 1. Baseline Clinical and Laboratory Characteristics with Data Related to Response to Standard Antiplatelet Therapy of Multivessel Patients Submitted to PCI

Characteristics	PCI patients (N=289)
Age (years), mean $\pm$ SD	69 $\pm$ 11
Male gender, N (%)	219 (75.8)
Admission diagnosis, N (%)	
STEMI	73 (25.3)
ACS	142 (49.1)
Stable angina	74 (25.6)
Cardiovascular risk factors, N (%)	
Arterial hypertension	215 (74.4)
Obesity (BMI >30 kg/m <sup>2</sup> )	37 (12.8)
Diabetes mellitus	93 (32.2)
Dyslipidemia	149 (51.6)
Smoking habit	152 (52.6)
Family history of cardiovascular disease	101 (34.9)
Comorbidities	
Peripheral arteriopathy, N (%)	118 (40.8)
Renal failure (eGFR <30 ml/min), N (%)	23 (8.0)
COPD, N (%)	33 (11.4)
EuroSCORE I, median (25 <sup>th</sup> -75 <sup>th</sup> percentile)	9.61 (0.88; 59.33)
Clinical history, N (%)	
Heart failure	32 (11.1)
Associated valvulopathy	4 (1.3)
Previous MI	57 (19.7)
Previous PCI	89 (30.8)
Blood chemistry	
TnI peak (mcg/L), median (25 <sup>th</sup> -75 <sup>th</sup> percentile)	5.29 (0.67 – 43.76)
CK-MB peak (ng/mL), median (25 <sup>th</sup> -75 <sup>th</sup> percentile)	16.6 (4.25 – 76.65)
CPK peak (U/L), median (25 <sup>th</sup> -75 <sup>th</sup> percentile)	346.0 (120.5 – 1109.0)
Creatinine (mg/dL), mean $\pm$ SD	1.4 $\pm$ 0.6
Response to antiplatelet therapy	
Response to ADP, N (%)	
RPA >70% (responder to clopidogrel)	234 (80.9)
RPA <70% (not responder to clopidogrel)	55 (19.0)
Shift to Prasugrel, N (%)	53 (18.3)
Response to Arachidonic Acid, N (%)	
RPA < 20% (responder to ASA)	210 (72.6)
RPA > 20% (not responder to ASA)	79 (27.3)
Shift to higher-dose aspirin, N (%)	27 (9.3)

Continuous variables are presented as mean  $\pm$  1 SD or median (25<sup>th</sup>-75<sup>th</sup> percentile); discrete variables are presented as N (percentage). PCI=Percutaneous coronary intervention; STEMI=ST elevation myocardial infarction; ACS=Acute coronary syndrome; BMI=Body mass index; COPD=Chronic obstructive pulmonary disease; eGFR=estimated Glomerular filtration rate; MI=Myocardial infarction; TnI= Troponin I; CK-MB=Creatine phosphokinase-MB; CPK=Creatine phosphokinase; ADP=Adenosine diphosphate; RPA= Residual platelet activity; ASA=Acetylsalicylic acid.

Table 2. Angiographic Data and Adverse Events at Follow-Up of Multivessel Patients Submitted to PCI

Variables	PCI patients N=289
SYNTAX score, mean $\pm$ SD	24.52 $\pm$ 7.18
SYNTAX score classes, N (%)	
≤ 22	84 (29.0)
23-32	145 (50.1)
> 33	60 (20.7)
3-vessel disease, N (%)	178 (61.6)
2-vessel disease, N (%)	111 (38.4)
Critical stenoses, N (%)	
Total	525 (100)
LM	23 (7.9)
LAD	193 (66.7)
CX	162 (56.0)
RCA	147 (50.8)
Chronically occluded vessels, N (%)	
Total	49 (16.9)
LM	0
LAD	11 (3.8)
CX	14 (4.8)
RCA	24 (8.3)
Total stents implanted (N)	708
Complete revascularization, N (%)	250 (86.5)
Stents length (mm), mean $\pm$ SD	51.32 $\pm$ 31.23
Post procedural TIMI flow grade III, N (%)	547 (99.8)
Primary Outcomes, N (%)	
MACCE	38 (13.1)
Death from any cause	19 (6.6)
Target lesion revascularization	8 (2.7)
Myocardial infarction	9 (3.1)
Stroke	2 (0.7)
Secondary Outcomes, N (%)	
Cardiovascular death	13 (4.5)
Stable angina	19 (6.6)
Contrast induced nephropathy	21 (7.3)
Bleedings	4 (1.4)
Others	
Left ventricular ejection fraction (%), mean $\pm$ SD	48 $\pm$ 14
Length of hospital stay (days), mean $\pm$ SD	9.0 $\pm$ 2.3

Continuous variables are presented as mean ( $\pm$ SD); Categorical variables are presented as N (percentage). PCI=Percutaneous coronary intervention; LM=Left main; LAD=Left anterior descending artery; CX=Circumflex artery; RCA=Right coronary artery; TIMI=Thrombolysis in myocardial infarction; MACCE=Major adverse cardiac and cerebrovascular events.

Table 2 shows the angiographic characteristics of patients who underwent PCI. About 70% of patients had a SYNTAX score higher than 22; 62% of patients had three vessel disease and left main was involved in 7.9% of patients. Complete revascularization was obtained in a high percentage of patients (86.5%). In 21 out of 49 patients with CTO (42.8%), the CTO was not treated with PCI because of the lack of demonstration of ischemia/viability in the corresponding myocardial segment. In the remaining 28 patients, ischemia/viability was demonstrated and 17 of them (60.8%) were successfully treated with PCI. Nineteen percent of patients showed a high RPA by ADP, and 27.3% by arachidonic acid: most of them were shifted to prasugrel and/or to a higher dose of ASA to obtain a RPA <70% for ADP and <20% for arachidonic acid, when not contraindicated. None of the patients in whom CIN occurred underwent chronic hemodialysis.

During a mean follow-up of 14.4  $\pm$  6.4 months, the incidence of MACCE (death from any cause, myocardial infarction, TLR and stroke) was 13.1% and TLR was detected in 2.7% of patients (Table 1). No patient developed any definite stent thrombosis, only one patient (0.3%) presented a possible stent thrombosis. Moreover, the incidence of bleedings was 1.4%, occurring in 4 patients: 2 patients developed major bleeding and other 2 patients developed minor bleeding.

No significant differences were observed in the clinical, angiographic and laboratory data between patients experiencing MACCE and those who did not, except for a higher prevalence of severe renal dysfunction ( $P < 0.001$ ), higher mean values of the EuroSCORE I ( $P < 0.001$ ) and higher values of residual platelet reactivity by ADP ( $P = 0.011$ ), as an index of poor response to clopidogrel, in patients in whom MACCE occurred (Table 3).

Moreover, we evaluated the SYNTAX score as a predictor of adverse events at univariate analysis (Table 4 Panel A). Considering MACCE as a composite end-point we did not observe any relationship with the different classes of the SYNTAX score. Accordingly, when we considered the single adverse events that composed the pri-

Table 3. Clinical Data, Angiographic Variables and Antiplatelet Response Values in Relation to Major Cardiac and Cardiovascular Events

Variables	No MACCE N=251 (86.9%)	MACCE N=38 (13.1%)	P value
<b>Cardiovascular risk factors, N (%)</b>			
Arterial hypertension	186 (74.1)	29 (76.3)	0.771
Diabetes mellitus	76 (30.3)	17 (44.7)	0.075
Dyslipidemia	130 (51.8)	19 (50.0)	0.837
Smoking habit	134 (53.4)	18 (47.4)	0.489
Family history of cardiovascular disease	89 (35.5)	12 (31.6)	0.640
<b>Comorbidities</b>			
Peripheral arteriopathy, N (%)	36 (14.3)	8 (21.1)	0.283
Renal failure (eGFR <30 ml/min), N (%)	15 (6.0)	8 (21.1)	<0.001
Chronic obstructive pulmonary disease, N (%)	26 (10.4)	7 (18.4)	0.145
EuroSCORE I (units), mean±SD	8.29±9.02	18.14±16.00	<0.001
<b>Angiographic data</b>			
SYNTAX score (units), mean±SD	24.6±7.1	26.7±8.4	0.169
Left main involvement, N (%)	20 (8.0)	3 (7.9)	0.988
2-vessel disease, N (%)	99 (39.4)	11 (28.9)	0.214
3-vessel disease, N (%)	152 (60.6)	27 (31.1)	
Stents implanted (N), mean±SD	1.86±0.95	1.90±1.08	0.865
<b>Antiplatelet therapy, mean±SD</b>			
Response to ADP - RPA (%)	49.5±19.3	58.2±17.9	0.011
Response to Arachidonic acid - RPA (%)	20.3±15.0	24.4±18.4	0.142

Continuous variables are presented as mean ( $\pm$  1 SD); Discrete variables are presented as frequency (percentage). eGFR=estimated Glomerular filtration rate; ADP=Adenosine diphosphate; RPA=Residual platelet activity.

mary end-point MACCE (death from any cause, myocardial infarction, TLR and stroke) and the secondary end-point (stable angina, CIN, cardiovascular death and bleedings) comparing patients with low-SYNTAX score (0-22) and intermediate SYNTAX score (23-32), no significant difference in event rates between the two groups was observed. In contrast, when we compared patients with high SYNTAX score ( $\geq 33$ ) with patients with low SYNTAX score (0-22) we observed a significant difference between the two groups in relation to death from any cause and CIN that was higher in patients with SYNTAX score  $\geq 33$ . Considering instead SYNTAX score by unit step increase (Table 4 Panel B) we observed a significant increase in death from any cause and cardiovascular death.

However, at multivariable analysis, EuroSCORE I (1 unit step) was shown to be the only independent predictor of overall mortality after adjustment for renal failure, response to ADP (1%

step) and SYNTAX score (1 unit step) in a model in which variables were added separately ( $P < 0.001$  in comparison with all the variables), while SYNTAX score was not shown to be independently associated with death from any cause after adjustment for EuroSCORE I (OR 1.05 95%CI 0.98-1.13,  $P = 0.179$ ).

Finally, it was possible to identify a cut-off value of SYNTAX score by ROC curve analysis, under which the risk of adverse events was lower. In fact, the best specificity and the best sensitivity of SYNTAX score to cardiovascular events was 29.75 (Figure 1). The ROC curve (outcome: MACCE) for SYNTAX score showed an AUC of 0.68 (95%CI 0.53 to 0.83,  $P = 0.028$ ) with a value of 29.75 as the best discriminant (sensitivity 54%, specificity 79%).

Table 4. Association between Syntax Score, Either Considered by Classes ( $\leq 22$ , 22-32 and  $\geq 33$ ) (Panel A) and by One Unit Step Increase (Panel B), and Adverse Events

## Panel A

Adverse Events in relation to Syntax Score Classes	Unadjusted OR	95%CI	P value
<b>MACCE (N=38)</b>			
Class 2 (23-32) vs. Class 1 ( $\leq 22$ )	1.01	0.42-2.40	0.982
Class 3 ( $\geq 33$ ) vs. Class 1 ( $\leq 22$ )	2.15	0.84-5.52	0.111
<b>Death from any cause (N=19)</b>			
Class 2 (23-32) vs. Class 1 ( $\leq 22$ )	2.66	0.56-12.62	0.218
Class 3 ( $\geq 33$ ) vs. Class 1 ( $\leq 22$ )	6.50	1.33-31.90	0.021
<b>TLR (N=8)</b>			
Class 2 (23-32) vs. Class 1 ( $\leq 22$ )	0.14	0.02-1.24	0.076
Class 3 ( $\geq 33$ ) vs. Class 1 ( $\leq 22$ )	0.70	0.12-3.98	0.691
<b>Myocardial Infarction (N=9)</b>			
Class 2 (23-32) vs. Class 1 ( $\leq 22$ )	0.85	0.14-5.18	0.858
Class 3 ( $\geq 33$ ) vs. Class 1 ( $\leq 22$ )	3.00	0.53-16.98	0.214
Stroke (N=2);	NA (only 2 cases observed, all of them in Class 2)		
<b>Cardiovascular death (N=13)</b>			
Class 2 (23-32) vs. Class 1 ( $\leq 22$ )	4.13	0.50-34.16	0.189
Class 3 ( $\geq 33$ ) vs. Class 1 ( $\leq 22$ )	7.75	0.88-68.22	0.065
<b>Stable Angina (N=19)</b>			
Class 2 (23-32) vs. Class 1 ( $\leq 22$ )	1.04	0.37-2.94	0.936
Class 3 ( $\geq 33$ ) vs. Class 1 ( $\leq 22$ )	0.46	0.09-2.35	0.349
<b>CIN (N=8)</b>			
Class 2 (23-32) vs. Class 1 ( $\leq 22$ )	1.96	0.52-7.34	0.318
Class 3 ( $\geq 33$ ) vs. Class 1 ( $\leq 22$ )	4.28	1.08-16.92	0.038
<b>Bleedings (N=4)</b>			
Class 2 (23-32) vs. Class 1 ( $\leq 22$ )	0.56	0.08-4.06	0.567
Class 3 ( $\geq 33$ ) vs. Class 1 ( $\leq 22$ )	No bleeding in Class 3		

## Panel B

Adverse Events	PCI pts N=289 N (%)	Unadjusted OR	95%CI	P value
MACCE	38 (13.1)	1.04	0.99-1.09	0.115
Death from any cause	19 (6.6)	1.08	1.02-1.15	0.012
TLR	8 (2.7)	0.97	0.88-1.08	0.629
Myocardial Infarction	9 (3.1)	1.06	0.97-1.15	0.206
Stroke	2 (0.7)	1.03	0.86-1.24	0.755
Cardiovascular death	13 (4.5)	1.09	1.01-1.17	0.022
Stable Angina	19 (6.6)	0.99	0.93-1.06	0.796
CIN	21 (7.3)	1.06	0.99-1.12	0.062
Bleedings	4 (1.4)	0.87	0.74-1.03	0.111

PCI=Percutaneous coronary intervention; MACCE=Major adverse cardiac and cardiovascular events; TLR=Target lesion revascularization; NA=Not applicable; CIN=Contrast induced nephropathy.

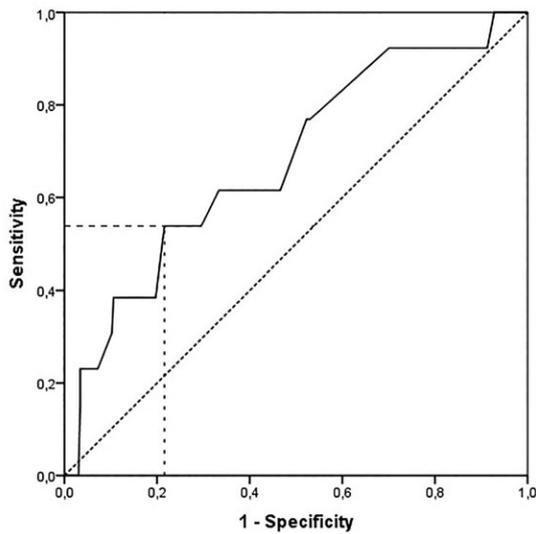


Figure 1. Analysis by ROC Curve of the Optimal Cut-Off Value of SYNTAX Score for the Occurrence of Major Cardiac and Cardiovascular Events.

## Discussion

The main finding of the present study was that, in our study population, the different classes of SYNTAX score, as defined in the homonymous trial (1) did not result clearly related to the adverse events at mid-term follow-up. On univariate analysis, when we considered overall MACCE as a composite end-point, we did not observe any relationship with any class of the SYNTAX score. On the contrary, when we considered the single adverse events that composed MACCE (death from any cause, myocardial infarction, TLR and stroke), the patients in class 3 showed a higher incidence of deaths from any cause in comparison with the patients in classes 1 and 2. However, on multivariable analysis, the SYNTAX score did not prove to be an independent predictor of overall mortality at mid-term follow-up after adjustment for other variables. It should also be noted that, in our case series, overall and cardiovascular mortality were higher than that in the SYNTAX trial, and this may have several explanations. First, in our study there was a higher percentage of acute coronary syndrome (ACS) patients than in the SYNTAX trial; about 75% of patients enrolled were ACS and a quarter of them were STEMI, while in the SYNTAX trial

acute myocardial infarction was an exclusion criteria. Second, our mean follow-up was longer than in the SYNTAX trial (14.4 vs. 12 months). Finally, in our case series, the high rate of overall death was also caused by an increased number of non-cardiovascular deaths including neoplasms, infections or fatal traumas.

Our results are not in agreement with a recent review by Head et al. that found CABG has a mortality benefit over PCI, and this was associated with the anatomical SYNTAX score complexity (20). However, that review included studies in which PCI was also performed with bare metal stents (26.6%) and first generation DES (39.2%), and this might have impacted the outcome unfavourably; moreover, data from that review also demonstrated that 5-year all-cause mortality was similar after CABG or PCI, regardless of the degree of anatomical complexity, confirming the previous results of the EXCEL trial (21).

Our results also differ from those of Garg et al. showing that the SYNTAX score is able to stratify risk in a population of patients treated with PCI and second generation DES (22). However, the percentage of patients with multivessel disease, the SYNTAX score cutoff and the type of stent analyzed were different from those of our study population. A second interesting finding of our study is that we observed a low incidence of MACCE and other complications, such as CIN or major bleedings, at mid-term follow-up.

When we compared our results with those of multivessel patients enrolled in the SYNTAX study and treated with PCI, we observed that the incidence of TLR and MACCE were significantly lower in our study population: 2.7% versus 13.7% and 13.1% versus 17.8%, respectively. Also comparing the subgroups of patients matched for SYNTAX score categories, the incidence of MACCE was significantly lower than that reported in the SYNTAX study: 13.6%, 16.7% and 23.4% in patients with low, intermediate and high scores in the SYNTAX trial, 8.3%, 14.3% and 16.7% in our population. Unlike the SYNTAX trial that reported a higher risk of cardiovascular events in patients with SYNTAX score >22, in our study population even patients with

SYNTAX score >22 showed a very low incidence of adverse events, and the ROC curve analysis showed a higher cut-off of the score predicting cardiovascular events, equal to 29.75. These results suggest that the differences observed in patient outcome between our study and the SYNTAX trial are not exclusively ascribable to anatomical complexity.

There are several possible reasons for this: first of all, the relatively small sample size of our population could have favourably impacted the incidence of adverse events. Moreover, in our group of patients, the percentage of those with a SYNTAX score >32 was about 20% versus 33% in the SYNTAX study, and the mean value of the SYNTAX score was 24.5 versus 29, respectively. Another main difference was the kind of stent used in our patients: the Xience V stent instead of the now obsolete Taxus, a paclitaxel eluting stent (PES), which has not been used in daily practice since the availability of EES; the Xience V stent has a less inflammatory impact and, consequently, earlier coverage than the Taxus stent (23), and recent evidence suggests that EES is associated with a lower incidence of MACCE with respect to PES (4-6, 24, 25). Moreover, in our population in a high percentage of patients (86.5%) we achieved complete anatomical revascularization that is associated with a better outcome (26-28). Even if the concept of complete revascularization has mainly been emphasized as a point in favour of cardiac surgery, our results demonstrated, according to a recent study (29), that complete anatomical revascularization can be achieved in a high percentage of multivessel patients treated with PCI. The main reason for failure to achieve complete anatomic revascularization in our study population was represented by CTO not associated with regional ischemia (21 patients) or unsuccessful treatment with PCI (11 patients). Moreover, also the “complete revascularization” provided by CABG has limitations such as: 1) the proximal part of native coronary arteries bypassed frequently undergoes occlusion after the intervention; 2) when a stenosis is located before a bi- or trifurcation, only one branch is usually bypassed; 3) venous grafts have a short duration (30).

In addition, the radial artery as the first line approach in the majority of patients (92.3%), with the consequent reduction in peripheral complications and bleedings, the choice of a tailored DAPT strategy, the systematic prevention of CIN with hyper-hydration, and the use of CRRT in patients with eGFR <30ml/min, might have favourably impacted our patients’ outcome, independently of the SYNTAX Class. With these considerations, we do not deny the importance of the anatomical complexity on the outcome of patients submitted to PCI, but we would like to underline that the results of PCI are due to a “sum of care”, including not only the skills and the tools of interventional cardiologists, but also a holistic approach to the patients. Similarly, the patient’s outcome is the result not only of anatomical complexity but also of other clinical potent factors that should be weighted in the choice of the revascularization strategy. In an attempt to consider these factors, after the conclusion of our study, a number of new predictive models, have been built with encouraging results (31). Among them, the SYNTAX score II combines the anatomical SYNTAX score with several clinical, demographic and functional variables (8, 9) and has superior results to the purely angiographic SYNTAX score in predicting 2 year and long-term mortality in patients with severe CAD, undergoing PCI or CABG (10, 11) also in diabetic patients (32-35). Moreover, SYNTAX II showed the ability to detect several clinical characteristics in favour of PCI or CABG (36-38). However, the search for more complete prognostic scores is continuing and more recently the SYNTAX score III has been introduced, which integrates comorbidities and anatomy with a functional assessment of stenotic lesions by means of fractional flow reserve (39, 40).

### **Limitations of Study**

Our study retrospectively analyzed the data of multivessel patients who underwent PCI at our Institution in the course of one year. Our population was relatively small, unselected and heterogeneous regarding the clinical presentation of coronary dis-

ease at hospital admission, including patients with stable angina, non-ST elevation ACS, and STEMI. However, by including patients with STEMI in our study population, we strengthened the importance of our results since MACCE, bleedings, access site complications and CIN are known to be usually higher in this group of patients than that we observed.

## Conclusions

In our study of multivessel disease patients treated with PCI and Xience V stents, the SYNTAX score, that is an index of anatomic complexity, does not seem to be an independent predictor of MACCE or any other post-treatment outcome. Moreover, in our study population the incidence of MACCE is lower than that previously reported for multivessel disease patients treated with angioplasty and first generation DES. These results can be mainly ascribed to the technical characteristics of the new generation of stents implanted, as well as to the holistic approach carried out on our patients, which mainly consists of optimization of antiplatelet therapy, as well as procedural and periprocedural management. The continuous search for new predictive scores, considering not only anatomical complexity but also several clinical and functional factors to increase the accuracy of outcome, indirectly corroborate our results.

### What Is Already Known on this Topic:

*The SYNTAX trial demonstrated the superiority of coronary artery bypass graft (CABG) over percutaneous coronary intervention (PCI) in patients with multivessel and/or left main disease and a high SYNTAX score. However, in that trial, first generation drug eluting stents (DES) were used. The results of more recent studies exploring the use of second generation DES, with a better safety profile, have allowed interventional cardiologists to consider PCI even for more complex coronary disease patterns for which CABG should be recommended according to the SYNTAX trial.*

### What this Study Adds:

*In patients with multivessel disease treated with PCI and second generation DES, the SYNTAX score is not an independent predictor of MACCE or any other post-treatment outcome. Moreover, in our study the incidence of MACCE was lower than that previously reported with first generation DES, with a higher percentage of complete revascularization. These results suggest that PCI with newer DES and optimized*

*therapeutic and periprocedural management should also be considered in patients with a SYNTAX score higher than the cut-off suggested in the homonymous trial above which CABG would be recommended.*

**Authors' Contributions:** Conception and design: CG, EC and NM; Acquisition, analysis and interpretation of data: MC and SMR; Drafting the article: AM, CZ and MB; Revising it critically for important intellectual content: CG, EC and NM; Approved final version of the manuscript: CG, EC and NM.

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## References

1. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med.* 2009;360(10):961-72. Erratum in: *N Engl J Med.* 2013;368(6):584.
2. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stähle E, Colombo A, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet.* 2013;381(9867):629-38.
3. Head SJ, Davierwala PM, Serruys PW, Redwood SR, Colombo A, Mack MJ, et al. Coronary artery bypass grafting vs. percutaneous coronary intervention for patients with three-vessel disease: final five-year follow-up of the SYNTAX trial. *Eur Heart J.* 2014;35(40):2821-30.
4. Kereiakes DJ, Smits PC, Kedhi E, Parise H, Fahy M, Serruys PW, et al. Predictors of death or myocardial infarction, ischaemic-driven revascularisation, and major adverse cardiovascular events following everolimus-eluting or paclitaxel-eluting stent deployment: pooled analysis from the SPIRIT II, III, IV and COMPARE trials. *EuroIntervention.* 2011;7(1):74-83.
5. Dangas GD, Serruys PW, Kereiakes DJ, Hermiller J, Rizvi A, Newman W, et al. Meta-analysis of everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease: final 3-year results of the SPIRIT clinical trials program (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions). *JACC Cardiovasc Interv.* 2013;6(9):914-22.
6. Gada H, Kirtane AJ, Newman W, Sanz M, Hermiller JB, Mahaffey KW, et al. 5-year results of a randomized comparison of XIENCE V everolimus-eluting and TAXUS Paclitaxel-eluting stents: final results from the SPIRIT III trial (clinical evaluation of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions). *JACC Cardiovasc Interv.* 2013;6(12):1263-6.

7. Park SJ, Ahn JM, Kim YH, Park DW, Yun SC, Lee JY, et al. Trial of Everolimus-Eluting Stents or Bypass Surgery for Coronary Disease. *N Engl J Med.* 2015;372(13):1204-12.
8. Yadav M, Palmerini T, Caixeta A, Madhavan MV, Sanidas E, Kirtane AJ, et al. Prediction of coronary risk by SYNTAX and derived scores: synergy between percutaneous coronary intervention with taxus and cardiac surgery. *J Am Coll Cardiol.* 2013;62(14):1219-30.
9. Farooq V, Head SJ, Kappetein AP, Serruys PW. Widening clinical applications of the SYNTAX Score. *Heart.* 2014;100(4):276-87.
10. Song Y, Gao Z, Tang X, Ma Y, Jiang P, Xu J, et al. Usefulness of the SYNTAX score II to validate 2-year outcomes in patients with complex coronary artery disease undergoing percutaneous coronary intervention: A large single-center study. *Catheter Cardiovasc Interv.* 2018;92(1):40-7.
11. Xu B, Genereux P, Yang Y, Leon MB, Xu L, Qiao S, et al. Validation and comparison of the long-term prognostic capability of the SYNTAX score-II among 1,528 consecutive patients who underwent left main percutaneous coronary intervention. *JACC Cardiovasc Interv.* 2014;7(10):1128-37.
12. Roques F, Nashef SA, Michel P, Gauducheau E, de Vincentiis C, Baudet E, et al. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. *Eur J Cardiothorac Surg.* 1999;15(6):816-22.
13. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI), Wijns W, Kolh P, Danchin N, Di Mario C, et al. Guidelines on myocardial revascularization. *Eur Heart J.* 2010;31(20):2501-55.
14. Ong AT, Serruys PW. Complete revascularization: coronary artery bypass graft surgery versus percutaneous coronary intervention. *Circulation.* 2006;114(3):249-55.
15. Aradi D, Komócsi A, Price MJ, Cuisset T, Ari H, Hazarbasanov D, et al. Tailored Antiplatelet Treatment Study Collaboration. Efficacy and safety of intensified antiplatelet therapy on the basis of platelet reactivity testing in patients after percutaneous coronary intervention: systematic review and meta-analysis. *Int J Cardiol.* 2013;167(5):2140-8.
16. Cecchi E, Marcucci R, Chiostrì M, Mecarocci V, Spini V, Innocenti L, et al. Dual antiplatelet therapy tailored on platelet function test after coronary stent implantation: a real-world experience. *Intern Emerg Med.* 2015;10(7):805-14.
17. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. *J Am Coll Cardiol.* 2012;60(16):1581-98.
18. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med.* 2004;350(3):221-31.
19. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials. A consensus report from the Bleeding Academic Research Consortium. *Circulation.* 2011;123(23):2736-47.
20. Head SJ, Milojevic M, Daemen J, Ahn JM, Boersma E, Christiansen EH, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. *Lancet.* 2018;10;391(10124):939-48.
21. Stone GW, Sabik JF, Serruys PW, Simonton CA, Généreux P, Puskas J, et al. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. *N Engl J Med.* 2016;8;375(23):2223-35.
22. Garg S, Serruys PW, Silber S, Wykrzykowska J, van Geuns RJ, Richardt G, et al. The prognostic utility of the SYNTAX score on 1-year outcomes after revascularization with zotarolimus- and everolimus eluting stents: a sub-study of the RESOLUTE All Comers Trial. *JACC Cardiovasc Interv.* 2011;4(4):432-41.
23. Otsuka F, Vorpahl M, Nakano M, Foerst J, Newell JB, Sakakura K, et al. Pathology of second-generation everolimus eluting stents versus first-generation sirolimus- and paclitaxel-eluting stents in humans. *Circulation.* 2014;129(2):211-23.
24. Gada H, Kirtane AJ, Newman W, Sanz M, Hermiller JB, Mahaffey KW, et al. 5-Year results of a randomized comparison of XIENCE V everolimus-eluting and TAXUS paclitaxel-eluting stents: final results from the SPIRIT III trial (clinical evaluation of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions). *JACC Cardiovasc Interv.* 2013;6(12):1263-6.
25. Onuma Y, Kukreja N, Piazza N, Eindhoven J, Girasis C, Schenkeveld L, et al. The everolimus-eluting stent in real-world patients: 6-month follow-up of the X-SEARCH (Xience V Stent Evaluated at Rotterdam Cardiac Hospital) registry. *J Am Coll Cardiol.* 2009;54(3):269-76.
26. Archbold RA, Robinson NM, Schilling RJ. Radial artery access for coronary angiography and percutaneous coronary intervention. *BMJ.* 2004;329(7463):443-6.
27. Hannan EL, Wu C, Walford G, Holmes DR, Jones RH, Sharma S, et al. Incomplete revascularization in the era of drug-eluting stents: impact on adverse outcomes. *JACC Cardiovasc Interv.* 2009;2(1):17-25.
28. Farooq V, Serruys PW, Garcia-Garcia HM, Zhang Y, Bourantas CV, Holmes DR, et al. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. *J Am Coll Cardiol.* 2013;61(3):282-94.

29. Xu B, Yang YJ, Han YL, Lu SZ, Li B, Liu Q, et al. Validation of residual SYNTAX score with second-generation drug-eluting stents: one-year results from the prospective multicentre SEEDS study. *EuroIntervention*. 2014;10(1):65-73.
30. Ahn JM, Park DW, Lee CW, Chang M, Cavalcante R, Sotomi Y, et al. Comparison of Stenting Versus Bypass Surgery According to the Completeness of Revascularization in Severe Coronary Artery Disease. *JACC Cardiovasc Interv*. 2017;10(14):1415-24.
31. Head SJ, Farooq V, Serruys PW, Kappetein AP. The SYNTAX score and its clinical implications. *Heart*. 2014;100(4):169-77.
32. Campos CM, van Klaveren D, Iqbal J, Onuma Y, Zhang YJ, Garcia-Garcia HM, et al. Predictive Performance of SYNTAX Score II in Patients With Left Main and Multivessel Coronary Artery Disease-analysis of CREDO-Kyoto registry. *Circ J*. 2014;78(8):1942-9.
33. Campos CM, Garcia-Garcia HM, van Klaveren D, Ishibashi Y, Cho YK, Valgimigli M, et al. Validity of SYNTAX score II for risk stratification of percutaneous coronary interventions: A patient-level pooled analysis of 5,433 patients enrolled in contemporary coronary stent trials. *Int J Cardiol*. 2015;187:1111-5.
34. Stanetic BM, Ostojic M, Campos CM, Marinkovic J, Farooq V, Kovacevic-Preradovic T, et al. Appropriateness of myocardial Revascularization assessed by the SYNTAX score II in a country without cardiac surgery facilities; PROUST study. *Int J Cardiol*. 2017;227:478-84.
35. Cavalcante R, Sotomi Y, Mancone M, Whan Lee C, Ahn JM, Onuma Y, et al. Impact of the SYNTAX scores I and II in patients with diabetes and multivessel coronary disease: a pooled analysis of patient level data from the SYNTAX, PRECOMBAT, and BEST trials. *Eur Heart J*. 2017;38(25):1969-77.
36. Campos CM, van Klaveren D, Farooq V, Simonton CA, Kappetein AP, Sabik JF 3rd, et al. Long-term forecasting and comparison of mortality in the Evaluation of the Xience Everolimus Eluting Stent vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial: prospective validation of the SYNTAX Score II. *Eur Heart J*. 2015;36(20):1231-41.
37. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet*. 2013;381(9867):639-50.
38. Sotomi Y, Cavalcante R, van Klaveren D, Ahn JM, Lee CW, de Winter RJ, et al. Individual Long-Term Mortality Prediction Following Either Coronary Stenting or Bypass Surgery in Patients With Multivessel and/or Unprotected Left Main Disease: An External Validation of the SYNTAX Score II Model in the 1,480 Patients of the BEST and PRECOMBAT Randomized Controlled Trials. *JACC Cardiovasc Interv*. 2016;9(15):1564-72.
39. Serruys PW, Chichareon P, Modolo R, Leaman DM, Reiber JHC, Emanuelsson H, et al. The SYNTAX score on its way out or ... towards artificial intelligence: part I. *EuroIntervention*. 2020;16(1):44-59.
40. Collet C, Onuma Y, Andreini D, Sonck J, Pompilio G, Mushtaq S, et al. Coronary computed tomography angiography for heart team decision-making in multivessel coronary artery disease. *Eur Heart J*. 2018;39(41):3689-98.

## Norovirus Infections Drop 49% in the United States with Strict COVID-19 Public Health Interventions

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### Abstract

Norovirus is a substantial burden on the U.S. We compared norovirus outbreaks before and during COVID-19. There were fewer norovirus outbreaks during COVID-19 compared to a similar time period in 2019 (326 versus 638,  $P < 0.001$ ). **Conclusion.** COVID-19 public health interventions may be considered to decrease the burden of norovirus. This demonstrates the ability of more restrictive interventions to decrease other outbreaks of known or emerging viruses.

**Key Words:** Coronavirus ■ Norovirus ■ Public Health.

### Introduction

Norovirus places a substantial burden on the U.S., with 19-21 million illnesses and 109,000 hospitalizations per year and an estimated annual cost of \$6.2 billion (inflation adjusted for 2020) (1, 2). Norovirus, like coronaviruses, can spread through person-to-person contact. Interventions to prevent COVID-19 infection should also decrease norovirus infection. Stay-at-home (“lockdown”) orders to decrease the spread of COVID-19 were implemented in 32 states by 31 March, 2020 (3). There is evidence suggesting that COVID-19-related restrictions decreased influenza rates in the United States (R.P. Lennon, E.L. Miller, H. Dong, D. Rabago, A.E. Zgierska, unpublished data, August 2020). To our knowledge, the impact of COVID-19-related restrictions on norovirus infection rates has not been evaluated.

Our objective was to compare norovirus infection rates in the U.S. before and after COVID-19 lockdown.

### Materials and Methods

Data from the Centers for Disease Control and Prevention (CDC), which collects norovirus outbreak data reported by health departments through the National Outbreak Reporting System (NORS), were used to compare weekly norovirus outbreak rates during the pre-COVID-19 2018-19 and 2019-20 seasons (August 1 through January 30) (4). In addition, weekly outbreaks rates after the COVID-19 lockdown (February 6 through June 6, 2020) were compared to the pre-COVID-19 rates (February 6 through June 6, 2019). This research is exempt per 45 CFR 46.101(b) (4). The differences in outbreak rates were assessed with a Wilcoxon signed rank test, with significance level established at two-tailed  $P < .05$ , using R statistical software, Version 3.6.2.

### Results

There were no significant differences ( $P = 0.384$ ) in pre-COVID-19 norovirus weekly outbreak rates

between 2018-19 and 2019-2020 seasons through January 30, 2020 (Table 1). There were fewer norovirus weekly outbreaks post-COVID-19 lockdown in 2020, compared to a similar time period in 2019 (326 versus 638,  $P < 0.001$ ) (Table 1)

Table 1. Comparison of Norovirus Outbreaks Pre- and Post -COVID-19

Weeks	Norovirus outbreaks*	Norovirus outbreaks†	Key events	Wilcoxon rank test, 2-tailed to 95% confidence
<b>Pre-COVID-19 lockdowns in the United States</b>				
1-Aug	8	5	-	
8-Aug	4	4	-	
15-Aug	5	2	-	
22-Aug	7	6	-	
29-Aug	7	11	-	
5-Sep	4	9	-	
12-Sep	11	11	-	
19-Sep	8	11	-	
26-Sep	6	12	-	
3-Oct	5	6	-	
10-Oct	13	10	-	
17-Oct	10	15	-	
24-Oct	11	12	-	
31-Oct	13	23	-	Comparing outbreaks per week from August 1, 2019 through January 30, 2020
7-Nov	12	25	-	$P=0.384$
14-Nov	21	24	-	
21-Nov	40	17	-	
28-Nov	54	52	-	
5-Dec	62	48	-	
12-Dec	79	43	-	
19-Dec	36	48	-	
26-Dec	67	46	-	
2-Jan	81	59	-	
9-Jan	65	41	-	
16-Jan	56	46	First U.S. case (5)	
23-Jan	61	49	-	
30-Jan	48	57	-	
<b>Post-COVID-19 lockdowns in the United States</b>				
6-Feb	53	55	U.S. declares public health emergency (5)	
13-Feb	50	48	-	
20-Feb	49	57	-	
27-Feb	68	61	-	
6-Mar	53	33	-	
13-Mar	49	34	Lockdowns start (3)	
20-Mar	51	13	-	
27-Mar	47	10	32 States in lockdown (3)	
3-Apr	53	7	-	Comparing outbreaks per week from February 6, 2020 through June 5, 2020
10-Apr	32	1	-	$P < 0.001$
17-Apr	21	2	-	
24-Apr	18	1	-	
1-May	22	1	-	
8-May	27	0	-	
15-May	10	1	-	
22-May	16	2	-	
29-May	11	0	-	
5-Jun	8	0	-	

\*2018-2019; †2019-2020.

## Discussion

During the COVID-19-related lockdown period, the norovirus outbreak rates were lower than the year prior. Limitations of this comparison include potential changes in public care-seeking behaviors or physician testing patterns during the COVID-19 pandemic, and the NORS system approach to data collection, which relies on voluntary reports by health departments. Further, the 2020 norovirus data will not be finalized until 12-18 months after the end of the current season and, therefore, these estimates may still change.

## Conclusion

The reductions in norovirus burden associated with COVID-19 restrictions suggest the power of restrictive public health measures to impact infectious disease burden more generally. Such measures may be considered for other high-burden outbreaks of known and emerging viruses now and in the future.

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critically for important intellectual content: RL, CG, EM, HD, DR and AZ; Approved final version of the manuscript: RL, CG, EM, HD, DR and AZ.

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## References

1. Centers for Disease Control and Prevention. Burden of Norovirus Illness in the U.S. [cited 2020 Jul 22]; Available from: <https://www.cdc.gov/norovirus/trends-outbreaks/burden-US.html>.
2. Bartsch SM, Lopman BA, Hall AJ, Parashar UD, Lee BY. The potential economic value of a human norovirus vaccine for the United States. *Vaccine*. 2012;30(49):7097-04.
3. Higham A. US lockdown: When did the US go into lockdown?, in *Express* [Internet]. 2020, Express Newspapers PLC: London (UK). [cited 2020 Aug 15]; Available from: <https://www.express.co.uk/news/world/1270061/US-lockdown-When-did-the-US-go-into-lockdown>.
4. Centers for Disease Control and Prevention (CDC). Norovirus Outbreaks Reported by State Health Departments by Week of Illness Onset, 2012-2019. [cited 2020 Jul 22]; Available from: <https://www.cdc.gov/norovirus/reporting/norostat/data-table.html>.
5. American Journal of Managed Care. A Timeline of COVID-19 Developments in 2020. [cited 2020 Aug 15]; Available from: <https://www.ajmc.com/view/a-timeline-of-covid19-developments-in-2020>.

## Rosa Einhorn (1872–1950): A Woman Pioneer in Medicine between Bosnia (1902–1913), New York, and Palestine

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### Abstract

This short biography details the life and medical activities of Rosa Einhorn, mariée Bloch (1872–1950), who practised as an Austro-Hungarian (AH) official female physician in Travnik in occupied Bosnia and Herzegovina (BH) from 1902 to 1904, and as a semi-official private physician from 1905 to 1912/13. Born in Hrodna district in the Russian Pale of Crescent, Einhorn had qualified and practised as a “*feldsheritsa*” in Russia and went to Switzerland to study medicine in 1896. Upon receiving her medical doctorate from the University of Lausanne in 1901, she became recommended as a particularly adequate candidate for the not-yet-created position of an AH official female physician in BH. After Einhorn functioned as a general practitioner for women and children in Travnik and the adjacent districts for two years, the AH public health authorities officially dismissed her due to her engagement and marriage to the AH judiciary Sigismund Bloch (1850–1927). However, she obtained a right to private practice in 1905 and was employed as a private physician in AH anti-syphilis campaigning. Struggling for her reinstatement as an official female physician in Travnik, she also strove for the accreditation of her Swiss diploma in Austria, though in vain. After two attempts to emigrate to the United States in 1904 and 1913, Rosa Einhorn finally left Europe to work as a physician in the United States and Mandatory Palestine/Eretz Israel in 1923. She died in New York on May 27, 1950. **Conclusion.** Rosa Einhorn was employed as a provisory official female physician in Travnik in 1903/1904, the AH authorities accepting her only as a local private female physician after her marriage in 1905. Struggling in vain for her reinstatement, she finally left Bosnia in 1913.

**Key Words:** AH Official Female Physicians ▪ Rosa Einhorn ▪ Travnik ▪ Bosnia and Herzegovina.

### Introduction

In February 1903, a Viennese daily newspaper published a brief report on the medical activities of Rosa Einhorn among Muslim women in Bosnian Travnik and a hand drawing showing “Miss Doctor” at work in her local outpatient ward (Picture 1) (1). Attentive readers may have noticed that the press reported in December 1902 that a “fifth” official female physician had been appointed in Bosnia and Herzegovina (BH) (2). Although Rosa Einhorn is the only Austro-Hungarian (AH) official female physician in BH who has ever been featured in the German Austrian daily press, a de-

tailed biography has never been dedicated to her. The reason for this is not least that Einhorn was dismissed as a still provisory officer in 1904, although official Austrian sources continued to list her as a private physician settled in Travnik (3).

The Czech historian Ctibor Nečas, author of a historical study of the AH extraordinary institution of publicly employed female physicians for Muslim women in BH, briefly mentioned Einhorn as an official female doctor who never acquired permanent status because of her marriage to the locally settled AH judiciary Sigismund Bloch (1850–1927) in 1905 (4). Nečas suggested that Rosa Einhorn, mariée Bloch functioned like



**Beim Fräulein Doktor.**  
Die ärztliche Behandlung der Mohammedanerinnen.

Die bosnische Landesregierung hat sich mit Erfolg bemüht, im Cepanowagbiet geordnete Beschäftigung herbeizuführen, wozu sich durch mehrüberlebige ärztliche Unterstützung gerietene Hand auf das Stimmvermögen der Bevölkerung erhalten werden sollte. Mit allen Geisteskräften hat sich die ärztliche Tätigkeit, wenn auch nur langsam und unvollständig, ohne eigentlichen Nebenbühnen, begonnen. In der ärztlichen Behandlung trafen Mohammedanerinnen große Schwierigkeiten. Man durfte aber durchaus nicht darauf verzichten, wenn nicht die Bevölkerung der familiären Misere, die wegen der hohen und blühenden Bevölkerung mit dem Christen und seinen Angehörigen von besonderer Wichtigkeit ist, auch Spielplatz werden sollte.

Mit milden Worten war in dieser Beziehung nichts auszusagen. Die viel eingeengte mohammedanische Welt, die von den mohammedanischen Vätern und Vätern mit jenseitiger Gerechtigkeit eingehalten wird, läßt es als unentbehrlich erscheinen, daß ein männlicher Arzt an das Stimmvermögen einer

Mohammedanerin komme oder daß gar eine solche bei einem Defekt ärztliche Hilfe finde. Die bosnische Landesregierung hat daher zu dem eben genannten als praktischen Arbeitsmittel gewählten, weibliche Krankenschwestern und gegenwärtig sind in Bosnien und der Herzegovina bereits fünf Doktorinnen als Krankenschwestern tätig. Hier hat letztgenannte Heilende Doktorin, die in Soran bringen wie nun in Mostar und Süd einige Heilungen. Dr. Dr. Wehner hat ihren Namen in Soran mit und erweist sich bei einer sehr umfangreichen Praxis. Ihre Ordinationen haben bei Heilung des Kopfes und der Brust von Mohammedanerinnen gefastet sich trotz der kurzen Zeit sehr leicht. Wie unterhalb zeigt, läßt die Welt der Ordinationen der muslimischen Frauen. Die Patientinnen werden nicht abgelehnt, sondern die Patientinnen befinden sich gern in Gesellschaft und sind auch nicht gern mit ihren Schmerzen oder ihren Freunden ohne Jenseitigen. Nichts als ein binner weicher Vorhang, hinter dem die jugendliche Heilerin ihre Untersuchungen

vornimmt, trennt die Wartenden von den Heilenden. Zuweilen ist es, wenn eine der ungeliebten Patientinnen, um die Heilungsfähigkeit der Patientin aber doch wartenden Publikum früher auf sich zu lassen, einen Stuhlplatz oder bei. Inmitten dieser Zeit ist eine junge Patientin, die sich zu diesem Zweck auf den Boden geworfen hat und fortgesetzt jammert. Hier hat Heilende Doktorin diesen Stuhl fassen. Sie läßt sich durch die schlecht gepolsterte Stühle nicht aus dem Stuhl bringen. Die Heilerin Gheffanin kommt jetzt noch schnell weg mit ihrem Mantel. Sie wird bei der Ordination gegen später gefundene Patientinnen zurückgelassen und dadurch auf die Heilungsfähigkeit aufmerksam gemacht, die schließlich zu heilen. Sie nimmt sich diese Stelle auch zu zeigen und beim zweiten Besuch ist sie ganz ruhig und macht geduldig auf die endliche Heilung der Patientin.

Picture 1. 'At Miss Doctor's. The Treatment of Muslim Women'. Source: Neugigkeitsweltblatt, 19 February 1903, s.p.

Gisela Januszewska in Banja Luka<sup>1</sup> as a semi-official female physician of Travnik, as she was not replaced with another official. Barbara Martin, who evaluated the AH sources concerning Einhorn in a grey literature research report (5), revealed that Nečas avoided mentioning the bullying that Ein-

<sup>1</sup>Fuchs B, Tahirović H. Gisela Januszewska (née Rosenfeld), an Austro-Hungarian 'Woman Doctor for Women' in Banjaluka, 1899-1912. Acta Med Acad. 2020;49(1):75-83. [cited 2020 Aug 12]. Available from: <https://pubmed.ncbi.nlm.nih.gov/?term=Tahirovic+h&filter=simsearch1.fha>

horn experienced from the local authorities and AH physicians in Travnik. When she reacted with a months-long absence over leave from her service, she legitimised her dismissal in November 1904. As soon as she returned in 1905, she married her fiancé and struggled for her reinstatement as an official female physician. Her only success was that she was granted the right to practice as a private physician with a Swiss diploma in BH in 1905 because the provincial public health authorities sought to keep a female physician for syphilis eradication on site (4, 5). However, it is uncertain whether the hostility was directed predominantly against Einhorn's person or her office as a modernising agent in which she incorporated and was considered to facilitate the recognition of female physicians in Austria and Hungary.

Against this background, Einhorn's presence and medical practice in Travnik went largely unnoticed by its residents (5). She was mentioned neither in the contemporary Travnik daily press (5) nor in the memories of the local Sephardi, who gave prominence to AH medical institutions and Ashkenazi physicians who came

in from 1879 to 1918, because of their tradition as medical practitioners (6, 7, 8, 9). Few narrative sources exist on Einhorn's life except the documents she and AH authorities in BH produced in the outlined conflict. Therefore, the following fragmentary biography of Rosa Einhorn is based in the administrative traces she left, particularly in BH, on her numerous transatlantic passages, and finally, as a physician in the United States and Mandatory Palestine/Eretz Israel. Rosa Einhorn's life and medical activities are the subjects of this review.

## Einhorn's Family Background and Education

Rosa Einhorn was born on April 24, 1872<sup>2</sup> in Suchowola, then a small city situated in the Russian Pale of Crescent in Hrodna (then Grodno), Belarus, today situated in Eastern Poland. She was the fourth child of local Rabbi Avraham Einhorn (died in 1911) and his wife Sara(h) Hoffmann (10, 11, 12). Among her older siblings was Max Einhorn (1862–1953) (Picture 2) who, after studying medicine in Kiev and Berlin, emigrated to the United States in 1885 and subsequently became one of the most renowned gastroenterologists of his time (13, 14, 15). Max Einhorn noted in an autobiographical sketch published in 1929 that his family lived in materially modest circumstances and that he had to fund his studies himself (13). He is the one who ensured that his younger sisters were able to study at 'German' universities in the 1890s.

Rosa Einhorn attended a girls' gymnasium in Hrodna and took her school-leaving examination with honours in 1889.<sup>3</sup> Subsequently, she attended medical courses for 'learned midwives' ('uchenye akusherki') at the Military Medical Surgery Academy in St. Petersburg (16). These courses provided a qualification equivalent to a medical degree until 1882 but were downgraded afterwards. In light of the low quota for Jewish students introduced in 1886 to Russian higher and academic education,<sup>4</sup>

<sup>2</sup>When Einhorn petitioned for her US-nationalization in 1928, she gave 1874 as her year of birth; before her US-emigration, she used to give – quite probably correctly – her year of birth as 1872; see "Rosa Einhorn"; New Jersey, U.S., Naturalization Records, 1878-1945. The National Archives at Washington, D.C.; Washington, D.C.; Series Title: Petitions for Naturalization from the U.S. District Court for the District of New Jersey at Newark, New Jersey, 1924-1945; Series Number: M2123; Record Group Title: Records of the Immigration and Naturalization Service, 1787-2004; Record Group Number: 85; NARA Microfilm Number: 040 [Ancestry.com. New Jersey, U.S., Naturalization Records, 1878-1945 Lehi, UT, USA: Ancestry.com Operations, Inc., 2016 [database on-line; cited 2020 Nov. 18].

<sup>3</sup>Rosa Einhorn's petition for reinstatement as an official physician in Travnik from April 23, 1912, ABH, ZMF No. 6212, April 26, 1912.

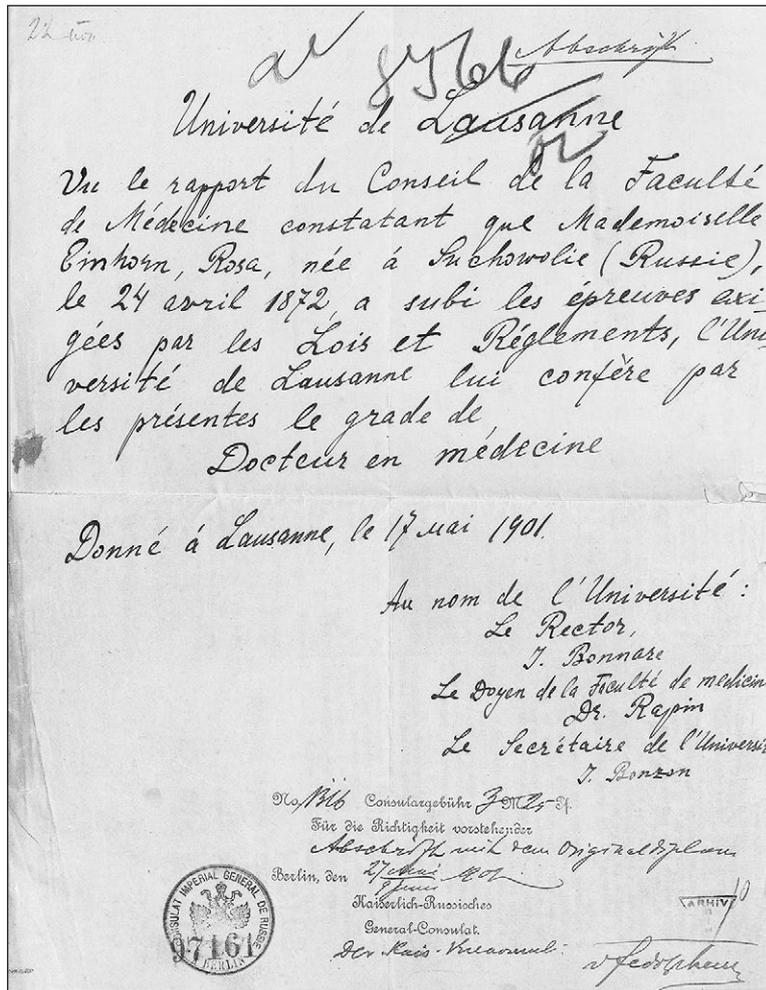
<sup>4</sup>Both the downgrading of the courses (1882) and the low quota for Jewish students (1886) in Russia contributed to the flow of young women aspiring academic education in Switzerland and,



Picture 2. Rosa Einhorn's brother Prof. Dr. Max Einhorn (1862-1953), inventor of surgical instruments, first professor of gastroenterology at the New York Post-Graduate Medical School and Hospital and physician at the then 'German' Lenox Hill Hospital in New York.

Einhorn could not consider studying medicine but passed her midwife exam in December 1892. In the same year, her brother Max was married in New York to Flora Strauss (1863–1934), the US Macy's

after 1900, also in Prussia. According to Daniela Neumann (1987: 75c) the share of Russian-Jewish female students studying at Swiss universities increased from 10% in the 1870-s to 60-80% between 1880 and 1914 (17). The willingness of Eastern Jewish parents to let their daughters acquire an academic qualification (abroad) has been attributed besides a secularized preference for 'studying' to the fact that studying was considered still less expensive than a marriage (dowry), cf. Hirsch 2013 (18). The overrepresentation of Jewish women particularly among female medicine students and physicians in both Prussia and Austria has been demonstrated by Harriet Freidenreich 1996; 2002 (19, 20) and Miriam Offer 2020 (21); for female Jewish students in Germany, see also Grossmann 1994 (22).



Picture 3. Rosa Einhorn's award certificate of her doctor-title from the University of Lausanne, dated from 17 May 1901. Source: Vgl. ABH, ZVS 1902, Signaturengruppe 52-113, kut. 151 [cited 2020 Nov 2].

department store owner's daughter, thus becoming a wealthy man (15). Einhorn started to study medicine in St. Petersburg, although she was not entitled to graduate as a woman. After completing an internship in two clinics in St. Petersburg, she accepted the strenuous and poorly paid position as a community (zemstvo) "feldsheritsa" (paramedic) in Afanasyeva Sloboda, a rural village in the Oblast of Pskow in north-western Russia in 1895 (4, 5).

Perhaps encouraged by her brother, she gave up her service after one year, with the zemstvo authorities attesting to her 'exemplary diligence and humane demeanour towards patients' (5). In 1896, she and her younger sister Rahel left Russia for

Berlin (18). Einhorn enrolled at the medical faculty of Berlin University and completed another internship at the local ophthalmological clinic (5). Still, in 1896, she moved her medical studies to Berne, Switzerland (16). Einhorn elaborated her thesis on lower limb fractures titled "Beitrag zur Kenntnis der Unterschenkelfracturen" (23) at the University Clinic of Berne under the auspices of its director, the Swiss surgeon Theodor Kocher (1841–1917). Based on the clinic's collection of lower limb fractures, she developed analytically impressive systematics published also in *Archiv für klinische Chirurgie* (1901) (24). However, she did not finish her studies in Berne but enrolled at the University of Lausanne (25) in the spring of 1900, where she received her doctorate on May 17, 1901 (Picture 3).

She could not turn her preference for orthopedic surgery, which she might have practiced as a "feldsheritsa", into a career, however. Upon finishing her studies, Rosa Einhorn completed numerous internships at various clinics and hospitals first in Berlin,<sup>5</sup> then

in Vienna (5). Among others, she volunteered at the dermatological clinic of Vienna University where she met the head Professor Isidor Neumann (1832–1906) (5). Neumann was the consultant for syphilis eradication at the 'Bosnian Bureau' – the supreme authority of BH at the AH Ministry of Finance – and was the first to recommend the use of female doctors for this purpose. Neumann's recommendation was taken up by the AH Minister of Finance and governor of BH, Beni de Kállay,

<sup>5</sup>In her Petition for Reinstatement, 1912 (see note 2), she claimed that she had been employed as an assistant physician at the Gynaecological Clinic in Berlin for two years before she left Berlin for Travnik in December 1902.

who personally took care of institutionalising official female physicians (26).<sup>6</sup> Neumann kept pushing the supreme authority to extend the system of official female physicians across all BH districts. Neumann probably considered Einhorn a highly adequate candidate and invited her to apply for a never officially advertised position in Travnik (5).<sup>7</sup> In February 1902, Einhorn applied to the AH provincial public health authorities in Sarajevo who, after scrutinising her credentials and police records concerning her political behaviour and moral conduct in St. Petersburg and Berne, recommended her appointment (4). As soon as Einhorn had acquired Austrian citizenship in Götzendorf, a village at Vienna's outskirts, she was appointed as a provisional female official physician of Travnik by decree on November 25, 1902 (4, 5). She left Berlin and arrived at Travnik on December 22, 1902, to work as an official female physician.

### **Einhorn's Professional Activities as an Official Female Physician 1903 – 1904**

When Rosa Einhorn arrived at Travnik (Picture 4), the city had about 7000 inhabitants (including the present AH civil and military population),

<sup>6</sup>De Kállay died in office in 1903, and his successor Bilinski showed all the less interest in the matter that the academic education for women had meanwhile been established.

<sup>7</sup>Both Ctibor Nečas (1991: 105) and Barbara Martin (2018: 5) point at the fact that Einhorn left behind Carola Meyer (also Maier, Meier) Milobar, MD (1876-1945) who obviously had been promised (unofficially) the not yet created office of a female physician of Travnik (cf. ABH, ZMF 13246, November 19, 1900). Carola Meyer, the renowned Croatian gastroenterologist, was originally a German citizen who had grown up in Switzerland and finished her medical studies in Zurich. After marrying the Croatian conservative philosopher and politician Fran Milobar (1869-1945), she came to BH and worked as an assistant physician at the provincial hospital in Sarajevo. When Rosa Einhorn turned up as new candidate, Milobar's application as an official female physician was rejected, because she was considered "too academic" and did not speak the "popular language". Milobar left BH, obtained an imperial special permission to practice as a female physician in Austria and opened a private medical office in Zagreb in 1906. Sertić K. Karola Maier Milobar – The first female doctor in Croatia [in Croatian] [updated 2019 March 19; cited 2020 July 17]. Available from <https://www.zeneimediji.hr/karola-maier-milobar-prva-lijecnica-u-hrvatskoj/>

who were 42% Muslim, 41% Roman Catholic, 10% Orthodox, and 7% Israelite according to the AH Census of 1910 (27). Travnik served as an AH garrison with a military hospital and comprised a community-funded hospital with 44 hospital beds, relocated and enlarged in 1899 (28). Travnik, situated at an elevation of 514 m, was BH's capital in the 18<sup>th</sup> and early 19<sup>th</sup> centuries and was considered an attractive place by the AH occupants.

Einhorn took her oath of office on December 23, 1902 and started to work without delay. As demonstrated by the mentioned daily press feature, she had established her outpatient ward within a few weeks of her arrival. According to her reports for the first half of 1903, she had been consulted by 554 local women for all kinds of disorders, and 55% of the women were Muslims (5). In the summer of 1903, she was called on her first official trip to the subdistricts of Bugojno, Jajce, Zenica, and Žepče and treated 520 patients (5).

Having just returned to Travnik, she was among the victims of a fire disaster caused by a spark jumping from a locomotive that destroyed the historic city of Travnik on September 3 and 10, 1903. More than 3000 residents were left homeless and sheltered in barracks, military tents, and rural emergency quarters (7, 29). Rosa Einhorn's outpatient ward burnt down (30), but her report suggests that she treated more women than ever from September to December in 1903. She apparently saw the disaster as an opportunity to examine and treat as many women as possible, although local women (of any religion) were probably unprepared to consult modern physicians, even if they were female.

The report indicates the incredible number of 2450 (female) patients, 1376 of whom Einhorn must have visited in their emergency quarters. Following the AH conceptualisation of her office, she preferentially 'targeted' Muslim women because her statistics indicate that two-thirds of her patients were Muslims (5). Additionally, she vaccinated 3260 persons in 1903 (5). Therefore, Einhorn proved to be the most effective AH official female physician ever; even Teodora Krajewska in Sarajevo did not treat more than a maximum of 1500 patients per year (27).



Picture 4. Travnik at the time when Rosa Einhorn started working there. Published with kind permission of the Museum of Travnik.

Einhorn's preserved report for the second quarter of 1904 again provided the extraordinary ciphers of 674 (female) patients treated for all kinds of disorders predominantly during her official trips from April to June (5). While her status had not been made permanent at the end of her provisory year in December 1903, it seems that the public health authorities informed her of her imminent dismissal in July 1904. The allegations brought against her bluntly stated that 'people disliked' her and that she lacked politeness and exceeded her competencies (5). Among others, she made herself unpopular by taking advantage of the emergency in Travnik to compel the local Muslim women to undergo medical examinations. Einhorn seems to have been bullied predominantly because of her alleged overzealousness, although she carried out her duties exactly according to the service description for AH female official physicians. Representing herself as a zealous moderniser in 1903 (1), she believed in female physicians' civilising mission in the sense of the top-down approach promoted by Teodora Krajevskaja<sup>8</sup> (31), the official female physician of Sarajevo.

<sup>8</sup>Fuchs B, Tahirović H. Teodora Krajevskaja: Medical Practitioner, Woman of Science, Polish Patriot and Feminist. *Acta Med*

This bullying was even less scrupulous due to Einhorn's engagement to Sigismund Bloch in late Autumn 1903 when the authorities informed her immediately that marrying a court official would not only result in her dismissal but a professional ban in her husband's judiciary district.<sup>9</sup>

Learning that she would be dismissed, Einhorn did not react in a well-conceived way. She applied for a two-month leave 'in the monarchy', from which she did not return until 1905. After visiting her sister in Vienna, Einhorn embarked for New York in Cuxhaven in mid-August and asked her superiors only at that point for an extension of her leave to attend a medical congress in the United States (5). Upon entering the United States, she stated that she

was visiting her brother 'Prof. Dr. Max Einhorn' and did not plan to return.<sup>10</sup> She participated as a guest in an international meeting of the US Association of Military Surgeons held in St. Louis, Missouri from October 10 to 15, 1904 (32, 33). Subsequently, Einhorn passed the state examination at Columbia University in New York, entitling her to practice as a physician in the United States and was employed at the Gynaecological Department of the University Hospital in St. Louis.<sup>11</sup> As she admitted later, she had never had the intention to return at that point. In late 1904, the public health authorities sent her certificate of dismissal to the United States and gave her months-long absenteeism in BH as the main reason (5). Rosa Einhorn changed her mind and decided to return in spring 1905. She excused her long absence with a medical certificate

*Acad.* 2019;48(3):317-27. [cited 2020 Aug 12]. Available from: <https://pubmed.ncbi.nlm.nih.gov/32124632/>

<sup>9</sup>Einhorn's Petition for Reinstatement 1912, see note 2.

<sup>10</sup>New York Passenger Arrival Lists (Ellis Island), 1892-1924, database with images, Family Search, Rosa Einhorn, 1904. [cited 2019 Aug. 20]. Available from: <https://familysearch.org/ark:/61903/1:1:JNMB-822>

<sup>11</sup>Einhorn's Petition for Reinstatement 1912, see note 2.

attesting that she had suffered from abdominal typhoid and its consequences (5). Back in Travnik, she commenced a long struggle for her reinstatement as an official physician in the district.

### Rosa Einhorn's Activities as a Private Physician, 1905–1912

After Rosa Einhorn returned to Travnik in spring 1905, she married Sigismund Bloch at the end of the year<sup>12</sup> and called herself from that point on 'Einhorn-Bloch'<sup>13</sup>. On October 30, 1906, she gave birth to a son, Hermann. As indicated by her involvement in a committee that sought to establish children's convalescent homes in Crikvenica on the Croatian Adriatic coast in 1910 (34), her son might have been of frail health.

In 1905, she obtained an imperial special permission to practise as a private physician with a Swiss diploma in BH. Her petition was endorsed by the BH provincial public health authorities (5), and we might assume that, while still in the United States, she had been unofficially informed that she would be used, like Gisela Januszewska in Banja Luka, as a semi-official private physician. However, things turned out badly for Rosa Einhorn-Bloch. Her private practice seems to have been only moderately popular, as expected in a rural area. She was called upon for official syphilis eradication campaigning in 1908<sup>14</sup> and 1909 (4) but declined participation in 1910 when she filed a petition to the provincial authorities stating that she should either be reinstated as an official female physician or be replaced (5).

In 1912, she directed a last appeal for either reinstatement 'or possibly any other position' to Governor Leon de Bilinski (1846–1923) personally because the provincial public health authorities had conditioned her possible reinstatement at that point on the accreditation of her Swiss diploma for Austria ('nostrification'). She asked the governor

to refrain from nostrification in her case, explaining that she had already spent five months volunteering at hospitals in Graz and Vienna to become considered but wished not to be separated any longer from her family in Travnik (Picture 5).<sup>15</sup> Her reemployment efforts as an official physician in BH and for accreditation in Austria proved to be in vain, however, and Rosa Einhorn-Bloch decided to leave Bosnia forever.

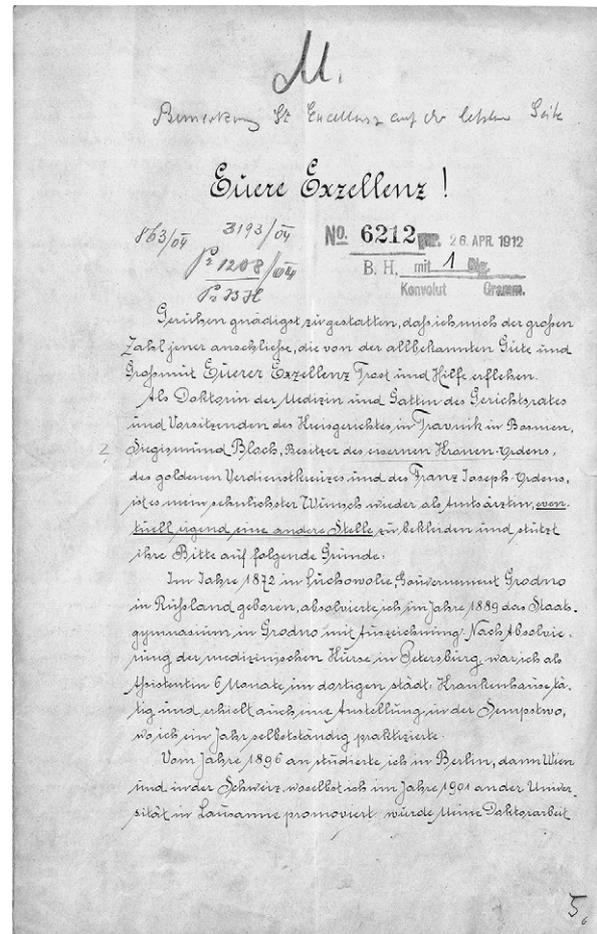


Figure 5. Rosa Einhorn's Petition for Reinstatement to Governor Leon de Bilinski from April 23, 1912. Source: Vgl. ABH, ZMF 6212, BH 1912, kut. 29 [cited 2020 Nov 2].

### Emigration to the United States

At the end of 1912, Rosa Einhorn-Bloch's situation as a professional in the Austro-Hungarian Empire was desperate. She decided to move to the United

<sup>12</sup>Ibidem.

<sup>13</sup>It was common that female professionals combined the father's name with the husband's name upon marriage. However, the authorities insisted on the reverse order, in this case "Bloch-Einhorn".

<sup>14</sup>Einhorn's Petition for Reinstatement 1912, see note 2.

<sup>15</sup>Einhorn's Petition for Reinstatement 1912, see note 2.

States and embarked with her son for New York in late March 1913.<sup>16</sup> In the United States, she started to work as a physician in Newark, New Jersey in the New York metropolitan area in 1914.<sup>17</sup> On March 30, 1914, her son Hermann died in a sanatorium in New York of 'lobar pneumonia' at the age of seven and was buried in Mt. Judah Cemetery in New York.<sup>18</sup> Rosa Einhorn was still listed as a physician living in Newark, Peshine avenue in 1915.<sup>19</sup> It is uncertain whether she ever returned to Travnik, although she returned to Europe during World War I. Martin's thorough archival research reveals that she was employed as an assistant physician in a mental asylum in Münsterlingen in Thurgau, Switzerland from April to November 1917 (5; note 149). Her husband joined her at this location for some weeks (*ibid.*).

Moreover, quite probably, the couple divorced at that point. When Rosa Einhorn took her passage to the United States in 1923, she called herself 'Einhorn' again and registered her status as single.<sup>20</sup> She stated she was a Polish citizen and designated a sister-in-law, Mina Einhorn in Bialystok, as her next relative. She gave Cairo, Egypt as her latest permanent residence.<sup>21</sup> Cairo is indicative

that Rosa Einhorn may have considered settling in Palestine/Eretz Israel after the region had become controlled by the British in 1917 and obtained a mandatory status in 1920. The British Mandate administration granted at least a physician's license 'No 140' to Rosa Einhorn, who was living in Tel Aviv in the 1930s.<sup>22</sup>

After immigrating to the United States in 1923, "Rosa Einhorn, MD" is recorded in the Newark City directories at an address on Clinton avenue from 1924 to 1928.<sup>23</sup> She officially practised as a physician in Newark until 1929 and subsequently moved to Manhattan, New York.<sup>24</sup> The 1930 US census data show her as a 'roomer' in Manhattan.<sup>25</sup>

She probably left for Mandatory Palestine in 1930 or during the early 1930s, after receiving US citizenship in February 1929. Her name appears in an address booklet of physicians in Tel Aviv,<sup>26</sup> which was a rapidly growing city at the time due to middle-class immigration from Soviet Russia, Austria, Hungary, and Germany. She shared an address with a physicians' couple from Soviet Russia,

<sup>16</sup>Rosa Einhorn-Bloch, 1913; Hermann Einhorn-Bloch, 1913; New York Passenger Arrival Lists (Ellis Island), 1892-1924, database with images, Family Search. Available from: <https://familysearch.org/ark:/61903/1:1:JMM4-QZH> [cited Aug 16, 2019].

<sup>17</sup>Rosa Einhorn, 1950. United States Deceased Physician File (AMA), 1864-1968", database with images, FamilySearch. Available from: <https://familysearch.org/ark:/61903/1:1:WDDR-GNZM> [cited Sept 2, 2019].

<sup>18</sup>Herman Bloch [sic; recte: Bloch], New York City Department of Records & Information Services; New York City, New York; New York City Death Certificates; Borough: Brooklyn; Year: 1914. (Ancestry.com. New York, New York, Index to Death Certificates, 1862-1948 Lehi, UT: 2020 [database on-line, cited Sept 7, 2020].

<sup>19</sup>Einhorn, Rosa MD 1915; Newark, New Jersey, City Directory, 1915 (Physicians, p. 1617). U.S., City Directories, 1822-1995. Provo, UT, USA: Ancestry.com Operations, Inc., 2011 [database on-line, cited 2020 Nov 15].

<sup>20</sup>See also Einhorn's Petition for Nationalization, cf. note 1.

<sup>21</sup>Rosa Einhorn, 1923. New York Passenger Arrival Lists (Ellis Island), 1892-1924, database with images, FamilySearch. [cited 2019 June 16]. Available from: <https://familysearch.org/ark:/61903/1:1:JNQX-6ZG>; <https://familysearch.org/ark:/61903/1:1:JNQX-6ZG>

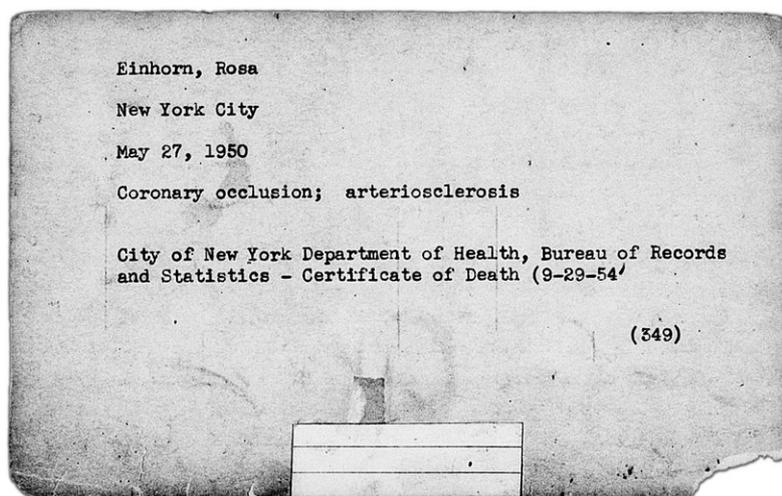
<sup>22</sup>Rosa Einhorn. List of Doctors, Pharmacists, Dentists and Midwives who have been licensed (מיאפור לש המישר), 1936; 1938; 1939. Medical Practitioners 1921-1948 (האופר ידוע) 1948-1921) database, page 17, IGRA number 8234 (original records: National Library of Israel (תימואלה היירפסה) [on-line database; cited on 2020 Dec 7].

<sup>23</sup>Rosa Einhorn MD. Newark, New Jersey, City Directory, 1925; 1926; 1927; 1928. Ancestry.com. U.S., City Directories, 1822-1995 Provo, UT, USA: Ancestry.com Operations, Inc., 2011 [database on-line; cited 2020 Nov 19].

<sup>24</sup>Rosa Einhorn, 1950. United States Deceased Physician File (AMA), 1864-1968, database with images, Family Search (<https://familysearch.org/ark:/61903/1:1:WDDR-GNZM:2> September 2019). [cited 2020 Nov 5]. Available from: <https://www.familysearch.org/ark:/61903/3:1:3Q57-99QG-599Y-W?i=322&cc=2061540&personaUrl=%2Fark%3A%2F61903%2F1%3A1%3AWDDR-GNZM>.

<sup>25</sup>Rosa Einhorn [sic]; 1930; Manhattan, New York, New York; Page: 28A; Enumeration District: 0443; FHL microfilm: 2341291. Ancestry.com. 1930 United States Federal Census Provo, UT, USA: Ancestry.com Operations Inc, 2002. Original data: United States of America, Bureau of the Census. Fifteenth Census of the United States, 1930. Washington, D.C.: National Archives and Records Administration, 1930. T626, 2,667 rolls [database on-line; cited 2020 Nov 18].

<sup>26</sup>"Rosa Einhorn". List of Doctors, Pharmacists, Dentists and Midwives who have been licensed (מיאפור לש המישר), 1936; see note 20.



Picture 6. Rosa Einhorn's index card; United States Deceased Physician File (AMA), 1864-1968. Source: FamilySearch, database with images. [cited 2019 Sept 2]. Available from: <https://familysearch.org/ark:/61903/1:1:WDDR-GNZM>

Simon and Esther Baskin Einhorn, who practised at municipality-funded Tel Aviv 'Health House' founded in 1932.

The 'Health House' was one of three venues for sexual consultation as conceptualised by the European contemporaneous East-Central European movement for sexual reform (35, 36) that, while aiming at popularising birth control, also pursued a civilising mission vis-à-vis the traditional ("Mizrahi") populations (37). Rosa Einhorn was an experienced expert in this matter, though it is not clear whether she regularly practised or volunteered at the Tel Aviv 'Health House' or was even among its organisers. When the movement for sexual reform came to a halt in the run-up to World War II, Einhorn left the country in 1938 for the United States.<sup>27</sup>

In New York, she asked the local public health authorities about the possibility of obtaining a license for California.<sup>28</sup> However, she abandoned

<sup>27</sup>Rosa Einhorn (1938); New York, New York Passenger and Crew Lists, 1909, 1925-1957. Havre, France, New York, New York, United States, NARA microfilm publication T715 (Washington, D.C.: National Archives and Records Administration, n.d.). [Cited 2019 June 17]. Available from: <https://www.familysearch.org/ark:/61903/3:1:33S7-95NZ-9R5N?i=65&cc=1923888> „Rosa Einhorn, MD“ had travelled between Tel Aviv, Europe and the U.S. also in 1934 and 1937 (ibidem).

<sup>28</sup>Rosa Einhorn, 1950. "United States Deceased Physician File

this plan and settled in Manhattan.<sup>29</sup> As indicated in an obituary for Max Einhorn, 'Dr. Rosa Einhorn' spent much time with her widowed brother, providing him 'considerable comfort until she also died' (14). Rosa Einhorn, MD, died on May 27, 1950, of coronary occlusion and was buried on May 28 in Mount Judah Cemetery in Queens, New York (Picture 6).<sup>30</sup>

### Concluding Remarks

After qualifying as a 'learned midwife' in St. Petersburg in 1892, Rosa Einhorn left no stone unturned to acquire her MD. Her brother, the reputed US gastroenterologist Max Einhorn, probably encouraged and supported her medical studies in St. Petersburg (where women were not permitted to graduate) and, subsequently, in Berlin, Vienna, Berne, and Lausanne. Her enthusiasm to augment her medical knowledge is outstanding and related to her idea that modern medicine and physician-modernisers might change the world for the better.

In fulfilling this mission, she developed an extraordinary degree of mobility and determination. Though she may have settled as a physician in the United States after being dismissed as an official female physician in Bosnia in 1904, she preferred to continue her work in Bosnia. Moreover, she also preferred working in Mandatory Palestine on modernising Mizrahi women over her practice in the United States. Having received her doctorate

(AMA), 1864-1968," database with images, FamilySearch. [cited 2020 Sept 2]. Available from: <https://familysearch.org/ark:/61903/1:1:WDDR-GNZM>

<sup>29</sup>Rosa Einhorn MD; New York, New York, City Directory, 1942; 1943; 1946; 1948; Ancestry.com. U.S., City Directories, 1822-1995. Provo, UT, USA: Ancestry.com Operations, Inc., 2011. [database on-line; cited 2020 Nov 16].

<sup>30</sup>Rosa Einhorn, 1950; United States Deceased Physician File (AMA), 1864-1968", see note 20; Rosa Einhorn, U.S., Find A Grave Index, 1600s-Current [Provo, UT, USA: Ancestry.com Operations, Inc., 2012 [database on-line; cited 2020 Nov. 17].

from the University of Lausanne in 1901, Rosa Einhorn's employment as an official female physician in Travnik was sponsored by the Bosnian government in Vienna. She worked 18 months as a provisory officer in Travnik and the Travnik district and treated 3125 female patients within 15 months in 1903 and 1904. Therefore, Einhorn was the most efficient female health officer ever but aroused the 'dislike' of the local authorities and physicians not least for that reason. After she reacted to the threat of dismissal by 'escaping' to the United States, she was dismissed in November 1904 because of her months-long absenteeism. Einhorn returned in 1905 to marry Sigismund Bloch, a locally settled AH judiciary, which made her situation even more difficult because the AH supreme authority did not approve of the wife of an Austrian judge working in the same judiciary district as her husband. However, she petitioned successfully for her right to practise privately in BH in 1905 and was supported by the provincial public health authorities who, regarding syphilis eradication campaigning, insisted on the presence of a female physician on site. After Rosa Einhorn had been called on for syphilis eradication in 1908 and 1909, she appealed in vain for her reinstatement as an official physician and for the accreditation of her Swiss diploma in Austria. She left Bosnia for the United States in 1913 but emigrated to the United States only in 1923. Practising as a physician in Newark in the 1920s, Einhorn left the United States to work as a sexual reform consultant and physician in Tel Aviv in Mandatory Palestine. She returned to the United States because of the decline of the sexual reform movement in 1938 and settled in Manhattan, New York, where she died and was buried in May 1950.

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## References

1. Anon. Beim Fräulein Doktor. Die ärztliche Behandlung der Mohamedanerinnen. In *Neuigkeitsweltblatt*. 1903; February 19.
2. Note [in German]. *Neues Wiener Journal*. 1902;3275, December 7:7. (see also notes e.g. in: *Mährisches Tagblatt*. 1902;281, December 6:7; *Oesterreichische Zeitschrift für Pharmacie*. *Zeitschrift des Allgemeinen Apotheker-Verains*. 1902;40(51):522.
3. Steiner L, editor. Address book of civil and military physicians, pharmacists, hospitals, civil and military medical institutions as well as health resorts and spas in Austria, Hungary, Bosnia and Herzegovina [in German]. 1905/06;5. Vienna: Georg Szelinski, Vienna 1905.
4. Nečas C. Among Muslim Women. The activities of the female health officers in Bosnia and Herzegovina, 1892-1918 [in Czech]. Brno: Masaryk University, 1992, p. 102-8.
5. Martin B. As female physician in Bosnia and Herzegovina: Rosa Bloch-Einhorn's professional activities in Travnik, 1902-1917(?) [in German]. [cited 2020 Oct. 17]. Available from: <https://www.scribd.com/document/386555172/Als-Arztin-in-Bosnien-Herzegowina-zur-Tatigkeit-Rosa-Bloch-Einhorns-in-Travnik-von-1902-bis-1917>.
6. Omanić A, Dodig-Karaman Ž, Serdarević M, Kabiljo M. The contribution of Jewish health care professionals to the development of health care in Bosnia and Herzegovina [in Croatian]. *Acta med-hist. Adriat*. 2008;6(1):41-54.
7. Konforti J. Jews of Travnik [in Bosnian]. [cited 2020 Oct. 12]. Available from: <https://www.jews.ba/post/12/Jevreji-Travnika>.
8. Yad Vashem 1988. "Travnik". Translation from Pinkas ha-kehilot; entsiklopediya shel ha-yishuvimle-min hivasdam ve-ad le-aher shoat milhemet ha-olam ha-sheniya: Yugoslavia/Encyclopaedia of Jewish Communities: Yugoslavia, edited by Zvi Loker, Jerusalem: ad Vashem, 1988, pp. 162-165. [cited 2020 Oct. 14]. Available from: [https://www.jewishgen.org/yizkor/Pinkas\\_Yugoslavia/yug\\_00162.html](https://www.jewishgen.org/yizkor/Pinkas_Yugoslavia/yug_00162.html).
9. Anon. The first Jews in Travnik [in Bosnian]. [cited 2020 Oct. 12]. Available from: <https://www.jews.ba/post/11/Prvi-Jevreji-u-Travniku>.
10. Einhorn M. *Wolkovisker Yizkor Book (Volkovysk. The Trilogy, Part I)*, New York: Dr. Moses Einhorn, 1949, p. 1.
11. Sefer Sukhovola / Suchovola (Memorial Library of Jewish Communities), Editorial board: Kh. Shteynberg, M. Vonkhotsker, Y. Levin, Y. Tsaban. Jerusalem/Tel-Aviv: 1957. Translation by Peter Zinn, pp. 25-27. [cited 2019 June 20]. Available from: <https://www.jewishgen.org/Yizkor/suchowola/suc019.html>.
12. "Einhorn, Max". Biographical Sketches of Jews Prominent in the Professions etc., in the United States. In: *The American Jewish Yearbook*, vol. 6 (September 10, 1904, to September 29, 1905/5665). p. 52-213; p. 84.

13. Max Einhorn. Autobiography [in German]. In: Grote L.R. (ed). *Die Medizin der Gegenwart in Selbstdarstellungen*. Leipzig: Verlag von Felix Meiner; 1929. p. 1-24.
14. Andresen AF. In memoriam Dr. Max Einhorn, 1862-1953. *Gastroenterology*. 1954;26(1):121-2. PMID: 13117226.
15. Bockus, HL. The Einhorn Story. Historical Profiles. *Gastroenterology* 1978;74:949-50. PMID: 346433.
16. Einhorn, Rosa, Matrikel-No.: 8166, vol. BB IIIb 1161. *Matrikelbücher der Universität Bern 1805-1925*. [cited 2020 Nov. 17]. Available from: <http://www.archivwissenschaft.ch/uab/suchresultate.php>.
17. Neumann D. Female Students from the Russian Empire in Switzerland, 1867–1914 [in German]. Zürich: Hans Rohr, 1987.
18. Hirsch L. *From the Shtetl to the Lecture Hall: Jewish Women and Cultural Exchange*. Lanham: University Press of America; 2013.
19. Freidenreich HP. Jewish Women Physicians in Central Europe in the Early Twentieth Century. *Contemporary Jewry*. 1996;17(1):79-105.
20. Freidenreich HP. *Female, Jewish, and Educated: The Lives of Central European University Women*. Minneapolis: Indiana University Press; 2002.
21. Offer M. Introduction: Jewish Women Medical Practitioners in Europe before, during and after the Holocaust. *Nashim*. 2020;36:10-21.
22. Grossmann A. Motherhood and modernity: German women doctors in the Weimar Republic, during the Nazi era, in exile and in the post-war period [in German]. In: Institut für Sozialforschung Frankfurt, ed. *Geschlechterverhältnisse und Politik*. Frankfurt a.M.: Edition Suhrkamp; 1994. p. 288-309.
23. Einhorn R. Beitrag zur Kenntniss der Unterschenkelfracturen. Berlin: Druck L. Schumacher, 1901 (Universität de Lausanne: med. thèse, 1900). [cited 2020 Nov. 17] Available from: <https://db-prod-bcul.unil.ch/dbbcu/theses/thesaut.php>.
24. Einhorn R. For knowledge of lower leg fractures [in German]. *Archiv für klinische Chirurgie*. 1901;64(4):791-848.
25. “Einhorn, Mlle. Rosa, Russe”. *Catalogue des étudiants de l’université de Lausanne*, No. 21. Année universitaire 1900-1901, semestre d’hiver. Lausanne: Imprimerie J. Couchoud. p. 14.
26. Fuchs B. Orientalising Disease. Austro-Hungarian Policies of ‘Race’, Gender, and Hygiene in Bosnia and Herzegovina, 1878–1914. In: Trubeta S, Turda M, Promitzer C, eds, *Health, Hygiene and Eugenics in Southeastern Europe until 1945*. Budapest: CEU Press; 2011. p. 57-85.
27. *Die Ergebnisse der Volkszählung in Bosnien und der Herzegovina vom 10. Oktober 1910*, ed. by Bosna Wilāyet/Landesregierung für BH. Sarajevo: Landesdruckerei; 1912.
28. Landesregierung für Bosnien und die Herzegovina (ed): *Public Health in Bosnia and Herzegovina 1878–1901* [in German]. Sarajevo: Landesdruckerei; 1903. p. 246.
29. Anon. Big Fire in Bosnia [in German]. *Feuerwehr-Signale*. 1903;24 (September 20):17.
30. Anon. The Fire Disaster in Travnik [in German]. *Agramer Zeitung*. 1903;204 (September 7):5-6. (p. 6: Einhorn’s name is given incorrectly as “Eichhorn”).
31. Krajewska T. The experience of a female physician’s in Dolnja Tuzla (Bosnia) [in French]. In: Schoenflies R, Morgenstern L et al., editors. *Der Internationale Kongress für Frauenwerke und Frauenbestrebungen in Berlin*, 10. bis 26. Sept. 1896. Berlin: Hermann Walther; 1897. p. 185-90.
32. Meeting of the Association of Military Surgeons St. Louis, October 10-15, 1904. In: *Annual Report of the Surgeon General of the Public Health and Marine Hospital Service of the United States for the Fiscal Year 1905*. Washington Governmental Printing Office 1906 (Treasury Department Doc. No. 2427, Public Health and Marine Hospital Services). p. 229-31.
33. Steiner J. The international congress of military surgeons in St. Louis in October 1904 [in German]. *Militärarzt*. 1905;(39):81-3.
34. Anon. A children’s sanatorium and recreation home in Crikvenica [in German]. *Die Zeit*. 1910;2811;(July 23)1910:11.
35. Grossmann A. *Reforming Sex. German Movement for birth control and abortion reform, 1920-1950*. New York et al.: Oxford University Press; 1995.
36. Lehner K. *Proscribed Interventions: Social democratic efforts to reform the abortion regulations in the interwar period* [in German]. Vienna: Picus; 1989.
37. Liat K. Sexology in the Yishuv. The Rise and Decline of Sexual Consultation in Tel Aviv, 1930-39. *International Journal of Middle East Studies*. 2010;42:231-49; p. 238-40.

## Tracing Ocular Conditions in 15,921 Interwar Refugees, Veria, Greece (1926-1940)

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### Abstract

**Objective.** This historical epidemiological study aims to investigate ocular conditions in Greek refugees during the Interwar period (1926-1940) in the region of Imathia, Greece. **Materials and Methods.** The archival material encompasses 15,921 patients who were admitted to the Refugee Hospital of Veria, Imathia, Greece. Descriptive statistics were estimated. **Results.** Twenty-two cases of ocular conditions were identified. Ten patients had anterior segment conditions, such as keratitis, blepharoconjunctivitis, conjunctivitis, epithelioma, leukoma and an operated cataract. Another patient was diagnosed with ocular trachoma. Four patients presented sympathetic ophthalmia; two additional patients suffered from ophthalmia due to syphilis. One patient was diagnosed with ocular malaria. Four cases of ocular traumas were recorded, among which an ocular burn due to gunpowder, a motorcycle accident leading to a retro-ocular hematoma, and a kick in the eye resulting in ocular trauma were notable. **Conclusion.** The disease spectrum in Greek refugees reflects the adverse conditions during the Interwar era.

**Key Words:** Trachoma ▪ Keratitis ▪ Malaria ▪ Syphilis ▪ Ophthalmology.

### Introduction

Refugees are considered highly vulnerable, and their movements are a matter of concern for contemporary societies. During the early 20<sup>th</sup> century, eye disorders were a global health issue (1). Following the end of World War I, and especially after the Asia Minor Catastrophe (1922), approximately 1,500,000 refugees from Pontus, Asia Minor and Constantinople arrived in Greece. This study begins with the Lausanne Peace Treaty of 1923, which ended the Greco-Turkish War and called for the first obligatory exchange of populations in history, based exclusively on the criteria of religion. After the end of the Balkan Wars and the First World War, the violent uprooting of local populations occurred on a massive scale. The catastrophic defeat of the Greek army in Asia Minor in September 1922 resulted in a huge refugee wave

from Turkey to Greece, when thousands of Greek Christians abandoned their ancestral homes. The Treaty of Lausanne, signed on July 24, 1923, delineated the compulsory exchange of populations between Greece and Turkey.

In 1924, the General Hospital of Veria was founded under the name “Refugee Hospital of Veria” by the mayor of that period (1924-1929), Ioannis Markou. The hospital had 45 beds, and was housed in the two-story building of the National Bank of Greece, at number 12, 16th October Street. Doctor Stavros Mouratoglou (1893-1941/1944) was the first director of the hospital, and Vori Grizanovsky the first nurse. During its first years of operation, only internal medicine patients were treated. In 1927, it was renamed “Municipal Hospital”, and the first Board of Directors was appointed on July 28, 1929. The Chairman of the Board was the Bishop of Veria, Naoussa Polykarpos, and Stavros Mouratoglou

was its director. During the 1930s the departments were the following: Internal Medicine, Gynecology, Surgery, Radiology, and Microbiology (2).

This study aims to evaluate ocular disorders in Greek refugees during the Interwar period in the region of Central Macedonia, Greece, by examining the archives of the Refugee Hospital of Veria, Imathia, which includes 15,921 cases from between March 5, 1926 and October 27, 1940, namely the entry of Greece into World War II.

## Materials and Methods

Our data were collected from the General Hospital of Veria, a city in northern Greece. The Hellenic Data Protection Authority issued a “Data Controller’s permit” (21.11.2013, Ref. ΓΝ/ΕΞ/5965-2, Permit Number 1235) for the above archival material. Additionally, permission was granted by the 3rd Health District of Macedonia (09.01.2014, Reference Number Δ3β/297). Moreover, the details of the study were reviewed and approved by the relevant institutional review board committee (22.01.2014, Reference Number 472). The unpublished archival material encompasses 15,921 patients who were admitted to the Refugee Hospital from 5.3.1926 to 27.10.1940. The archives were entered into a pre-coded database; de-identified information about gender, age, place of residence, region of origin, cause of hospitalization, length and date of hospitalization, was entered into the database from the archive records. Quality control of the database was performed by the research team, by double checking the records using random selections of unique codes. Cases of ocular conditions were identified in the database. Descriptive statistics were estimated, including frequencies for categorical variables and range for numeric variables. Statistical analysis was conducted with STATA/SE, version 13 (Stata Corp., College Station, TX, USA).

## Results

Twenty-two cases of ocular conditions were identified (Table 1). Ten patients (four males, six fe-

males, of ages ranging between 10 and 75 years) had anterior segment conditions, such as: keratitis (bullous, parenchymatous, ulcer of the cornea), blepharoconjunctivitis, conjunctivitis, epithelioma, leukoma and operated cataract. Another patient was diagnosed with ocular trachoma, manifesting as bullous keratitis.

Four patients (three females, one male, of ages ranging between 1 and 45 years) presented sympathetic ophthalmia, which may have been associated with previous trauma, or a severe infection in the other eye.

Interestingly, two patients, a 10-year-old male and a 22-year-old female, suffered from ophthalmia due to syphilis. Malaria was the leading cause of hospitalization in general (8,408 of 15,921 cases). One female, a 16-year-old patient, was diagnosed with ocular malaria.

We also noticed four cases of ocular trauma, among which three were rather impressive. An ocular burn due to gunpowder was noted in a 19-year-old male; a motorcycle accident led to a retro-ocular hematoma in a 3.5-year old child; and a case of potential child abuse was also noted, with a kick in the eye resulting in ocular trauma in a 2-year-old male.

## Discussion

Ocular disorders were noted in our large cohort of patients. Anterior segment diseases prevailed, including keratitis, blepharoconjunctivitis, conjunctivitis, inflammation of the eyelid, epithelioma, leukoma and operated cataract. Nevertheless, cases that would seem rare even today also emerged in this historical cohort.

Ocular manifestations of malaria are rare (3). Although our cohort included 8,408 malaria cases, only one patient was diagnosed with ocular malaria. At that time, malaria was a considerable public health issue in Greece. After a fierce anti-malaria battle that spanned many decades of the 20th century, Greece has been declared “malaria free” since 1974. Notably, the Hellenic Center for Disease Control and Prevention reported an outbreak of malaria between 2015 and 2018, which coincided with the current movement of refugee populations (4).

Table 1. Details about Ocular Conditions in the Study Sample

Conditions grouped	Admission (year)	Gender	Age (years)	Diagnosis
Anterior segment conditions	1933	F	18	Blepharoconjunctivitis-keratitis
	1934	F	65	Conjunctivitis
	1935	F	70	Epithelioma
	1935	M	75	Blepharoconjunctivitis
	1935	F	20	Leukoma
	1936	F	60	Operated cataract
	1938	M	40	Bullous keratitis
	1938	F	40	Keratitis
	1939	M	10	Parenchymatous keratitis
	1939	M	43	Keratitis - ulcer of the cornea
Trachoma	1938	M	38	Ocular trachoma, manifesting as bullous keratitis
Ophthalmia	1927	M	36	Ophthalmia
	1932	F	45	Ophthalmia
	1933	F	1	Ophthalmia
	1933	F	17	Ophthalmia
Ocular syphilis	1939	M	10	Ophthalmic syphilis
	1940	F	22	Ophthalmic syphilis
Malaria	1933	F	16	Ocular malaria
Ocular trauma	1931	M	36	Ocular trauma
	1933	M	19	Ocular burn due to gunpowder
	1939	M	2	Ocular trauma, kick onto the eye
	1939	M	3.5	Retro-ocular hematoma due to motorcycle accident

F=Female; M=Male.

Two cases of ophthalmia due to syphilis were also noted; indeed, syphilis may affect the eye in various ways, yet rarely. Manifestations of syphilis in the eye can include ocular inflammation associated with vasculitis, vitritis and anterior uveitis (5, 6).

Trachoma was also identified in our study sample. Some cases of keratitis may also have harbored trachoma, but no specific designation of trachoma was noted, except for one case. Nearly one hundred years after our study period, trachoma is the leading cause of infectious blindness worldwide, especially in developing countries. Although the World Health Organization has established an international effort to prevent and treat trachoma, under the acronym "SAFE", trachoma may be still a public health problem due to mass displacement of populations (7).

As a total, the small number of hospitalizations due to ocular diseases could be attributed to a lack of seeking healthcare, or treatment administered by general practitioners on an outpatient basis. Tracing the history of ophthalmology in the Greek state before the establishment of the Chair of Ophthalmology, we learned that the scientific domain of ophthalmology was taught as part of the curriculum of the General Surgery course. The first Professor of General Surgery was Ioannis Olympios (1802-1869), who was appointed to this position in 1837 at the newly established Othonian University, later and still today known as the National and Kapodistrian University of Athens. The modern and contemporary history of Ophthalmology in Greece begins with the establishment of the Athens Eye Hospital in 1843, and the Chair

of Ophthalmology in 1856 at the Othonian University of Athens, with the first Professor Andreas Anagnostakis (1826-1897) (8, 9).

Greek refugees faced major adversities during their integration following the Asia Minor Catastrophe. Thousands of refugees were arriving daily in Greece from the ports of Smyrna, Çesme, Aivali, Panormos, Artaki, Mudania, Kios, Dikeli of Samson (Samsun), Kerasous (Giresun), Constantinople, etc. The first refugee wave included Greeks who had abandoned the coast of Asia Minor and were evacuated in panic to the ports of Thessaloniki and Piraeus (10). By mid-December 1922 around 890,000 people had already been transported by ship from Thrace, Pontus, and Anatolia to Greece and the islands (11). The exodus of Greeks from their homes was completed in 1925, with the assistance of the Joint Exchange Committee (11). The Asia Minor Catastrophe forced the Greek Government to rebuild and reorganize its public institutions. The resettlement of 1,221,849 refugees led to an unprecedented increase in the country's population in just a few months, and it entailed economic, public health, and social upheaval. The extensive health problems proved to be challenging for the Greek Government. The high mortality rates among the refugees indicated the lack of preparedness for health care in the Greek public infrastructure (12, 13).

At a later phase, the events that followed the Asia Minor Catastrophe had an important effect on the evolution of ophthalmology in Greece. The increased need for treatment of ocular disorders led to the establishment of ophthalmology departments in many Greek hospitals. Moreover, the spread of transmissible diseases, such as ocular trachoma, resulted in the foundation of anti-trachoma medical centers. In addition, numerous ophthalmologists that had resided in Constantinople (Istanbul), and other areas of Asia Minor, settled in Athens and Thessaloniki.

Although the Ophthalmology Department at the University of Athens was established in 1856, the University Department in the co-capital Thessaloniki was set up much later (in 1943), possibly leading to differences in perceptions and health-care seeking behavior in the region. In any case,

refugees have unique eye care needs, according to a recent systematic review (14).

### **Limitations of this Study**

The limitations include the fact that there was no independent validation of diagnoses by other experts of this period. There was no information about the total set of clinical findings and laboratory tests conducted. Moreover, the subcohort of ocular disorders was small compared to the abundance of 15,921 cases hospitalized during this period. Furthermore, there was no information regarding the specific treatments that the hospitalized patients received for their ocular conditions. In addition, there were no data regarding cases of ocular disorders recorded in Veria prior to the Asia Minor Catastrophe 1922, as the Veria hospital was founded in 1924, and no health records were available before that.

### **Conclusion**

Refugees and immigrants are vulnerable populations. The disease spectrum of Greek refugees reflects the adverse conditions faced by this heterogeneous group upon their arrival in Greece. Further studies are needed as refugees seem to have unique eye care needs across various time periods.

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#### **What Is Already Known on this Topic:**

*After the Asia Minor Catastrophe, approximately 1.5 million refugees arrived in Greece. In 1924, the Refugee Hospital of Veria was founded in Veria, Central Macedonia, Greece, and was responsible for the treatment of refugees that settled in that area. Greek refugees faced great adversity during their integration into Greek society, including poor health conditions.*

#### **What this Study Adds:**

*The ocular health of Greek refugees has not been adequately studied. For this reason, we evaluated ocular disorders in Greek refugees, during the period of 1926-1940 in the region of Central Macedonia, Greece, by examining the archives of the Refugee Hospital of Veria, Greece, which includes 15,921 patients. Ocular disorders were noted in our large cohort. Anterior segment diseases prevailed, including keratitis, blepharconjunctivitis, conjunctivitis, inflammation of the eyelid, epithelioma, leukoma and operated cataract. Various ocular traumas were also noted. Nevertheless, cases that would seem rare today also emerged in this historical cohort, such as ophthalmia due to syphilis, ocular malaria and sympathetic ophthalmia.*

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**Authors' Contributions:** Conception and design: SM, TS, IC, TP and MK; Acquisition, analysis and interpretation of data: SM, TS, IC, TP and MK; Drafting the article: SM, TS, IC, TP and MK; Revising it critically for important intellectual content: SM, TS, IC, TP and MK; Approved final version of the manuscript: SM, TS, IC, TP and MK.

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## References

- Allen SK, Semba RD. The trachoma "Menace" in the United States, 1897–1960. *Surv Ophthalmol.* 2002;47(5):500-9.
- Liolios G, Betsa O. Refugee - National - General Hospital of Veria [in Greek]. *Chronicles of History and Culture of the Prefecture of Imathia.* 2012;18:13-6.
- Jamshidi E, Eftekhari Ardebili H, Yousefi-Nooraie R, Raeisi A, Malekafzali Ardakani H, Sadeghi R, et al. A social network analysis on immigrants and refugees' access to services in the malaria elimination context. *Malar J.* 2019;18(1):1.
- Michaleas SN, Sergeantanis TN, Tsoucalas G, Vladimirov L, Diamantis A, Tentolouris N, et al. Ioannis Kardamatis (1852-1942): Pioneer of the Anti-Malaria Battle in Greece. *Infez Med.* 2020;28(1):104-7.
- Balaskas K, Sergeantanis TN, Giulieri S, Guex-Crosier Y. Analysis of significant factors influencing visual acuity in ocular syphilis. *Br J Ophthalmol.* 2011;95(11):1568-72.
- Chang GC, Young LH. Sympathetic ophthalmia. *Semin Ophthalmol.* 2011;26(4-5):316-20.
- Sanders AM, Abdalla Z, Elshafie BE, Nute AW, Long EF, Aziz N, et al. Prevalence of trachoma within refugee camps serving South Sudanese refugees in White Nile State, Sudan: Results from population-based surveys. *PLoS Negl Trop Dis.* 2019;13(6):e0007491.
- Athens Eye Hospital (Ophthalmiatreio Athinon) [homepage on the Internet]. Athens: History of the Athens Eye Hospital; c2014 [cited 2020 Aug 10]. Available from: [http://www.ophthalmiatreio.gr/?page\\_id=13234.html](http://www.ophthalmiatreio.gr/?page_id=13234.html).
- Rodopoulos P. Medicine in Greece during the period 1821-1921 [in Greek]. *Medical Progress.* 1930;35:125-36.
- Morgenthau H. *I was sent to Athens.* New York: Doubleday, Doran & Company; 1929.
- Alexandris A. Pontic Greek refugees in Constantinople 1922-1923: The human cost of the exchange of populations. *Archive of Pontus.* 1982;37:280-94.
- Kopnaris F. Public health in Greece [in Greek]. Athens: Chr. Chronopoulos; 1933.
- Theodorou V, Karakatsani D. Health policy in Interwar Greece: The intervention by the League of Nations Health Organization. *Dynamis.* 2008;28:53-75.
- Bal S, Duckles A, Buitenheim A. Visual health and visual healthcare access in refugees and displaced persons: A Systematic Review. *J Immigr Minor Health.* 2019;21(1):161-74.

## Letter to the Editor: Regarding “An Unusual Bilateral Duplication of the Suprascapular Vein and Its Relation to the Superior Transverse Scapular Ligament Revealed by Anatomage Table”

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### Dear Editor,

We read with interest the case presented by Panagouli et al. (1) concerning the unusual bilateral duplication of the suprascapular vein revealed by the *Anatomage* table. It is valuable to report findings on the cadavers incorporated into the *Anatomage* table because this resource is accessible worldwide. However, we would like to bring attention to the fact that the suprascapular vein (SV) may be rather more variable than the Panagouli et al. (2019) report states.

The SV is rather variable. It is not unusual to find the SV duplicated (2-5) and its site of drainage is variable as well (6). A duplicated SV was reported in 30 out of 103 cadaveric specimens of Korean origin (29.7%) by Yang et al. in 2012 (2) and in 9 out of 88 cadaveric specimens of Polish origin (12.2%) by Jezierski et al. 2016 (3). Furthermore, Podgorski et al. (2014) demonstrated detailed observations on the SV around the suprascapular notch (SSN) area. They reported 35 out of 60 selected dissections exhibiting variable suprascapular vascular arrangements. Twenty SSNs showed a duplicated SV, while 15 featured a triplicated SV. They proposed denominating the vein passing within the SSN by the term “suprascapular notch vein” on the basis of the fact that its course was distinguishably duplicated in 11 specimens (4).

The SV was found to drain into the external jugular vein in 60% of cases, and in the remaining cases it drained into the subclavian vein and into some other veins (6).

Regarding SV involvement in suprascapular nerve entrapment, it is not a definite risk factor. An existing SV within the SSN does not necessarily reduce the space to a critical point, and it may rather serve as a protective cushion for the suprascapular nerve against the bony margins of the SSN during dynamic movements (3, 5).

In conclusion, we endorse reporting this variant structure in a cadaver used by multiple global users via the *Anatomage* table. Indeed, this report will draw attention to SV variability. However, we emphasize that it is not an unusual case, and that a duplicated SV is rather common.

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## References

1. Panagouli E, Tsigirigi A, Kotsira G, Demesticha T, Skandalakis P, Troupis T, Filippou D. An Unusual Bilateral Duplication of the Suprascapular Vein and Its Relation to the Superior Transverse Scapular Ligament Revealed by Anatomage Table. *Acta Med Acad.* 2019;48(3):307-11.
2. Yang HJ, Gil YC, Jin JD, Ahn SV, Lee HY. Topographical anatomy of the suprascapular nerve and vessels at the suprascapular notch. *Clin Anat.* 2012;25(3):359-65.
3. Podgórski M, Sibiński M, Majos A, Stefańczyk L, Topol M, Polguy M. The suprascapular vein: a possible etiology for suprascapular nerve entrapment and risk of complication during procedures around the suprascapular foramen region. *Orthop Traumatol Surg Res.* 2014;100(5):515-9.
4. Jezierski H, Wysiadecki G, Sibiński M, Borowski A, Podgórski M, Topol M, et al. A quantitative study of the arrangement of the suprascapular nerve and vessels in the suprascapular notch region: new findings based on parametric analysis. *Folia Morphol (Warsz).* 2016;75(4):454-9.
5. Labetowicz P, Synder M, Wojciechowski M, Orczyk K, Jezierski H, Topol M, et al. Protective and Predisposing Morphological Factors in Suprascapular Nerve Entrapment Syndrome: A Fundamental Review Based on Recent Observations. *Biomed Res Int.* 2017;2017:4659761.
6. Deslaugiers B, Vaysse P, Combes JM, Guitard J, Moscovici J, Visentin M, et al. Contribution to the study of the tributaries and the termination of the external jugular vein. *Surg Radiol Anat.* 1994;16(2):173-7.

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