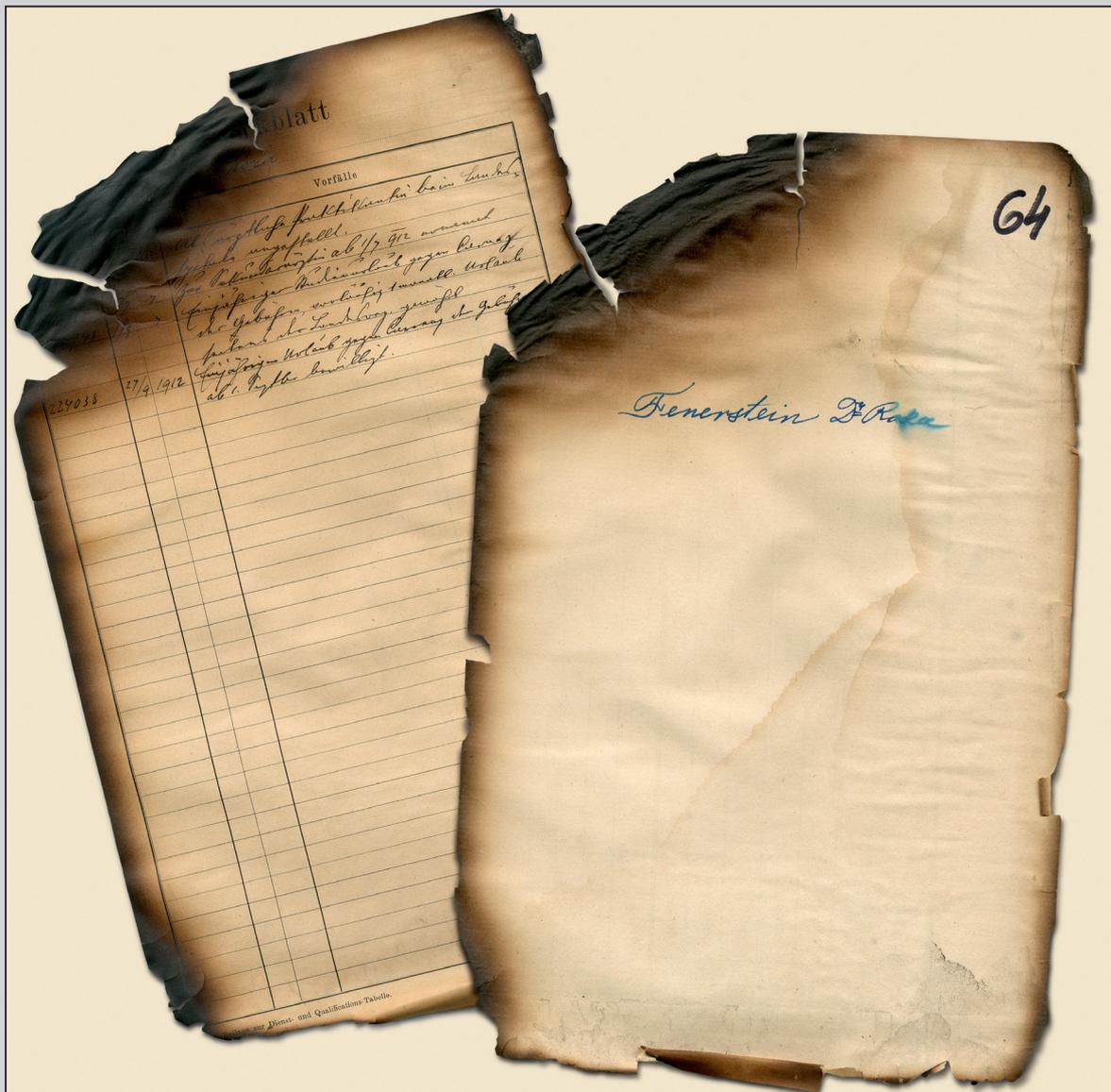


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# Acta Medica Academica

Journal of Department of Medical Sciences  
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Dragana Antonić (1981), Traces of violent protests: February 7, 2017. Remains of Dr. Rosalie Feuerstein's dossier in the Archives of Bosnia and Herzegovina: Collection of personal files: No. 68. Photo illustration made by composing scanned archival documents.

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## Effects of Transcutaneous and Percutaneous Tibial Nerve Stimulation in Bosnian Female Patients with an Idiopathic Overactive Urinary Bladder

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### Abstract

**Objective.** The purpose of this study was to evaluate the efficacy of daily transcutaneous tibial nerve stimulation (TTNS) versus weekly percutaneous tibial nerve stimulation (PTNS) on the quality of life of patients with idiopathic overactive bladder (OAB). **Patients and Methods.** The study was designed as a randomized controlled trial. The diagnosis of OAB was made on the basis of clinical symptoms, and urodynamic tests were performed to check whether uncontrolled contractions of the detrusor during bladder filling were responsible for the OAB symptoms. The tests used to assess symptoms and quality of life were Overactive Bladder Questionnaires (OAB-q) SF. The patients were divided into 2 groups of 30 patients each. The first group was treated with TTNS every day for 3 months and the second group with PTNS once a week, also for 3 months. **Results.** Stimulation with both TTNS and PTNS led to the reduction of all clinical symptoms of OAB and improved quality of life, with statistical significance ( $P < 0.05$ ) and with no side effects. When comparing these two groups, the improvement was statistically more significant in the group treated with PTNS. When the quality of life scores and symptoms were compared to the type of treatment, it was found that the improved quality of life parameters and the reduced OAB symptoms were more statistically significant in the treatment with PTNS than TTNS therapy ( $P < 0.001$ ). **Conclusion.** The results of the study suggest good efficacy of both TTNS and PTNS in the treatment of OAB. Better effects are achieved with weekly PTNS, as it leads to a statistically significant reduction in symptoms as well as an improvement in quality of life, without side effects.

**Key Words:** Overactive Bladder ■ PTNS ■ TTNS.

### Introduction

The International Continence Society (ICS) defines an overactive urinary bladder (OAB) as an urge with or without urinary urge incontinence, and with increased frequency during the day and night (1). These symptoms greatly affect the patient's quality of life. In order for patients to be treated as adequately as possible, it is necessary to first make an accurate diagnosis, which is most safely done through urodynamic examination. Due to the presence of urgent incontinence,

the overactive bladder can be divided into the so-called "wet type" with urge incontinence and the so-called "dry type" without incontinence, which is more common and present in about 63% of patients (2). The excessive activity of the detrusor is associated with the excessive activity of the bladder. The ICS states that the hyperactive detrusor is characterized by the presence of unwanted contractions of the detrusor, which is diagnosed with urodynamics (3). However, the link between an overactive bladder and hyperreflexia of the detrusor is not completely clear. It is reported that in

urodynamic examinations, hyperreflexia of the detrusor is only found in 54% of women who have symptoms of an overactive bladder (4).

The emptying of the urinary bladder occurs as soon as a small amount of urine has accumulated in it. Usually the sphincter muscle function is preserved. With regard to etiology, the cause may be neurological or idiopathic. OAB prevalence differs between individual studies. According to the ICS, the incidence in the general female population is about 13-17% and increases with age. In women under the age of 35, the prevalence is up to 5%, while in women over the age of 65 the prevalence is 20-30% (5-7). There are several ways to treat a hyperactive bladder, from behavioral treatment, medication, by injecting botulinum toxin, electrostimulation, and surgical treatment. Success depends on an adequate diagnosis and a well-chosen treatment. Modern therapeutic methods achieve the best treatment outcomes and improve the quality of life. In the treatment of OAB, electrical nerve stimulation is also used. It is a non-invasive method which uses exponential current (low frequency current) to effectively suppress excessive bladder activity.

In the late 1990s, Dr. Marschall Stoller presented tibial nerve stimulation, first known as the SANS (Stoller Afferent Nerve Stimulator) protocol like promising therapy for nonneurogenic lower urinary tract dysfunction (8). The term percutaneous or transcutaneous tibial nerve stimulation is now used, depending on which electrodes are used. If an acupuncture needle is inserted into or near SP 6, connected to a stimulator and then the tibial nerve is stimulated, this is called percutaneous tibial nerve stimulation (PTNS), and, if self-adhesive electrodes are used, this is called transcutaneous tibial nerve stimulation (TTNS). In most studies, in which PTNS or TTNS stimulation were used, improvements were demonstrated in terms of a significant reduction in symptoms and an improvement in the quality of life of patients with OAB, without side effects (9-11). So far, no such studies have been carried out in Bosnia and Herzegovina.

The aim of this study was to evaluate the efficacy of daily TTNS versus weekly PTNS on the qu-

ality of life and clinical symptoms of patients with an idiopathic overactive bladder (OAB).

## Patients and Methods

The study was a randomized controlled trial. Participants were enrolled consecutively during their visits to the Urodynamics unit of the Physical Medicine and Rehabilitation Clinic, University Medical Center Tuzla (Bosnia and Herzegovina) for a period from January 2016 until December 2019. The inclusion criteria were female patients who presented with clinical symptoms, and urodynamic testing that showed an OAB with maximum bladder capacity of less than 300 ml.

Each patient had to have a normal urine sample before the urodynamic testing. Exclusion criteria were symptoms lasting less than 6 months, pregnancy, sacral peripheral nerve lesion, urinary tract infection confirmed by microbiological analysis, serious secondary illnesses (such as renal failure, nephrolithiasis, bladder and kidney tumors..) and detrusor-sphincter dyssynergia confirmed by a urodynamic investigation. 62% of patients had used anticholinergic drugs for at least 3 months without improvement, 11% of patients had discontinued anticholinergic therapy after a short time due to side effects, and 27% of patients had refused anticholinergic treatment.

Randomization was based on a single sequence of random assignments. The first group (30 patients) was treated with TTNS with TENS every day for 3 months, while the second group (also 30 patients) had PTNS with TENS once a week for a total of 3 months. The assessment of symptoms and quality of life was completed immediately after detecting OAB, as well as before and after treatment.

TTNS stimulation of the tibial nerve was performed using two 50×50 mm self-adhesive electrodes, with one electrode placed behind the medial malleolus and the other electrode approximately 10 cm above. The current intensity, frequency, and pulse duration were set on each apparatus at a frequency of 10 HZ, pulse duration of 200 μs and duration of stimulation of 30 min. The intensity level was immediately above the threshold determining a



Figure 1. Stimulation with transcutaneous tibial nerve stimulation.

net perception of the current, without induced pain. Medio Tens devices (Iskra Medical device) were used, which were given to patients to use at home daily for 3 months (Figure 1). Detailed instructions were given to the patients on how to operate the device at home with the specified parameters set.

For PTNS stimulation we placed an acupuncture needle, 0.25×25 mm in size, above the medial malleolus directly into the acupuncture point SP 6 located near n. tibialis three cun (cun is a traditional Chinese measure of thumb width, used to map acupuncture points on the human body) or a distance of four transverse toes above the medial malleolus and behind the posterior edge of the tibia and one self-adhesive electrode was placed on the medial plantar part of the right foot (Figure 2). The needle was placed at an angle of 90 degrees, on the right leg 2 cm deep. The frequency was 10Hz, with pulse duration of 200  $\mu$ s and stimulation length of 30 minutes. We decided to place electrodes and an acupuncture needle in the right leg because, according to Chinese traditional medicine (acupuncture), the points for solid organs (in this case the spleen) that belong to the yin are on the right side of the body. In addition, the rules state that when the needles are inserted in only one side, in women it should be in the right side of the body.

OAB-q SF (OAB-S=Overactive bladder S-symptoms, OAB-Q=Overactive bladder Q-quality of life), a specific questionnaire that consisted of



Figure 2. Stimulation with percutaneous tibial nerve stimulation.

two subscales, was used to assess the frequency of hyperactive bladder symptoms and the quality of life of patients with urinary disorders. The symptom subscale contained six questions rated separately from 1 to 6 and quality of life subscale included 13 questions rated from 1 to 6. The lowest score for symptoms is 6, and the highest is 36. A lower score is a better finding that indicates less pronounced symptoms. To assess the quality of life, the lowest score is 13 and the highest is 78. The higher score shows a better finding, i.e. a better quality of life. It was validated, culturally adapted and translated for use in the population of Bosnia and Herzegovina. The symptoms which were monitored and affected the quality of life are: urgency (>than 3 to 24 h), daily voiding (frequency >8 in 24 h), nocturia and urge incontinence. The OAB-q SF questionnaire was completed before treatment and 3 months after treatment.

### Statistical Analysis

All statistical analyses have been done by MedCalc software (ver.12.1.4.0 for Windows; MedCalc, Mariakerke, Belgium). The differences between the groups in categorical variables, Wilcoxon sum rank tests were done as well as one-way ANOVA test.  $P < 0.05$  was considered significant.

## Results

Sixty female patients who had symptoms of OAB were examined. Urodynamic testing proved detrusor overactivity in 72% of women who had symptoms of an overactive bladder. Patients who had electrostimulation with TTNS were on average 47.4±8.0 years old, and patients who had electrostimulation with PTNS were on average 49.0±6.9 years old. The groups were homogeneous in age and baseline clinical characteristics (Table 1). Stimulation with TTNS has shown a statistically significant reduction in all clinical symptoms of the bladder and improved quality of life (Table 2). The

symptom score before treatment with daily TTNS was 61.2±14.6 and decreased after treatment to 50.8±12.3 ( $P<0.0001$ ). The quality of life score increased from 28.5±12.6 after treatment with daily TTNS to 38.3±11.4 ( $P<0.0001$ ). Stimulation with PTNS has shown a statistically significant reduction in all clinical symptoms of the bladder and improved quality of life. The symptom score before treatment with weekly PTNS was 54.3±14.9 and decreased after treatment to 26.8±15.3 ( $P<0.0001$ ). The quality of life score increased from 35.3±16.8 after treatment with weekly PTNS to 64.9±16.9 ( $P<0.0001$ ) (Table 3).

Table 1. Demographic and Basic Clinical Parameters

Variable	Groups		P
	TTNS	PTNS	
Age (years)	47.4±8.0	49.0±6.9	<0.41
Daily micturition number	12.9±4.4	14.1±3.9	0.27
Night micturition number	3.8±1.9	4.3±2.6	0.46
Daily incontinence number	3.8±1.8	3.3±2.4	0.436
Night incontinence number	1.9±1.4	1.7±1.3	0.706
OAB-Q	28.5±12.6	35.3±16.8	0.085
OAB-S	61.2±14.6	54.3±14.9	0.074

TTNS=Transcutaneous tibial nerve stimulation; PTNS=Percutaneous tibial nerve stimulation; OAB-Q=Overactive bladder quality of life; OAB-S=Overactive bladder symptoms.

Table 2. OAB-S Clinical Symptoms and OAB-Q Quality of Life in the TTNS Group before and after Treatment

Clinical symptoms	Treatment		P*
	Before	After	
Daily micturition number	12.9±4.4	9.4±3.4	<0.0001
Night micturition number	3.8±1.9	2.4±1.4	<0.0001
Daily incontinence number	3.8±1.8	2.4±1.4	<0.0001
Night incontinence number	1.9±1.4	1.3±1.0	0.0002
OAB-Q	28.5±12.6	38.3±11.4	<0.0001
OAB-S	61.2±14.6	50.8±12.3	<0.0001

OAB-Q=Overactive bladder quality of life; OAB-S=Overactive bladder symptoms; TTNS= Transcutaneous tibial nerve stimulation; \*Paired t test.

Table 3. OAB-S Clinical Symptoms and OAB-Q Quality of life in the PTNS group before and after Treatment

Clinical symptoms	Treatment		P*
	Before	After	
Daily micturition number	14.1±3.9	6.8±2.8	<0.0001
Night micturition number	4.3±2.6	1.5±1.2	<0.0001
Daily incontinence number	3.3±2.4	1.2±1.0	<0.0001
Night incontinence number	1.7±1.3	0.6±0.7	<0.0001
OAB-Q	35.3±16.8	64.9±16.9	<0.0001
OAB-S	54.3±14.9	26.8±15.3	<0.0001

OAB-Q=Overactive bladder quality of life; OAB-S=Overactive bladder symptoms; PTNS=Percutaneous tibial nerve stimulation; \*Paired t test.

Table 4. Comparison of Clinical Symptoms and Quality of Life after Treatment with TTNS and PTNS Stimulation

Clinical symptoms	TTNS	PTNS	P
Daily micturition number	9.4±3.4	6.8±2.8	0.02
Night micturition number	2.4±1.4	1.5±1.2	0.016
Daily incontinence number	2.4±1.4	1.2±1.0	<0.001
Night incontinence number	1.3±1.0	0.6±0.7	0.004
OAB-Q	38.3±11.4	64.9±16.9	<0.001
OAB-S	50.8±12.3	26.8±15.3	<0.001

TTNS=Transcutaneous tibial nerve stimulation; PTNS=Percutaneous tibial nerve stimulation; OAB-Q=Overactive bladder quality of life; OAB-S=Overactive bladder symptoms.

Comparing the quality of life scores and symptoms measured by the OAB-q SF questionnaire, in relation to the type of treatment, statistically significantly improved quality of life parameters and statistically significantly reduced symptoms were found in favor of PTNS treatment compared to TTNS therapy ( $P<0.001$ ) (Table 4).

It is possible that the localization of the right leg and use of the acupuncture point SP 6 itself led to extremely good results. There were no side effects after treatment with both TTNS and PTNS therapy.

## Discussion

The results of our study showed good effectiveness of TTNS in reducing all clinical symptoms of a hyperactive bladder, and all this had a positive effect on quality of life. The TTNS treatment also showed good tolerability, without side effects. The effectiveness of the treatment was already evident in the second week of treatment and did not change significantly during the 3 months of the treatment. The efficacy of the treatment, as well as treatment tolerance, makes the treatment suitable for patients, especially if they have other diseases or symptoms due to which they would not be able to use anticholinergic drugs.

Voorham et al. (12) demonstrated the acute effect of a single application of TTNS in patients with OAB symptoms using urodynamic parameters. The results of urodynamic parameters for a group of 20 patients without stimulation were almost unchanged, and in the group after stimula-

tion there was a statistically significant improvement in bladder capacity, micturition volume and first detrusor contraction. The study was done as a diagnostic procedure, not a treatment. A multicenter study was conducted in France by De Seze et al. (9), where 70 patients treated with the TTNS technique who suffered from MS were followed. Stimulation with TTNS lasted 3 months, and the duration of therapy was 20 minutes per day. After treatment, 83.3% of patients had a statistically significant improvement in clinical symptoms as well as quality of life (9). Booth et al. (13) used a systematic literature review of four databases between 1980 and 2017 to evaluate the efficacy of transcutaneous tibial nerve stimulation (TTNS) for the treatment of adults with a hyperactive bladder (OAB) of idiopathic or neurogenic origin. Ten randomized controlled trials and three prospective cohort studies were reviewed, involving 629 participants. A meta-analysis of two trials comparing TTNS with a placebo showed a mean reduction in the total ICIQ Urinary Incontinence Short Form (ICIQ-UI SF). A review of 4 studies showed that TTNS and antimuscarinic treatment were equally effective. In two trials, TTNS provided greater benefits for OAB symptoms than behavioral therapy. The stimulation of the tibial nerve and sacral foramen were equally effective, but combined stimulation was the most effective (single study). No adverse events were reported. Martin-Garcia and Crampton (14) demonstrated the efficacy of TTNS stimulation in maintaining symptom improvement over a 6-month period in women with idiopathic OAB who responded positively to 12-week PTNS treatment.

PTNS is a minimally invasive procedure used to treat OAB. The Urgent® PC Neuromodulation System is usually used for stimulation, but we used a TENS device with a modified acupuncture needle outlet in our research. Stimulation with PTNS led to a statistically significant reduction in all clinical symptoms of a hyperactive bladder and improved quality of life. Gaziev et al. (15) investigated papers related to the effect of PTNS on lower urinary tract dysfunction using MEDLINE and ISI web databases. PTNS stimulation was effective in 37-100% of patients with OAB, in 41-100% in patients with nonobstructive urinary retention and up to 100% in patients with painful bladder syndrome. In a multicenter study, involving 53 patients who did not respond to conventional therapy, Govier et al. (16) used PTNS for 12 weeks, where a 0.22 mm wide acupuncture needle was placed near the tibial nerve, three fingers above the ankle. In 71% of patients there was a decrease in the frequency of day and night urination ( $P < 0.05$ ). Urge incontinence was reduced by an average of 35% ( $P < 0.05$ ). Statistically significant improvements were noted in the quality of life. No significant treatment-related adverse events were reported in any of the patients. It was concluded that PTNS is a safe, effective and minimally invasive method. In a multicenter study, Van Balken et al. (17) examined the effect of PTNS as a neuromodulatory treatment of lower urinary tract dysfunction in 37 patients with OAB symptoms and in 12 patients with non-obstructive urinary retention. A positive outcome was noted in 60% of all patients. In patients with OAB, a statistically significant decrease in incontinence, frequency of urination, and equal increases in medium and low volume were observed. Improvements have also been seen in patients with non-obstructive urinary retention. Only mild side effects were observed. Vandoninck et al. (18) assessed urodynamic changes in 90 patients, after 12 sessions of PTNS stimulation, and showed an increase in cystometric capacity and a delay in the onset of detrusor instability. De Wall LL and Heesakkers (19) investigated the efficacy studies of PTNS on symptoms of OAB and pelvic organ disorders, pain, and quality of life in the MEDLINE,

CINAHL, and EMBASE databases. Five randomized controlled trials showed improvement (range 36.7-80%) in HAB symptoms, frequency, urgency, nocturia, and incontinence. Peters and colleagues (20) examined a 12-week PTNS stimulation in a multicenter, double-blind, randomized controlled trial comparing it to placebo stimulation. A total of 220 patients were included. Patients receiving PTNS for 12 weeks showed a 55% moderate or marked improvement in frequency, nocturia, discharge with moderate/severe urgency, compared with an improvement of 21% in the placebo group. Finazzi et al. (21) analyzed the effect of PTNS stimulation frequency and concluded that stimulation three times per week gave the same results as once per week.

In our study, it was proven that PTNS stimulation once a week, for a total of 3 months, i.e. 12 treatments, gave excellent results in the treatment of OAB, where the parameters of quality of life and clinical symptoms significantly improved. Bhide et al. (22) reviewed papers related to n. tibialis stimulation techniques in the treatment of OAB, as well as their efficacy. PTNS stimulation of the tibial nerve was done by inserting a 22-mm profile needle, 3 to 4 fingers above the medial malleolus. The most commonly used current stimulation was 20 Hz, with intervals of 200  $\mu$ s. The intensity of the current was also set to the highest level the patient could tolerate. The main side effect of PTNS was pain at the site of needle insertion. The simulations usually lasted 30 min. The use of PTNS in patients with OAB showed improvement in symptoms, as seen in the two studies comparing PTNS with placebo treatment. However, studies, where a combination of treatment with PTNS and antimuscarinic drugs were used, showed a greater improvement in symptoms. However, TTNS showed similar results to PTNS.

Results of our study show better effectiveness of the process with PTNS versus TTNS. In each, the parameters of stimulation are the same and the only difference consists of the placement of the electrode. The use of an acupuncture needle placed in the acupuncture point SP6 has to be discussed. Acupuncture might have an effect in decreasing

the number of micturition episodes, incontinence episodes, and nocturia episodes. A lot of studies investigate the effects of acupuncture and/or electro-acupuncture (EA) on an overactive bladder (Mo Q 2015, Wen Q 2020, Zwang J 2018). However, the evidence is insufficient to show the effect of using acupuncture alone or the additional effect to drugs in treating OAB (23).

Padilha et al. (24) published a study protocol to be conducted as a randomized controlled clinical trial and to include 99 women with OAB and urgency. The aim of this study was to provide evidence for a more detailed discussion of electrostimulation electrode positioning for 2 TTNS and PTES (parasacral transcutaneous electrical stimulation) treatments as an option in terms of the positioning of electrodes relative to the tibial nerve region in specific populations, such as amputees or people with severe sensory damage to the lower limbs. Slovak M and al.'s (25) review of research on Pub Med found differences in descriptions of stimulation intensity, therapy strategy and electrode position, as well as in different symptoms and pathology of patients. Limited data on long-term follow-up have been published in the literature, so the treatment regimen that brings lasting benefits is unclear. The different effects shown in the studies can be explained by different stimulation parameters and electrode placement. We used a TENS device with a modified acupuncture needle outlet for PTNS stimulation. It is possible that the localization or use of the acupuncture point itself led to extremely good results, as well as the parameters used. Weaker results with TTNS stimulation may possibly be explained by insufficient stimulation intensity via electrodes. The drawback of this treatment is the need for daily stimulation of the n. tibialis, and for that reason patients have to be trained on how to use the device at home. The disadvantage of the study could be the inability to monitor patients to check if they are doing daily stimulation. Further large placebo-controlled studies are needed to obtain a solid evidence base.

Little is known about the underlying mechanism for efficacy of the procedures. Finazzi (26) studied long-latency somatosensory evoked poten-

tials providing information on the function of somatosensory cortical structures. Mean amplitude of P80 and P100 waves increased significantly after PTNS and might reflect long-term modifications in synaptic efficiency through the somatosensory pathway. The plastic reorganization of the cortical network triggered by peripheral neuromodulation can be hypothesized as a mechanism of the action of PTNS. However, the evidence does not support the efficacy of electro-acupuncture (EA) alone in the treatment of OAB. EA is similar to PTNS in some ways; however, the type of EA treatment used in this trial could stimulate not only the tibial nerve (through the acupoint of SP6) but also the 3 sacral (through the acupoint of BL33) and pudendal nerves (through the acupoint of BL35). Integrating PTNS and SNS stimulation points may have good benefits (27).

## Conclusion

There are several ways to treat an overactive bladder, and pharmacological treatment is still the first line in the management of patients with OAB symptoms. In addition to pharmacological therapy, electrical tibial nerve stimulation is used in the treatment of OAB, which is a non-invasive method of exponential current (low-frequency current) which suppresses excessive bladder activity. Adequate diagnosis and treatment can improve bladder control in patients with OAB symptoms. In this study, we confirmed the positive effects of two different electrical tibial nerve stimulation methods used for the treatment of OAB: the transcutaneous method with two self-adhesive electrodes and the percutaneous method of acupuncture electrostimulation. Our recommendation is to use PTNS stimulation with acupuncture needle and point SP6 on a right leg, once a week, for a total of 3 months, i.e. 12 therapies, because it is easily implemented. A TENS device with a modified needle outlet can be used and it is more effective than TTNS (which involves a total of 90 individual treatments) in improving quality of life and clinical symptoms.

**What Is Already Known on This Topic:**

There are a number of ways to treat OAB and electrical tibial nerve stimulation is used, which is a non-invasive exponential current (low-frequency) method that suppresses excessive bladder activity. We evaluated the efficacy of daily transcutaneous tibial nerve stimulation (TTNS) versus weekly percutaneous tibial nerve stimulation (PTNS) on the quality of life of patients with idiopathic overactive bladder (OAB).

**What This Study Adds:**

In this study, we confirmed the positive effects of two different electrical tibial nerve stimulation methods used for the treatment of OAB: the transcutaneous method with two self-adhesive electrodes and the percutaneous method of acupuncture electrostimulation. Our recommendation is to use PTNS stimulation (which is a minimally invasive procedure) with acupuncture needle and point SP6 on a right leg, once a week, for a total of 3 months, i.e. 12 therapies, because it is easily implemented, a TENS device with a modified needle outlet can be used and it is more effective than TTNS (which involves a total of 90 individual treatments) in improving quality of life and clinical symptoms. There were no side effects after treatment with either TTNS or PTNS therapy.

**Authors' Contributions:** Conception and design: MZI and MI; Acquisition, analysis and interpretation of data: MZI, MB and MI; Drafting the article: MZI, MM and SJ; Revising it critically for important intellectual content: OS and MZI; Approved final version of the manuscript: MZI, OS, MI, MM, SJ and MB.

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

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## Characteristics of Patients with Nonvariceal Upper Gastrointestinal Bleeding - Are We Underestimating Gastroprotection during NSAIDs Therapy?

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### Abstract

**Objective.** The aim of our study was to determine the etiological factors, treatment and outcome of patients with non-variceal bleeding from upper gastrointestinal tract. **Materials and Methods.** This study enrolled 200 patients admitted to Sarajevo University Clinical Center with signs and symptoms of upper gastrointestinal bleeding, from January 2019 to July 2020. All patients had undergone gastroscopy, confirming the cause of gastrointestinal bleeding. Clinical and laboratory data were collected retrospectively, including previous non-steroid antiinflammatory drugs (NSAIDs) and anticoagulant therapy, comorbidities, risk factors, as well as endoscopic findings, laboratory findings, treatment and clinical follow-up. **Results.** The majority of patients were men (59%) with an average age of 53±6 years. Duodenal and gastric ulcers were the most common cause, followed by other etiologies. In our study, previous NSAIDs therapy had been registered in 29.5% of patients, anticoagulants in 8%, and proton pump inhibitors (PPI) in 2.9% of patients. Endoscopic intervention was required in 34% of patients. The need for transfusion occurred in 44.5% of cases. Rebleeding during hospitalization was observed in 7.5% of patients, mortality in 1.5% and surgery in 3% of patients. **Conclusion.** The patients admitted to our hospital with symptoms of acute nonvariceal upper gastrointestinal bleeding were elderly, predominantly males, with significant comorbidities and a higher incidence of NSAID use. Gastroprotection is underutilized during NSAID treatment in patients with other coexisting risk factors, with a low rate of concomitant use of PPI during NSAIDs therapy. Endoscopic therapy, together with PPI, significantly reduces rebleeding rates, mortality and the number of emergency surgical interventions.

**Key Words:** Mortality ▪ Transfusion ▪ Forrest Classification.

### Introduction

Upper gastrointestinal bleeding can be a life-threatening condition and requires careful evaluation from admission to the emergency center. Epidemiological data are important to gain an insight into the actual healthcare problem. The outcome of patients with upper gastrointestinal bleeding depends on the adequate assessment of patients with a high risk of mortality and rebleeding requiring immediate intervention, and those at low risk who can be safely discharged as outpatients (1, 2).

Peptic ulcer bleeding is the most common cause of non-variceal upper gastrointestinal bleeding,

responsible for about 50% of all cases, followed by oesophagitis and erosive disease. Rebleeding occurs in 7-16% of cases, despite endoscopic therapy. Mortality ranges between 3 and 14%, increasing with age and in patients with significant comorbidities (3).

One of the main risk factors for peptic ulcer bleeding is non-steroid anti-inflammatory drugs (NSAIDs) use. The remaining risk factors include: *Helicobacter pylori* infection, age >65 years, past history of gastrointestinal ulcers, multiple-drug combination therapy, and comorbidities, such as cardiovascular disease and nephropathy. Cyclooxygenase-2 (COX-2) selective inhibitors

have an advantage over non-selective NSAIDs. In patients using NSAIDs, who are at risk for gastrointestinal bleeding, protective drugs are used in a small percentage of patients. Recommendations for prevention and treatment of non-steroidal anti-inflammatory drug-induced gastrointestinal ulcers include evaluation of gastrointestinal and cardiovascular function before using NSAIDs, as well as using PPI as the first choice of therapy for the prevention and treatment of these injuries. A high-dose of PPI in patients using NSAIDs effectively prevents rebleeding, and reduces the possibility of surgery and mortality rate (4, 5).

The aim of our study was to determine the etiological factors, treatment and outcome of patients with non-variceal bleeding from the upper gastrointestinal tract at the Clinic of Gastroenterohepatology.

## Material and Methods

This study enrolled 200 patients admitted to Sarajevo University Clinical Center with signs and symptoms of upper gastrointestinal bleeding, from January 2019 to July 2020. During this period, 260 patients came to the emergency center with suspected gastrointestinal bleeding. Twenty of them had variceal bleeding and 40 had a Glasgow-Blatchford score lower than 3 and normal endoscopic findings, which is why they were not taken into consideration in the study. All the patients underwent emergency gastroscopy within 6 hours from arrival at the emergency center, confirming the cause of non-variceal bleeding from upper gastrointestinal tract. Out of the 200 patients, 183 had a Glasgow-Blatchford score higher than 6 at the time of arrival at the emergency center, which classified them as high-risk patients, and the remaining 17 had a Glasgow-Blatchford score between 4 and 6, placing them in the moderate risk category. The indication for endoscopic intervention was active bleeding from the proximal gastrointestinal tract confirmed by gastroscopy, and the threshold of hemoglobin for transfusion was 80 g/L in a bleeding patient. Clinical and laboratory data were collected retrospectively, including previous NSAIDs and anticoagulant therapy, comorbidities, risk factors,

laboratory findings, treatment and clinical follow-up. The rate of rebleeding, surgical treatment and mortality was noted. Exhaustion of endoscopic methods, without successful cessation of bleeding, was an indication for surgical treatment.

## Statistical Analysis

The statistical analysis was performed with SPSS version 22, including descriptive statistics, diagrams of associations between the etiology of gastrointestinal bleeding and the need for endoscopic intervention and transfusion, as well as binary logistic regression to evaluate risk factors, comorbidities and drugs used as potential predictors for endoscopic intervention in patients with gastrointestinal bleeding.  $P < 0.05$  was considered statistically significant.

## Results

The majority of patients were men (59%). The average age of the patients was  $53 \pm 6$  years. Duodenal ulcer was verified in 45.5% of patients, gastric ulcer in 32%, neoplasm in 7.5%, anastomosis ulcer in 5.5%, erosions and gastroesophageal reflux disease in 4.5%, Sy Mallory Weiss in 3%, and angiodysplasia in 2% (Figure 1).

In the group of patients with ulcers, 22% of them had Forrest I, 34% Forrest II and 44% Forrest III type of bleeding. In 72% of cases the duodenal ulcer was classified as Forrest III, 14% Forrest II and 14% Forrest I, while the gastric ulcer in 16% of cases was classified as Forrest III, 54% Forrest II and 26% as Forrest I. All patients with Forrest I type bleeding needed endoscopic intervention, and 82% of patients with Forrest II as well. In 59% of patients, gastrointestinal haemorrhage presented as melena, while 21% of patients had melena and haematemesis simultaneously. 42% of patients were hypotensive with systolic blood pressure lower than 100 mm Hg and 30.5% of patients had tachycardia with heart rate above 100 beats per minute.

Previous NSAIDs therapy was registered in 29.5% of patients, anticoagulant use in 8% of patients, while PPI in 2.9% of patients. Comorbidi-

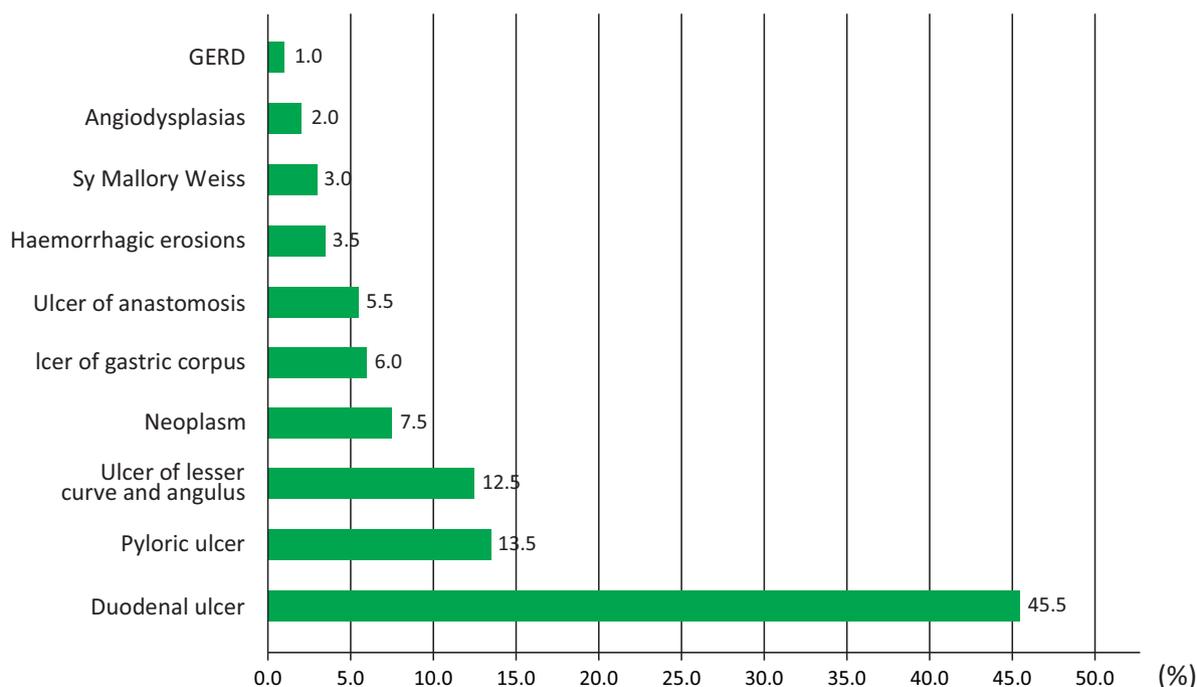


Figure 1. Localization of non-variceal bleeding in upper gastrointestinal tract.

ties were identified in 56% of subjects. An earlier episode of gastrointestinal bleeding within the previous 10 years, requiring endoscopic treatment, was observed in 22% of patients. Smoking was verified in 34% of the patients, alcohol consumption in 15%. Among comorbidities, the majority of patients had hypertension (42% of patients), an earlier vascular incident (8.5%), chronic renal insufficiency (3.5%) and malignant disease (2%). “Earlier vascular incident” refers to cerebrovascular insult, ischemic heart disease and peripheral blood vessel thrombosis, since this population requires the use of anticoagulant therapy. Among NSAIDs, patients most commonly used acetylsalicylic acid in a dosage of 100mg for pre-existing cardiovascular disease, and 400 mg ibuprofen for intermittent back and joint pain. Anticoagulant therapy was administered to patients with a previous vascular incident: acenocoumarol in a dosage of 4 mg, rivaroxaban 20 mg and antiplatelet drug clopidogrel in a dosage of 75 mg. All prescribed medicines were taken for 2 years before the study (Figure 2A and 2B).

Endoscopic intervention was required in 34% of patients, and the remaining patients underwent conservative treatment with PPI parenterally. Among those 34% of patients, in 6% hemostasis was achieved with adrenalin injection, 18% with endoscopic clips and in 10% with both adrenalin and clips. Since in all patients continuous IPP therapy was included within 24 hours after endoscopic treatment, in 6% of cases (12 patients in total) adrenalin injection therapy with continuation of IPP therapy for the next 24 hours proved to be effective. None of these patients had rebleeding. The need for transfusion occurred in 44.5% of cases, with an average of  $3.51 \pm 2.10$  blood doses of 250 ml. In-hospital rebleeding within 48 h of achieved hemostasis was observed in 7% of patients, and those patients required re-endoscopy, there was in-hospital mortality in 3% and surgery was required in 3% of patients. All patients from the rebleeding group had previously undergone endoscopic treatment. The average length of hospitalization was  $5 \pm 2$  days (Figure 3A and 3B).

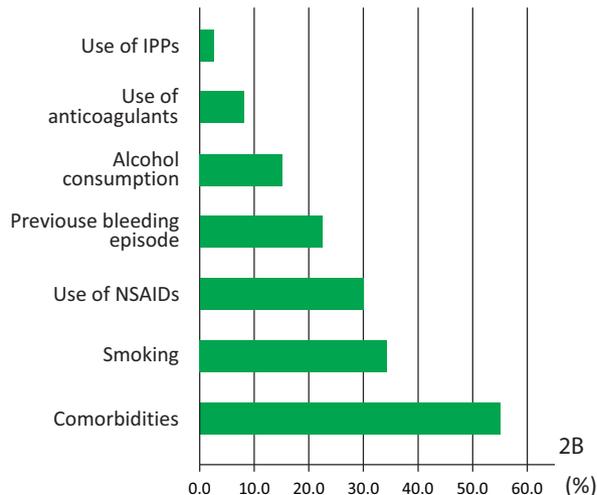
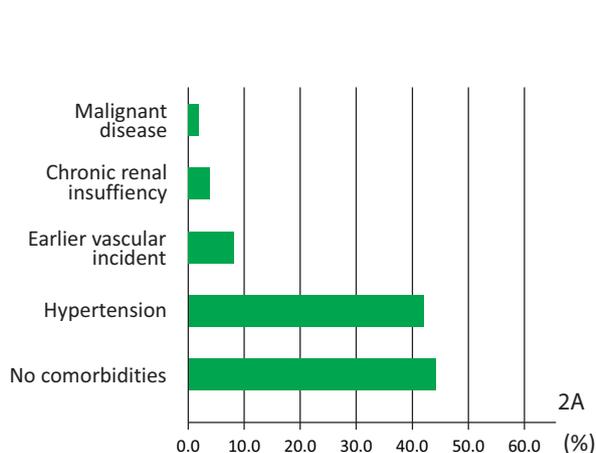


Figure 2A and 2B. Risk factors for gastrointestinal bleeding.

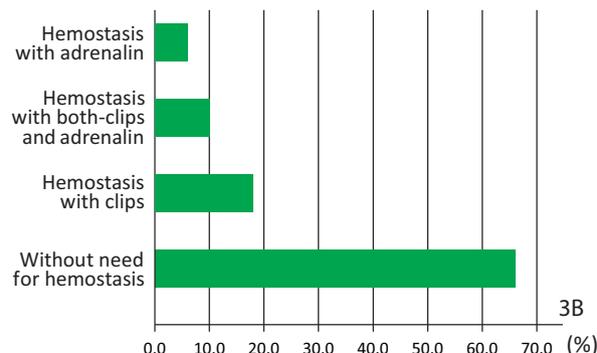
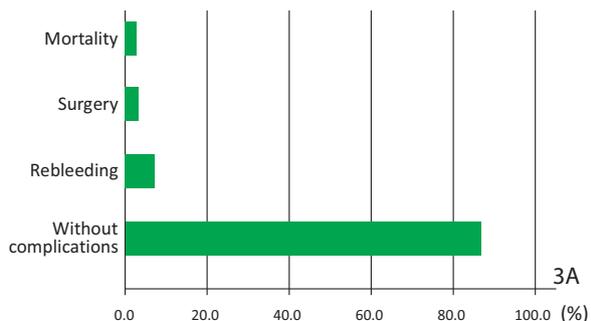


Figure 3A and 3B. Outcomes of gastrointestinal bleeding.

The association between the etiology of gastrointestinal bleeding and the need for endoscopic intervention. Lambda value 0.235, P=0.043 (Figure 4).

The association between the etiology of gastrointestinal bleeding and the need for transfusion. Lambda value 0.427, P<0001 (Figure 5).

Binary logistic regression was performed. There were 11 independent variables considered as predictors of endoscopic intervention and transfusion, as dependent variables. For endoscopic intervention the significance of the model was  $\chi^2(11,200)=202.30$ , P<0.001, with R<sup>2</sup> 0.636 and 0.881 and percent of accuracy 95.5%, which means that between 63.6%

and 88.1% of the variance in the dependent variable is explained by the independent variables and predicted correctly in 95.5% of cases. For transfusion, significance was  $\chi^2(11,200)=207.86$ , P<0.001, with R<sup>2</sup> 0.646 and 0.865 and 94% accuracy. The significance of each of the independent variables is shown separately in Table 1.

NSAIDs and alcohol showed predictive ability for endoscopic intervention (P<0.001; P=0.037), while for transfusion NSAIDs (P<0.001) and two categories of comorbidities, hypertension and malignant disease, were shown to be statistically significant (P=0.024, P=0.002 respectively).

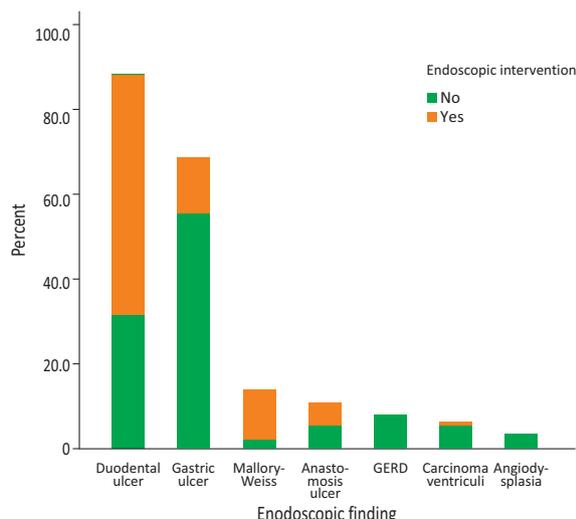


Figure 4. The association between the etiology of gastrointestinal bleeding and the need for endoscopic intervention.

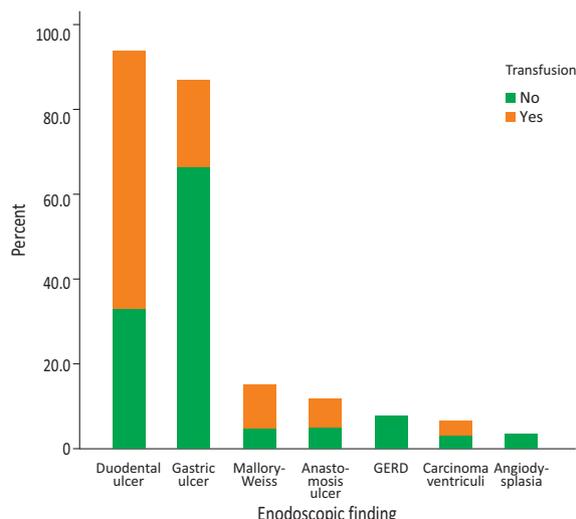


Figure 5. The association between the etiology of gastrointestinal bleeding and the need for transfusion.

Table 1. Predictive Ability of the Independent Variables

Independent variables	Endoscopic intervention			Transfusion		
	B	df	Sig.	B	df	Sig.
Melena	52.433	1	0.997	15.772	1	0.998
Hematemesis	50.272	1	0.997	14.616	1	0.998
NSAIDs	3.588	1	0.000	5.286	1	0.000
Anticoagulants	-17.415	1	0.998	2.044	1	0.220
Hypertension	1.333	1	0.164	2.190	1	0.024
Chronic renal disease	-17.974	1	0.999	1.822	1	0.110
Malignant disease	-17.696	1	0.999	4.125	1	0.002
Earlier vascular incident	-15.183	1	0.997	0.154	1	0.919
Earlier bleeding	-18.441	1	0.999	20.151	1	0.997
Smoking	-0.025	1	0.983	-0.450	1	0.743
Alcohol	2.850	1	0.037	-0.930	1	0.528

df=degrees of freedom; NSAIDs=Nonsteroid anti-inflammatory drugs.

## Discussion

The mean age of our patients was between 55-65, with male predominance, in accordance with other studies (6, 7). Upper gastrointestinal bleeding usually presents as melena or hematemesis (8). Our results confirmed this, with 59% of patients presenting with as melena and 21% of patients with melena and haematemesis simultaneously. A recent study showed that the most frequent non-variceal findings on proximal endoscopy were

duodenal ulcers, representing about two-thirds of cases, followed by antral gastropathy, gastric ulcers and duodenal/gastric mass, with GERD and Mallory Weiss syndrome much less frequent (9). Our results are in accordance with this study, confirming that duodenal ulcers the leading cause of gastrointestinal bleeding, followed by gastric ulcers, hemorrhagic erosions, neoplasm and GERD. The high percentage of malignant disease verified by emergency gastroscopy in our study is a consequence of the late arrival of patients, as well as

the small percentage of patients taking PPI, despite the presence of risk factors, considering that gastric ulcer is a premalignant condition if not treated in good time.

In the study by Young Joo Yang et al. which enrolled patients with peptic ulcer disease, 31.1% of patients had at least one comorbidity (cardiovascular disease, diabetes, chronic liver disease or cerebrovascular disease). The proportion of medication use was as follows: 11.2% NSAIDs and 7.8% antiulcer medications. About half the patients had alcohol consumption and smoking habits – 47.2% and 55.8% respectively (10). Comparing these results with the results of our study, we notice that a higher percentage of NSAIDs consumption (29.5%) and preexisting comorbidities (56%) are present in our population, without appropriate consumption of antiulcer drugs. On the other hand, a significantly lower percentage of alcohol and cigarette consumption was registered in our population. Other studies showed slightly higher NSAIDs use (43.7%, 52.4%) and comorbidities present (57.6%, 83%) than in our study, with a higher percentage of gastro-protective drugs as well (13.9%, 14.3%) (6, 7). According to this, gastroprotection was underutilized during NSAIDs treatment in our patients with comorbidities. Increased risk of hemorrhage is NSAIDs dose-dependent (11-13). Although PPI can prevent aspirin-induced upper gastrointestinal bleeding, a clinical dilemma exists about the increased risk of gastric cancer after long-term use of PPI. The study by Cheung KS et al. investigated the potential interaction between aspirin and PPI on gastric cancer development in patients who had eradicated *Helicobacter pylori*, and perceived that the potentially harmful effects of PPI appeared to be limited to non-aspirin users. Coprescription of PPI is therefore recommended for patients who are at risk of aspirin-induced upper gastrointestinal bleeding (14, 15). Other studies found no evidence that PPI increased the risk of gastric cancer development (16). One of these studies showed that aspirin use for five or more years had positive effects and was associated with a reduction in gastric cancer risk after *H. pylori* eradication (17). Current evidence

suggests that short-term use of PPI could be considered effective and safe in adult patients with acid-related disorders. On the other hand, their long-term and often inappropriate use in patients with vulnerability to adverse events and a high risk of drug-interaction, should be avoided (18).

In our study, endoscopic intervention was required in 34% of patients. The need for transfusion occurred in 44.5% of cases, with an average of  $3.51 \pm 2.10$  doses of blood. In the study by Ket SN and al. transfusion was needed in 85% of patients with manifested upper gastrointestinal bleeding (19). Rebleeding during hospitalization was observed in 7% of patients, surgical intervention in 3% and mortality in 3% of patients. The average length of hospitalization was  $5 \pm 2$  days. Other studies reported a rebleeding rate of 10% and 5.4% of patients, and mortality in 5.7% and 4% patients, respectively. Transfusions were needed in 43.9% patients, with an average length of hospital stay of  $9.29 \pm 5.58$  days (6, 7). Although a recent study showed that endoscopy performed within 6 hours after gastroenterological consultation was not associated with a lower 30-day mortality than endoscopy performed between 6 and 24 hours after consultation, our study showed that timely endoscopic intervention within 6 hours from admission enabled success in 94% of cases, reducing the need for surgery to 3% and rebleeding rate to 7% (20). The transfusion rate and length of hospital stay were lower in our study compared to other published ones.

Our results showed that knowing the etiology of bleeding improves our ability to predict the need for endoscopic intervention by 23.5% and a moderate correlation was found between the two variables. On the other hand, knowing the etiology of bleeding improves our ability to predict the need for transfusion by 42.7%, which is considered as a strong relationship between two variables. NSAIDs and alcohol use were good predictors of endoscopic interventions ( $P < 0.001$ ;  $P = 0.037$ ), while previous NSAIDs use ( $P < 0.001$ ), as well as the presence of hypertension and malignant disease ( $P = 0.024$ ,  $P = 0.002$  respectively) were shown to be statistically significant predictors for transfusion use.

## Conclusion

Upper gastrointestinal bleeding is a condition requiring immediate medical intervention. The most common cause of upper gastrointestinal bleeding is peptic ulcer disease, with malignant disease also presenting in a high percentage. The patients admitted to our hospital with symptoms of acute nonvariceal upper gastrointestinal bleeding were elderly, predominantly male, with significant comorbidities and a higher incidence of NSAIDs use. Gastroprotection was underutilized during NSAIDs treatment in patients with other coexisting risk factors. Emergency endoscopic therapy together with PPI significantly reduces rebleeding rates, mortality and the number of emergency surgical interventions.

### What Is Already Known on This Topic:

*Upper gastrointestinal bleeding can be a life-threatening condition and requires careful evaluation from admission to the emergency center. One the other hand, overuse of NSAIDs, the main risk factors for peptic ulcer bleeding, is common in everyday clinical practice. The question that remains is whether gastroprotection with PPI during NSAIDa therapy is considered sufficiently.*

### What This Study Adds:

*Our study provides insight into epidemiological data about upper gastrointestinal bleeding, which is very important for an insight into the actual healthcare problem. Our results showed that gastroprotection is underutilized during NSAIDs treatment in patients with other coexisting risk factors, with a low rate of concomitant use of PPIs during NSAIDs therapy. This is important for the development of guidelines for management of gastrointestinal hemorrhage at the level of primary, secondary and tertiary health care, in order to reduce the incidence of gastrointestinal hemorrhage.*

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## Psychological Distress in Primary Healthcare Workers during the COVID-19 Pandemic in Greece

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### Abstract

**Objective.** The present study aims to evaluate the symptoms of psychological distress during the COVID-19 pandemic, in Greek primary healthcare workers, correlating them with their individual characteristics. **Materials and Methods.** The research is based on a self-report questionnaire distributed to primary HCWs of Thessaloniki's public health care units. A sample of 143 respondents was gathered. The questionnaire consists of 21 items: 6 demographic questions, 9 on personal distress, 5 on work-related distress and 1 on one dominant feeling of the participants. These items were based on existing validated measures, such as the "Depression Anxiety Stress Scale-21", the "Kessler Psychological Distress Scale-10", "General Health Questionnaire-28" and "Hospital Anxiety and Depression Scale". The associations between participants' gender, education, specialty and parenthood were determined with Pearson's chi-squared ( $\chi^2$ ) test. **Results.** Overall, 70.4% of HCWs were generally affected by the pandemic. The personal distress factors revealed that the majority (67%) experienced distress due to routine changes. The effects on health behavior (sleep, eating behavior and substance use) were not high. Psychological/psychiatric needs were relatively low, while negative emotions and need of social support were high. 31.4% displayed intense emotional instability. All work-related distress factors were rated high. Worry about contracting COVID-19 in the workplace scored the highest (82.6%). Almost half of the participants felt exposed to COVID-19 infection (47.0%). Anxiety (47.2%) and burn-out (78.4%) symptoms were also revealed. Female participants appeared to be more anxious ( $P < 0.01$ ) and upset ( $P = 0.013$ ). **Conclusion.** The exposure to a constant risk could potentially lead to an increase in HCWs' psychological distress. Designing the right tools and organizing the right plans are of paramount importance to prevent the deterioration of their wellness and quality of life.

**Key Words:** SARS-CoV-2 ▪ COVID-19 ▪ Healthcare Workers ▪ Personal Psychological Distress ▪ Work-Related Psychological Distress.

### Introduction

The COVID-19 pandemic was caused by a coronavirus known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and has turned into an unprecedented health emergency (1). The outbreak of the first SARS epidemic in 2003 had a significant psychological impact on Healthcare Workers (HCWs). The need for addressing health professionals' distress was conspicuous then, as it is now (2). As the SARS-CoV-2 pandemic wreaks havoc throughout the entire planet, HCWs' psy-

chological well-being seems to be at risk. Distress, interpersonal sensitivity and anxiety have already been revealed (3).

Outlining the numbers, one can understand the unprecedented pressure on all Health Care Systems. During the first month of the pandemic, Australia reported that HCWs were 2.69 times more likely to contract COVID-19 in comparison with the general population (4). Up to May 2020, there were 152,888 infections and 143 deaths among HCWs globally. Most of the infected HCWs were women and nurses, with the major-

ity reported in Europe. The Eastern Mediterranean region had 5.7 deaths per 100 HCWs, in the same period of time (5) information sources used, publication status and types of sources of evidence. The AACODS checklist or the National Institutes of Health study quality assessment tools were used to appraise each source of evidence. Outcome measures Publication characteristics, country-specific data points, COVID-19-specific data, demographics of affected HCWs and public health measures employed. Results A total of 152 888 infections and 1413 deaths were reported. Infections were mainly in women (71.6%, n=14 058. By September 2020, 570,000 American HCWs were infected and 2,500 died (6). The first year of the pandemic revealed a global prevalence of 15.1% regarding HCW hospitalization and a mortality rate of 1.5% (7) 225 articles did not meet inclusion criteria; therefore, 97 full-text article were reviewed. Finally, after further revision, 30 articles were included in the systematic review and 28 were used for meta-analysis. Results: Twenty-eight studies were identified involving 119,883 patients. The mean age of the patients was 38.37 years (95% CI 36.72–40.03. By the time that this research took place (December 2020), there had been almost 6,500 confirmed COVID-19 deaths in Greece, without a separate report on HCWs (8). It is of great importance to assess the impact of this grim situation on medical staff who are constantly exposed, and are experiencing a gloomy job routine.

Apart from the endangerment of their physical health due to a COVID-19 infection, these circumstances indirectly increase stress, anxiety, depression and insomnia, compromising the safety of their psychological wellness (9, 10). A survey in Australia revealed alarming results regarding the impact of the pandemic on the mental health of the general population, since several negative behaviors and increased psychological distress were found (11). In the German population during the first months of the pandemic, a study revealed emotional and behavioral distress regarding the virus outbreak (12) research on specific vulnerability factors, such as health anxiety, intolerance of uncertainty, and distress (in. Emotional distress

has also been noticed in children and adolescents (13). Thus, the same or even worse effects are expected in HCWs, since the highest prevalence rates of PTSD-like (Post-Traumatic Stress Disorder) symptoms were reported in medical staff (14). Depression and anxiety levels were very much alike, at their highest peaks. In addition, health care specialists are exposed to critical situations, endangering not only their own physical health, but that of their families too. This pressure could be devastating for their mental, psychological and physical well-being (15). A systematic review revealed that one out of three nurses were suffering from anxiety, stress and depression during the first year of the pandemic (16). Similarly, another study reported almost 25% prevalence of anxiety and depression among HCWs (17) who are at the forefront of the fight against COVID-19, are particularly susceptible to physical and mental health consequences such as anxiety and depression. The aim of this umbrella review of meta-analyses is to determine the prevalence of anxiety and depression among healthcare workers during the COVID-19 pandemic. Methods: Using relevant keywords, data resources including PubMed, Scopus, Web of Science, Cochrane, ProQuest, Science Direct, Google Scholar and Embase were searched to obtain systematic reviews and meta-analyses reporting the prevalence of anxiety and depression among healthcare workers during the COVID-19 pandemic from the beginning of January to the end of October 2020. The random effects model was used for meta-analysis, and the I<sup>2</sup> index was employed to assess heterogeneity among studies. Data was analyzed using STATA 14 software. Results: In the primary search, 103 studies were identified, and ultimately 7 studies were included in the umbrella review. The results showed that the overall prevalence of anxiety and depression among healthcare workers during the COVID-19 pandemic was 24.94% (95% CI: 21.83–28.05, I<sup>2</sup> = 0.0%, P = 0.804. PTSD was confirmed among health specialists, with a prevalence of 21.5%. Psychological distress was also revealed at the same rate (18).

A Greek survey indicated that 63.0% of Greeks believe that this crisis will have an adverse im-

pact on their psychological wellness, and 57.9% on their income (which will indirectly affect their mental state) (19). Yet another Greek survey related to the COVID-19 crisis, conducted during April 2020, focusing on HCWs, reported moderate stress, with female participants fluctuating at significantly higher levels. The latter study suggested that HCWs should be screened for psychological symptoms, insomnia, and even PTSD symptoms (20).

The objective of the present study is to evaluate the symptoms of psychological distress during the COVID-19 pandemic in Greek primary healthcare workers, and to explore differences in psychological distress symptoms due to individual characteristics, such as gender, age, education, parental status, specialty and professional experience. This investigation could reveal some risk factors regarding the deterioration of HCWs' psychological well-being and efficiency.

## Materials and Methods

### *Participants and Procedure*

The research was conducted by distributing and collecting anonymous self-report questionnaires (N=143) amongst primary HCWs in several public healthcare units. The self-administered questionnaire was distributed randomly to primary HCWs and to some general or office workers in Thessaloniki's Public Health Care Units (HCUs). More specifically, it was distributed to the 3<sup>rd</sup>, 9<sup>th</sup> and 10<sup>th</sup> public HCUs which belong to the municipalities of Neapolis, Evosmos and Ampelokipoi of the Greater Area of West Thessaloniki. Our sample size was 143 participants who took the survey. The sampling used was cluster-sampling, as the data were collected from three primary HCUs in West Thessaloniki. The study took place on 2<sup>nd</sup> and 3<sup>rd</sup> of September 2020, and was distributed by hand to the respondents. They were asked to fill in the questionnaires during their breaks from work. Consent was obtained from each participant, and they were informed in detail about the survey and the aim of the study. All participants signed the detailed page of informed consent about the

study's objectives, benefits, and harm. They were also given some time to decide or pose questions regarding their participation. Participants were also informed that they could leave the questionnaire at any time. Participation was voluntary and anonymous.

### *Measures*

Before the creation of the survey, bibliography was searched in order to gain knowledge and address the right questions. The composition of our questionnaire, the content and certain details were based on validated tools. Specialized characteristics were drawn from the Depression Anxiety Stress Scale-21 (DASS21) (21) (nervous, overreact, lack of positive emotions and serenity, fear, irritable) [Greek-DASS21 (22)], the Kessler Psychological Distress Scale-10 (hopeless, nervous, tired, depressed) (23), the General Health Questionnaire-28 (24) which are complex, multifaceted, and affect a patient's rehabilitation and recovery. Due to the consequences of these challenges, psychosocial well-being should be considered an important outcome of the stroke rehabilitation. Thus, a valid and reliable instrument that is appropriate for the stroke population is required. The factor structure of the Norwegian version of GHQ-28 has not previously been examined when applied to a stroke population. The purpose of this study was to explore the psychometric properties of the GHQ-28 when applied in the stroke population included in the randomized controlled trial; "Psychosocial well-being following stroke", by evaluating the internal consistency, exploring the factor structure, construct validity and measurement invariance. Methods: Data were obtained from 322 individuals with a stroke onset within the past month. The Kaiser-Meyer-Olkin (KMO (insomnia, day-to-day routine activities, fear of infection) and the Hospital Anxiety and Depression Scale (fear, anxiety and depression questions) (25). The final questionnaire consists of 6 demographic questions and 15 specialized questions about their psychological distress and the general impact that they suffered because of the pandemic crisis. The demographic

questions were about age, gender, parenthood, education, specialty and years of professional experience. These questions represent the independent variables of this study. The 14 questions of Tables 2 and 3 were multiple choice style, built up in a 4-point Likert scale (1= not at all, 2= Little, 3= Much and 4=Very much). These questions were built upon the dependent variables that this study aimed to evaluate. Questions 1.1 to 1.9 evaluate the “personal distress” of each participant. This constitutes one of the two main measures of the study, assessing the worries, bad habits, emotional instability, personal relationships and the general impact on their psychological wellness due to COVID-19. The second main measure of the study is “work-related distress”, which is evaluated by questions 2.1 to 2.5. More specifically, in this section, fear of exposure, insecurity due to safety measures, exposure and worries at work are assessed. Finally, there was a single question that aimed to evaluate directly the participants’ most dominant feelings (Figure 1). “Fear”, “depression” and “anxiety” were the negative feelings from which they could use only one. “Calm” was also among the choices, as a positive one, alongside a neutral answer (“other”).

### **Ethics Statement**

Ethical approval for the study was obtained from the Aristotle University of Thessaloniki Bioethical Committee (*approval No: 27868/09-06-2020*). The Ministry of Health also granted permission for conducting this research. After the deposition of Bioethical Approval and consent papers to the Department of Human Resources and Development of HCUs, the present study was granted permission for the specific days and the specific local HCUs (Registration No: Δ3β/39919, Thessaloniki 14-08-2020). The whole procedure was welcomed by most of the HCWs, with the acceptance rate reaching 90% in total (159 HCWs contacted).

### **Statistical Analysis**

All statistical analyses were carried out using SPSS version 24.0 (IBM, SPSS Inc., Chicago, IL, USA).

In order to provide an analysis based on the respondents’ age, they were divided into two subgroups; one consisted of those above 45 years and the other from the age of 45 and below. The Kolmogorov-Smirnov (K-S) test was also performed on the participants’ age and years of work experience to decide whether we should present the mean or the median value (Table 1). Finally, one question was set to reveal the dominant feelings of the participants (Figure 1). The aim was to investigate whether or not there was a significant difference between the aforementioned independent variables (categorical variables) regarding the indicators of psychological distress in the participants. The presence or absence of an association between the participants’ gender, education, specialization and parenthood, was determined using Pearson’s chi-squared ( $\chi^2$ ) test. After extracting the descriptive results (Tables 1-3), we reported the associations and prevalence of the investigated items among the different groups, defined by gender, age group, profession, educational level and parenthood. The analysis of the indicators of the psychological distress of the respondents was performed by dichotomizing the Likert scale of the items (Low vs. High). Tables 4 and 5 provide a better insight into participants’ responses. These tables present the findings of the 2-scale analysis, by dichotomizing the Likert-4 scale. This method provides clear results about differences due to individual characteristics. The level of statistical significance was set at 0.05.

### **Results**

To begin with, the sample consisted of 143 participants. The median age was 44 years with a range of 26-60 y (Kolmogorov-Smirnov test,  $P < 0.05$ ). The median value of the years of experience was 15 y, with a range of 1 to 37 y (K-S test,  $P < 0.05$ ). Most of the participants (72%) were parents and females (72.7%). Almost half of them had a MSc/PhD degree. Nurses and physicians were the majority (Table 1).

Regarding participants’ dominant feeling, almost half of them (47.2%) declared that they felt

Table 1. HCW Characteristics and Demographics.

Characteristics	Number (%)
<b>Age</b>	
<=45	75 (52.4)
>45	68 (47.6)
<b>Gender</b>	
Female	104 (72.7)
Male	39 (27.3)
<b>Parenthood</b>	
Yes	103 (72)
No	40 (28)
<b>Education</b>	
High School	17 (12)
Bachelor's Degree (BSc)	51 (35.5)
Master's (MSc)/PhD Degree	75 (52.5)
<b>Specialty</b>	
Physician	55 (38.5)
Nurse	37 (25.9)
Midwife	8 (5.6)
Medical Lab/Radiology Assistant (M.L./R. Ass.)	23 (16.1)
Other	20 (14.0)

anxious during the pandemic, with just 6% remaining calm. Fear was also a common negative feeling, as 28.9% experienced it. Excluding those who felt calm or had other feelings, 88.7% of the participants experienced negative feelings during the COVID-19 crisis (Figure 1). HCWs' worries, habits and psychological evaluation are presented, based on their responses, in Tables 2 and 3. Table 2 presents the personal distress of the participants. Most of them declared they were upset due to routine changes, and significantly affected by the Covid-19 pandemic. However, sleep disturbances, eating and drinking habits were not changed during the pandemic. Most of them did not feel the need for psychiatric evaluation and assistance, but they were worried about the future and declared that they had experienced emotional instability. Table 3 presents the work-related distress. Most of our HCWs were quite worried about their exposure to Covid-19, and felt that they treated Covid patients differently. Burn-out was not of high prevalence.

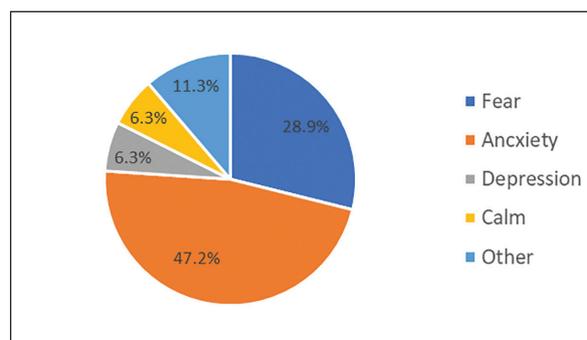


Figure 1. The feeling that survey respondents experienced the most during the pandemic.

The personal distress factors revealed that the majority (67%) experienced distress due to routine changes (Table 2). The effects on health behaviors (sleep, eating behavior and substance use) were low. Very few of the respondents declared that they were in need of psychological/psychiatric help. However, negative emotions and the need for social support were rated rather high. One out of three displayed intense emotional instability (Table 2). Of the two sexes, females appeared to be significantly more anxious and fearful (79.6%) in comparison to male participants (20.6%) ( $P < 0.01$ ) (Figure 1).

Sixty-five percent (65.0%) of high school graduate HCWs experienced emotional instability, ranging from 3 to 4 (Likert-4 scale), compared with those with a BSc (27.5%) or MSc/PhD (28%) in the same range ( $P = 0.013$ ,  $\chi^2 = 16,208$ ).

The majority of the respondents were parents, and most of them (80.0%) declared that they were quite affected by this crisis. However, the percentage was also high for those without children ( $P = 0.23$ ;  $\chi^2 = 9,490$ ; Likert-4 scale).

As mentioned, respondents were divided into two groups and this revealed a significant difference in relation to future worries due to the pandemic ( $P = 0.03$ ,  $\chi^2 = 14.251$ , Likert-4 scale). While 45.0% of the second group (age > 45 y) declared that they were anxious about the future, the counterpart of younger HCWs claimed to be rather concerned (72.0%).

All work-related distress factors were rated high (Table 3). Worry about contracting COVID-19 in

Table 2. HCWs<sup>†</sup> Personal Distress during the Pandemic

Personal distress factors	Likert scale			
	Not at all N (%)	Little N (%)	Much N (%)	Very much N (%)
Affected by COVID-19 pandemic	8 (5.6)	34 (23.8)	79 (55.2)	22 (15.2)
Got upset due to routine changes	6 (4.2)	41 (28.7)	71 (49.7)	25 (17.5)
Experienced sleep disturbances (duration/quality)	57 (39.9)	67 (46.9)	12 (8.4)	7 (4.9)
Increase in tobacco, alcohol or drugs intake	105 (73.4)	33 (23.1)	3 (2.1)	2 (1.4)
Changes to eating habits	77 (53.8)	46 (32.2)	15 (10.5)	5 (3.5)
Worried about the future	11 (7.7)	46 (32.2)	58 (40.6)	28 (19.6)
Experienced emotional instability	25 (17.5)	72 (50.3)	32 (22.4)	14 (9.8)
Felt the need for psychological or psychiatric help	132 (92.3)	10 (7.0)	0 (0.0)	1 (0.7)
Felt closer to your family during the crisis	32 (22.4)	47 (32.9)	50 (35.0)	14 (9.8)

<sup>†</sup>Healthcare workers.

Table 3. HCWs<sup>†</sup> Work-Related Distress during the Pandemic

Work-related distress factors	Likert scale			
	Not at all N (%)	Little N (%)	Much N (%)	Very much N (%)
Worried about getting COVID-19 in your workplace	10 (0.7)	24 (16.8)	71 (49.7)	47 (32.9)
Felt exposed to COVID-19 infection	15 (10.5)	61 (42.7)	45 (31.5)	22 (15.4)
Felt that safety measures at your workplace are adequate	25 (17.5)	68 (47.6)	46 (32.2)	4 (2.8)
Experienced burn-out from the constant shifts / on-call time	31 (21.7)	44 (30.8)	52 (36.4)	16 (11.2)
Felt that you treated patients who are suspected of COVID-19 infection differently	24 (16.8)	52 (36.4)	47 (32.9)	20 (14.0)

<sup>†</sup>Healthcare workers.

the workplace scored the highest (82,6%). Almost half of the participants felt exposed to COVID-19 infection (47.0%). Burn-out symptoms were also revealed (78.4%).

Regarding age, the sub-group of younger HCWs did not feel so anxious and worried about a potential COVID-19 infection. Only 5% of those under 45 y declared that they had undoubtedly been exposed, in comparison with 26.5% of older (age>45 y) participants ( $P=0.05$ ;  $\chi^2=12,908$ ; Likert-4 scale).

Almost all the independent variables present statistically significant differences with regards to routine changes. More specifically, female participants appeared more upset in comparison to males ( $P=0.013$ ), as 73% of females declared “high” and only half of the male respondents did the same (51%). Younger respondents (75% “high”) were also more upset than older ones (59% “high”) ( $P=0.044$ ). A strong statistical difference ( $P=0.003$ )

was observed in the specialty analysis in the same context. It seems that half of the physicians were not very upset (“low”), while all the other specialties declared “high” with a percentage of 70-85%. There are also strong statistical findings regarding future worries and age. Almost half of the older participants appeared to be rather worried about the future, while most of younger respondents (72%) declared the same ( $P=0.002$ ).

High school educated participants manifested higher emotional instability (65%) compared to those with a BSc (27%) or MSc/PhD (28%) ( $P=0.009$ ). Among specialties, apart from physicians who seem to be less affected, the others manifested higher emotional instability ( $P=0.049$ ).

The HCWs in the present study revealed a burn-out prevalence of 78.4%, which is quite significant and alarming. However, no significant difference was found among the variables (Table 5).

Table 4. HCWs<sup>††</sup> Personal Distress during the Pandemic. Dichotomized Likert-4 Scale (Low 1-2, High 3-4)

Table 2 analysis		Affected by COVID-19 pandemic		Got upset due to routine changes		Experienced sleep disturbances (duration/quality)		Increase in tobacco, alcohol or drugs intake		Changes to eating habits		Worried about the future		Experienced emotional instability		Felt the need for psychological or psychiatric help		Felt closer to your family during the crisis	
Dichotomized Likert-4 scale		L	H	L	H	L	H	L	H	L	H	L	H	L	H	L	H	L	H
Gender	Male	15	24	19	20	35	4	37	2	34	5	18	21	28	11	1	38	22	17
	Female	27	77	28	76	89	15	101	3	89	15	39	65	69	35	0	104	57	47
	P-value	0.144		0.013*		0.513		0.515		0.806		0.347		0.534		0.273 <sup>†</sup>		0.864	
Age	≤45 y	19	56	19	56	64	11	71	4	61	14	21	54	49	26	74	1	38	37
	>45 y	23	45	28	40	60	8	67	1	62	6	36	32	48	20	68	0	41	27
	P-value	0.266		0.044*		0.610		0.209		0.090		0.002*		0.502		0.524 <sup>†</sup>		0.248	
Parenthood	Yes	29	74	35	68	90	13	102	1	91	12	45	58	74	29	103	0	56	47
	No	13	27	12	28	34	6	36	4	32	8	12	28	23	17	39	1	23	17
	P-value	0.601		0.649		0.707		0.008*		0.196		0.133		0.01*		0.280 <sup>†</sup>		0.753	
Education	High School	6	11	3	14	12	5	16	1	14	3	3	14	6	11	16	1	9	8
	BSc	12	39	12	39	45	6	51	0	43	8	19	32	37	14	51	0	29	22
	MSc/PhD	24	51	32	43	67	8	71	4	66	9	35	40	54	21	75	0	41	34
	P-value	0.502		0.029*		0.112		0.244 <sup>†</sup>		0.757		0.078		0.009*		0.119 <sup>†</sup>		0.951	
Specialty	Physician	20	35	28	27	52	3	52	3	48	7	28	27	44	11	55	0	30	25
	Nurse/Midwife	9	36	8	37	36	9	43	2	36	9	12	33	30	15	44	1	24	21
	M.L./R.Ass.	7	16	7	16	21	2	23	0	20	3	9	14	12	11	23	0	13	10
	Other	6	14	4	16	15	5	20	0	19	1	8	12	11	9	20	0	12	8
	P-value	0.359		0.003*		0.058		0.739 <sup>†</sup>		0.426		0.108		0.049		0.615 <sup>†</sup>		0.965	

L=Low; H=High; \*Statistically significant correlation at the 0.05 level; <sup>†</sup>Fisher's Exact test; <sup>††</sup>Healthcare workers.

Table 5. HCWs<sup>†</sup> Work-Related Distress during the Pandemic. Dichotomized Likert-4 Scale (Low 1-2, High 3-4)

Table 3 Analysis		Worried about getting COVID-19 in your workplace		Felt exposed to COVID-19 infection		Felt that safety measures at your workplace are adequate		Experienced burn-out from the constant shifts / on-call time		Felt that you treated patients suspected of COVID-19 infection differently	
Dichotomized Likert-4 scale		L	H	L	H	L	H	L	H	L	H
Gender	Male	9	30	23	16	21	18	22	17	22	17
	Female	16	88	53	51	72	32	53	51	54	50
	P-value	0.281		0.392		0.086		0.561		0.632	
Age	≤45y	15	60	46	29	45	30	38	37	39	36
	>45y	10	58	30	38	48	20	37	31	37	31
	P-value	0.405		0.039 <sup>†</sup>		0.185		0.654		0.773	
Parenthood	Yes	17	86	54	49	63	40	51	52	56	47
	No	8	32	22	18	30	10	24	16	20	20
	P-value	0.621		0.782		0.119		0.260		0.638	
Education	High School	3	14	8	9	10	7	6	11	5	12
	BSc	12	39	26	25	34	17	31	20	33	18
	MSc/PhD	10	65	42	33	49	26	38	37	38	37
	P-value	0.335		0.743		0.839		0.172		0.034 <sup>†</sup>	
Specialty	Physician	8	47	31	24	37	18	29	26	30	25
	Nurse/Midwife	9	36	22	23	25	20	24	21	26	19
	M.L./R.Ass.	5	18	12	11	20	3	12	11	11	12
	Other	3	17	11	9	11	9	10	10	9	11
	P-value	0.825		0.898		0.054		0.996		0.747	

L=Low; H=High; <sup>†</sup>Statistically significant correlation at the 0.05 level. <sup>†</sup>Healthcare workers.

The majority of older participants (56%) felt highly exposed to COVID-19 infection, compared to the younger respondents who felt the same (39%) ( $P=0.039$ ). Regarding the differences between the educational level and treating suspected COVID-19 patients differently, the majority of high school participants (71%) and almost half of the MSc/PhD respondents declared that they did so ("high"). A minority of 35% of BSc participants declared "high" on treating these patients differently ( $P=0.034$ ).

## Discussion

A high prevalence of anxiety, depression and insomnia has been proportionally linked with exposure to COVID-19 during HCWs' routine (3, 4, 10, 11, 17, 18, 20, 26). Our findings revealed the prevalence of anxiety (47.2%) and fear (29%) as the main dominant feelings. In the current study, insomnia was not found at significant rates. Almost 70% of our HCWs declared themselves to be generally affected by the pandemic. The personal distress factors revealed that the majority (67%) experienced distress due to routine changes. The effects on sleep, eating behavior and substance use were relatively low. Despite the fact that the need for psychological/psychiatric need was rated low, negative emotions and need of social support were high. Moreover, a significant percentage of 31.4% displayed intense emotional instability.

College education is helpful when dealing with these dire situations, as college students exhibit high risk perception (27). Our HCWs declared that they were not in need of psychiatric or psychological assistance. However, the ongoing pressure might change that in the future. A cross-sectional study claimed that front-line workers are going to suffer from mental health disturbances as long as the pandemic lasts, and thus, are in need of personalized treatment from psychotherapists and psychiatrists (28). A statistically significant difference was found between the genders regarding being upset due to routine changes, with females appearing more troubled about this matter. Females also appeared to be significantly more anxious (20).

Alongside psychological distress are the dietary and eating disorders (29). In terms of dietary habits, the participants in the present study were not much affected, as only 14% experienced significant changes to their eating routine. However, it seems that the lockdown and the whole COVID-19 crisis has affected the dietary and activity habits of each gender differently (30). The respondents in the present study experienced mild sleep disturbances, with only 13.3% declaring otherwise. Insomnia and sleep disorders are also adverse outcomes brought on by the COVID-19 pandemic. Front-line workers are the most vulnerable to this predicament, as they demonstrate conspicuous high levels of insomnia (10).

All work-related distress factors were also rated high. The worry about getting COVID-19 in the workplace scored the highest (82,6%). Almost half of the participants felt exposed to COVID-19 infection (47.0%), and most of them (78.4%) declared that they had experienced burn-out symptoms.

The risk of viral transmission among HCWs is higher in comparison with any other job during the COVID-19 pandemic. A study, based on 23 family clusters of SARS-CoV-2 infection that occurred in Greece, reports a median infection rate of 60.0%, which demonstrates the high transmission dynamics of the novel coronavirus (31). Zheng et al (32) reported a tremendous rate of 52.1% of infected individuals in Wuhan, China, to be HCWs. Thus, HCWs must also deal with the anxiety and fear of putting their families in danger due to their everyday exposure.

Burn-out is another syndrome that requires special attention, as its prevalence was quite high in the present study (33). However, we did not observe any significant difference between male and female primary HCWs. Burn-out syndrome is one of the main culprits for the deterioration of HCWs' quality of life (QoL), especially during the pandemic. QoL increases with good sleep, steady working hours and free time (34).

All the above support the fact that the mental health and psychological well-being of HCWs are at risk of further deterioration. Indeed, reviews have confirmed that PTSD symptoms could fluctuate

tuates from 11% to 73% for HCWs during periods of pandemics and epidemics. As many studies have revealed, the prevalence of anxiety and depression during such crises soared to 80% in many cases, with an average of 25% in all HCWs globally (15). SARS, MERS, COVID-19, ebola, and influenza A. Greek HCWs manifest the same psychological distress (20). Our study revealed some significant results which indicate that primary Greek HCWs are indeed at risk for developing mental health problems, and these problems could be directly associated with several demographic and other characteristics. A meta-analysis of the adverse outcomes of HCWs during the pandemic showed several contradictory findings regarding the demographic and clinical characteristics of HCWs. Of course, the prevalence of distress was revealed, but gender, age and specialty were rather contradictory in relation to these cases. The effectiveness of protective measures at work were significantly associated with their mental and physical well-being. (35)health care workers (HCWs) At the beginning of the pandemic, a study conducted at a primary healthcare center in Athens assessed the mental health of primary HCWs. The results were rather optimistic, as they did not reveal any signs of severe psychological distress. However, it was shown that females were significantly more burdened in terms of distress, compared to males. Their statistical analysis did not divulge any evidence about specialty or age correlations with psychological distress symptoms (36). Half a year later, Malfa et al. (37) assessed the health-related quality of life and psychological distress of public healthcare personnel, working in the region of Western Greece. This study presented some alarming results, especially for nurses' quality of life. Their findings on female participants are aligned with other studies, including ours. It seems once more that women manifested worse psychological deterioration than men, during the pandemic in Greece (37).

Over the last decade, the ongoing economic crisis in the country has affected the mental health of the Greek population. Thus, it should be taken into consideration that anxiety and depression were already noticed in the general population (38), and

consequently, healthcare workers might have already been affected as well. In the same period of time (since 2015), even before the pandemic, Papatheanasiou I. (39) found a moderate prevalence of burn-out syndrome in healthcare employees, from units all over Greece. This study implicates emotional exhaustion as a co-culprit for burn-out syndrome that most of the employees said they experienced. Another Greek study reported an increase in anxiety symptoms in Greek oncology nurses in 2015-2016 (40). Despite the fact that the latter evaluation was restricted to a certain specialty and unit, it confirms once more the rising anxiety levels among health specialists. It is only logical that the burden of the pandemic is even greater for our HCWs. A similar study of the general population found increased anxiety and depression levels, using DASS-21, especially in women and lower income populations (41). Similarly, the majority of the participants in another Greek survey stated that they were quite worried about the future, and female participants also appeared to be affected the most (42). Another large-scale general population survey was launched in Greece during April 2020, at the beginning of the crisis, and revealed high levels of fear, and moderate depression and anxiety symptoms. As we are going through the second year of the pandemic and having already re-evaluated distress levels, it seems that the situation is not improving, especially for women who have shown a much more significant deterioration in their psychological wellness from the beginning (43). Returning to HCWs, Greek physicians' educational process has been diminished as a Greek study observed that surgical trainees felt increased stress and reduced confidence due to the lack of practical education (44). A multi-center cross-sectional study of Greek frontline HCWs revealed moderate to severe anxiety and depression levels. In comparison to our primary HCWs, frontline staff experienced even higher "burn-out" and exhaustion symptoms (45). Another study in a Greek hospital revealed moderate burn-out symptoms, with males at higher risk (33). Additionally, a Greek cross-sectional study on health professionals observed changes in HCWs' sleep quality, espe-

cially in women. Even though sleep disturbances were not observed in our study, all the evidence points to the fact that women are at risk for severe psychological distress (46). Finally, it is worth mentioning that the willingness of staff to work has not been reduced during the COVID-19 and other crises. The above findings in Greece call for special attention. It is of paramount importance that governments establish proper health strategies that will ensure the protection of health staff, in order to protect and assist them in their work (47). Increased preparedness of the health system and especially frontline HCWs and intensive care unit HCWs is fundamental (48).

### **Strengths and Limitations**

To the best of our knowledge, the present study contributes to further evaluation and be a point of comparison to other studies. This self-reported questionnaire, as a tailored-one, entails some comparative limitations. However, it is mostly based on widely used, validated tools. A shortcoming of this study is the limited size of the sample. This is due to the traditional distribution of the survey. Despite the several disadvantages of "hand to hand" surveys (i.e., far too much time needed for the respondent to fill it in, fewer responses returned, hesitancy to respond), this approach provides authentic and sincere responses, and diminishes any possible population biases (49). Due to safety reasons, we were only granted permission by the Ministry of Health for the specific units. Hence, our population was limited. It should also be noted that the aim of the question covered in Figure 1 was about the feeling that participants experienced the most. In order to answer this question, they were limited to only one response. Finally, we tried to perform a comparison with other studies during the pandemic and prior to it, in order to evaluate Greek healthcare providers' mental and psychological state, before and after the COVID-19 crisis. Due to the limited studies on this subject, we were not able to come to a solid conclusion about HCWs' state of mind prior to the pandemic, apart from a few implications due to the ongoing economic crisis.

### **Conclusions**

The COVID-19 outbreak expanded to a worldwide pandemic, with many countries taking extreme precautionary measures. The severe pressure has caused shock to healthcare systems and pushed HCWs to their limits. The present study assesses the prevalence of psychological distress in Greek primary HCWs during the pandemic. It was found that direct exposure to COVID-19 could have a profound impact on their psychological health and wellness. Moreover, routine changes caused intense emotional instability and distress. There is a dire need for proper health strategies that will ensure the safety and protection of HCWs, in order to increase their effectiveness and shield them both physically and psychologically. Specialized programs must be provided in order for the healthcare system to be fortified. Perhaps online tools for distance sessions and meetings might be useful. It seems that females are more prone to anxiety and worry than males. Taking this into consideration, governments could organize special online meetings for those in need of communication and advice on how to handle the everyday pressure (i.e., support sessions, personalized advice programs etc.).

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

*Psychological and mental distress among HealthCare Workers during the COVID-19 crisis have been assessed by several studies. The impact of this pandemic on HCWs affects not only their lives, but the effectiveness of the HealthCare Systems as well.*

#### **What This Study Adds:**

*Greek HCWs revealed a high prevalence of psychological symptoms and worry regarding their workplace and their quality of life during the pandemic. An important finding was that female HCWs seemed to be significantly more affected than males. Moreover, routine changes cause intense emotional instability and distress.*

**Authors' Contributions:** Conception and design: SC and TP; Acquisition, analysis and interpretation of data: DK, SC, DM, EK and DB; Drafting the article: DK, EK, DB and SC; Revising it critically for important intellectual content: TP and GP; Approved final version of the manuscript: SC and TP.

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

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## Adolescent Perspectives About Online Hate Speech: Qualitative Analysis in the SELMA Project

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### Abstract

**Objective.** This paper aims to study the views, perceptions and representations of online hate speech among adolescents in the Greek cohort of the SELMA Project. **Methods.** Qualitative research was conducted in focus groups of 36 Greek adolescents and the data were processed through thematic analysis method. **Results.** The majority was unfamiliar with the term "hate speech" and confused it with cyberbullying. The target characteristics of hate, ethnicity, race, gender, religion, physical weakness, disability, sexual orientation, and appearance emerged. Regarding people involved in hate speech, perpetrators in both hate speech and bullying were described to share common characteristics. The emphasis was placed on the victims' resilience, as well as their socialization, as protective behaviors. Participants stressed the value of the right to freedom of speech, although there was no agreement on its limits. Additionally, it was highlighted that awareness of what is right and wrong is mostly taught by parents, while the role of education was also important. An important finding was that the majority of teenagers were optimistic, supporting the belief that it is possible to find a realistic solution. **Conclusion.** The findings support the need for prevention strategies in the school environment, so that adolescents will be able to recognize and potentially combat hate speech in the online and offline worlds.

**Key Words:** Online Hate Speech ■ Qualitative Research ■ Thematic Analysis ■ Adolescents ■ Focus Groups.

## Introduction

Hate speech has attracted interest internationally and has raised increasing concerns at interpersonal, community and international levels (1, 2). Although the content and the meaning of the term can be roughly understood, on a scientific level there is no established, uniquely and universally accepted definition. According to the definition of the European Commission against Racism and Xenophobia (3), hate speech does not target the actions of the individual, but the basic characteristics of which his or her personality is composed,

such as race, religion, ethnic origin, sexual orientation and gender. People of different ethnicity or race, migrants and descendants of immigrants, members of the LGBT community and disabled people are often targeted; anti-Muslim (4), anti-Semitic (5, 6) and sexist language are forms of hate speech (7, 8).

The emergence and evolution of the internet has played an enormous role in spreading hate speech because of its multiplier effect, as opinions can "travel" around the world and gain enormous publicity. Moreover, the anonymity of the user makes the internet a very effective tool for dissem-

ination of opinions for both legitimate and non-legitimate purposes. Many messages are published on hate sites, that is, websites dedicated to the promotion or incitement of hatred against specific groups. Online hate speech can also be found in social media, blogs, forums, online games, videos and music, as well as electronic and personal messages (9).

Hate speech, online and offline, afflicts individuals, groups and society as a whole (10). Victims experience anxiety, feelings of depression, and the fear of actualization of online threats in the real world (11). Furthermore, frequent exposure to such behavior leads to desensitization, and normalization of the phenomenon (12).

Once the implications of hate speech have been understood, the right to speak without any restriction is under negotiation. However, freedom of expression is a constitutional human right in democratic societies, and has been a valuable tool for social minorities to be heard. To counteract hate speech, measures have been taken at the level of European legislation. The prohibition of discrimination was established in 2012 (13). In contrast, US governments have prioritized the protection of free expression years before [2005, development of policies in order to prevent an escalation of hate speech (14)]. The lack of alignment of legislation at an international level has had significant implications for tackling hate speech online. Countries with less restrictive internet policies may become havens for those who do not wish to comply with their own countries' laws (14).

In this context, SELMA (9) (Social and Emotional Learning for Mutual Awareness, <https://hackinghate.eu/>) is a two-year project co-funded by the European Commission, aiming to tackle online hate speech by promoting mutual awareness, tolerance, and respect. As the first step of the SELMA approach to online hate speech, the opinions of adolescent students from four European countries (Greece, Germany, the United Kingdom and Denmark) were evaluated through focus groups. Processing of these observations was taken into account in the design of the SELMA toolkit, which is aligned with the age groups under study, aim-

ing at acceptance of diversity. The present article focuses on the focus groups of Greek adolescents. Greek society has changed considerably over the past 30 years in terms of the composition of its population. Nowadays, immigrants from different national origins account for 10% of its population (15). As Greece has been experiencing inflows of people from the Middle Eastern war zones, xenophobia, racism and far-right parties have become a concern in Greek society (16).

The present study aims to evaluate online hate speech-related perceptions among adolescents in Greece, including attitudes and views, both relating to the phenomenon itself (from the perpetrator's, victim's and observer's point of view), and ways of dealing with it. Due to the insufficient number of previous studies of the phenomenon in Greece, and due to the absence of predetermined perceptions, qualitative research was considered to be the most suitable method. In this method, the researcher is not interested in the facts themselves in an objective dimension, but in the meaning attributed by the participant's personal interpretation. Concerning the research questions, the research design aimed at exploring the views of Greek adolescents on online hate speech. Their understanding of the concept of freedom of speech and possible limitations were explored. The perceptions of hate speech were recorded, as well as the distinction between hate speech and bullying. Also the teenagers' perceptions regarding perpetrator and victim characteristics, and observers' behavior were investigated.

## Subjects and Methods

### Focus Groups

The data were gathered through the research method of focus groups as a stand-alone method; the manuscript was reported according to the Consolidated Criteria for Reporting Qualitative Research (COREQ) (17), and the relevant COREQ checklist is provided as an online-only Supporting Information file. The focus group method was chosen *inter alia* because it enables participants to

interact both vertically with the moderator/facilitator and horizontally among the team members, offering rich material for processing (18). The aim of the survey was not only to identify individual participants' perceptions and attitudes, but also to create dynamic interaction among them. The facilitator's part was limited, and interest was focused on what is considered to be important by the participants themselves (19), and they were encouraged to speak their minds and describe detailed experiences.

A total of four focus group discussions were conducted, involving 36 participants from 8 schools (1st and 2nd Secondary School of Geraka, 13th and 21st Secondary School of Acharnes, 4th and 5th High School of Petroupoli, 1st High School of Kifissia, Hellenic American Educational Foundation High School). Quiet and spacious rooms at the schools were selected as venues, at a time convenient to the participants. They were moderated by two experienced moderators-researchers who collaborate with the Adolescent Health Unit, Second Department of Pediatrics, School of Medicine, National and Kapodistrian University of Athens, Greece. The interviewers were not part of the research decoding team. No relationship was established prior to research commencement between the researchers and the participants, who knew nothing about them. The participants neither had any information nor did they develop any further relationship with the researchers. No characteristics about the interviewers were reported.

The participants were sixth grade students of elementary school, and junior and senior high schools; this homogeneity allowed greater freedom in participant interaction, and different perspectives (20). The sample consisted of thirty-six teenagers, who were divided into four focus groups of 9 people each. In two of the four groups, the participants' ages ranged from 11 to 12 years, and in the other two from 14 to 16 years of age.

This resulted in two groups of younger teenagers (early-middle-adolescence) and two more mature (middle-late adolescence) groups. The girl:boy ratio was 1:3. Participants attended public and private schools in Athens. They were gathered

by the snowball method, through the network of schools collaborating with the Adolescent Health Unit, and were approached face to face. Written permission to participate was secured from the parents of the participants. Five students were not able to participate due to personal inconvenience. The focus groups were pilot tested prior to implementation with the students. The duration of the focus groups was 48min for FG1, 1h 22min for FG2, 1h for FG3, and 1h 25min for FG4. The interview data were audio recorded and transcribed; data saturation was not discussed and the transcripts were not returned to the participants for comment or correction. There was no need for repeat focus groups to be held. The details about the Methodological Framework for Data Analysis are provided in the online-only Supporting Information File.

### ***Ethics Statement***

Written informed consent was obtained from the parents of all adolescents for participation in this study

### **Results**

The results of the qualitative research using the thematic analysis method are presented in this chapter. The findings are listed by major themes, relevant to the research questions. Additionally the thematic tree representation map of the analysis which was generated is depicted in Figure 1.

#### ***Major Theme 1: Freedom of Speech***

Determination and conditions of freedom of speech: The debate on hate speech was reflected in an attempt to determine the concept of "freedom of speech", given the inextricable connection between the two concepts, since the unconditional defense of one can lead to the manifestation of the other. Freedom of speech was described as the right to express ideas, thoughts, emotions, desires, preferences, opinions, beliefs freely, without limitations and fear of possible criticism.

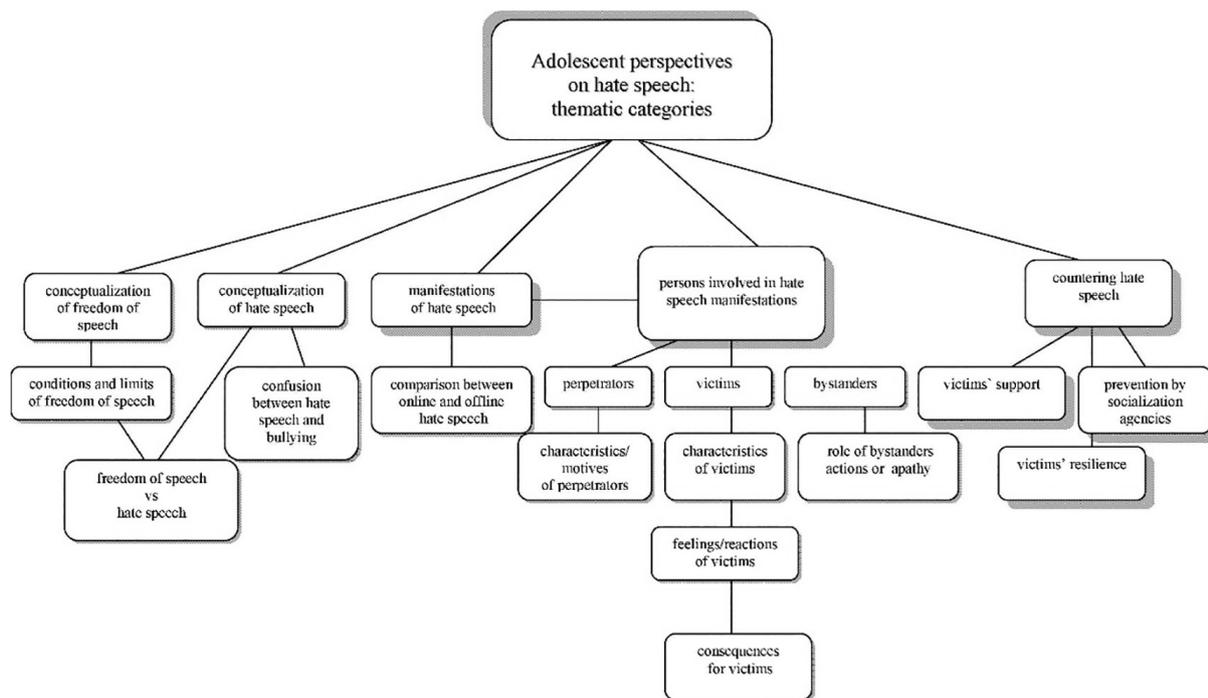


Figure 1. Thematic tree representation map - Thematic Categories concerning adolescent perspectives on hate speech.

B. “Do not restrain anyone from saying what they believe” (FG2: 9)

The results about forms of expression are provided in the online-only Supporting Information File.

*Limits to freedom of speech:* Regarding whether restrictions on freedom of expression should be imposed, the participants seemed to be divided. Most of them agreed that some restrictions are legitimate. The adolescents who were in favor of the restrictions, explained that speech should not offend, diminish or condemn the interlocutor or his views. They deemed it necessary to avoid negative characterization and references to sensitive matters, to restrain bad intentions, as well as seeking to impose one’s opinion on others. These practices constitute a violation of human rights, according to the participants.

G. “Religion in some countries is a very sensitive issue and it should not be so easily targeted” (FG2: 266-267).

However, a large proportion of the respondents supported the opposite view, according to which expression should not be subject to restric-

tions. The argument of the violation of freedom of speech was used to defend this position. The participants’ conflicting views reflect the dimension that exists both in society and in the laws of different states. Surprisingly, according to some adolescents, offensive speech and hate speech is “legitimized” in cases where the recipient of the messages is considered provocative. However, the participants’ opinions converged on the belief that a person’s conscience should act as a guide and measure of what it is permissible to say and what is not. Awareness of what is right and wrong is taught mostly by parents and other agents of socialization, such as schools.

**Major Theme 2: Hate Speech**

*An attempt to approach the concept of hate speech:* The majority of participants were unfamiliar with the term “hate speech”. According to the older teenagers, hate speech is abusive or threatening speech used with the purpose of attacking and negatively affecting the target person or group. It expresses prejudice on the basis of specific attributes and/or

weaknesses. Otherwise, it can be expressed with demeaning comments and gestures:

B. *“It’s speech, let’s say, that offends a person or a general group in relation to their mutual characteristics, let’s say gender, or some weakness that they have”* (FG4: 46-47).

It was observed that the concept of hate speech is not clear for many of the participants. In fact, it was confused with other problematic behaviors in the online and offline worlds, such as violence, extortion, deceit, harassment and pedophilia. Results about where hate speech is detected are provided in the online-only Supporting Information File.

*Targets of hate speech:* Adolescents and scientific literature concur on the characteristics that are often targeted by hate speech. Ethnicity, skin color and origin were the most frequently mentioned characteristics reported, and the targeting of migrants was discussed extensively.

G. *“Generally it targets weaknesses. It targets vulnerable people. For example, their origin”* (FG2: 91-92).

Although religion is not one of an individual’s physical characteristics, it was considered to be a core element of human personality which is often targeted. Furthermore, people with disabilities and physical weakness often become targets of hate speech. Gender also drew attention, with women often becoming victims of unfavorable sexist comments.

It was pointed out that gender identity, sexual orientation, sexual choices and homosexuality are often the subject of hate speech. Adults and children who do not behave according to stereotypes established in society on the basis of their gender often suffer from verbal and physical violence. One such “unacceptable” form of behavior is femininity in boys.

Finally, the discussion about the objectives of hate speech expanded beyond the established protected features. The reference to appearance as a reason for attracting negative comments was particularly noted. Somatometric features, such as height, weight, and body type, were identified as targets for offenders, but also choices in appearance, such as clothes and hair color. The growing volume of such comments is a matter of concern

for teenagers. In addition, lifestyle, political views, social order, economic background, family status and family issues are often subject to criticism and hate speech, according to the adolescents’ observations. Results about the differences between offline and online hate speech are provided in the online-only Supporting Information File.

*Comparison between hate speech and bullying:* Much confusion and overlapping of the concepts of hate speech and bullying was observed in the majority of the survey participants. The term “bullying” appeared in the discussions repeatedly in place of the term “hate speech”, as if they have the same meaning. This was observed in younger focus groups’ data in particular, and probably revealed that age group’s familiarity with the term “bullying” but not with the term “hate speech”. It was common for older adolescents to believe that hate speech is a wider term, whose subcategory is bullying.

### **Major Theme 3: People Involved in Hate Speech**

*Perpetrators:* The majority of participants pointed out that the perpetrators in both hate speech and bullying share common characteristics, such as insecurity and their desire to appear strong in the eyes of their peers. They experience feelings of fear, anger, and rage because of personal, psychological, or family problems, and they pass them on to others. Some of them have no friends, while others are unable to discuss anything in a civilized way. It is worth noting the view expressed by one participant, according to which a perpetrator could be any of us who has experienced traumatic conditions that have led them to behave in this way.

*Victims:* Adolescents referred to the traits of personality that attract victimization. People with low self-esteem, shy, isolated, weak or seemingly weak people were perceived as the most popular targets of hate speech. According to the participants, in this case the victims bear the responsibility for victimization if they do nothing to prevent it.

G. *“They have a responsibility for being the perpetrators’ victims because of their character, because the perpetrators know they will not react”* (FG1: 341-342).

According to the participants, victims' reactions may vary, and depend mainly on their character. The usual reaction is acceptance of the situation and passivity. This was perceived by adolescents either as a lack of courage or as fear of the perpetrators. The repetitiveness of such incidents was likely to lead to their normalization, with the victim being persuaded of their supposed inferiority. Sometimes the victims might choose not to report the incident, which makes the work of coping with their problem even more difficult. Results about the effects on the victim, feelings and behaviors, are provided in the online-only Supporting Information File.

*Bystanders:* Passivity and indifference were described as a common reaction of bystanders. This was attributed to a lack of empathy and compassion. As the adolescents stated, something that is not happening to them does not concern them; although in their self-criticism they pointed out that this is a wrong attitude. The abundance of such incidents might lead bystanders to consider hate speech as something normal and legitimate. As one participant also stated:

G. "I believe there is a condition of apathy, just because it is commonplace. Everyone ignores it. They say: "Ah, they are attacking him, okay, they are not attacking me. I'm leaving!" (FG4: 497-498).

When the offender happens to be a person who is popular in the school, or at the top of the community hierarchy, observers may imitate their behavior. Of course, there are bystanders who might sympathize with the victim, especially when they share common characteristics that are being mocked. Results about the consequences of observer passivity are provided in the online-only Supporting Information File.

#### **Major Theme 4: Support and Prevention**

The majority of teenagers were optimistic and they supported the belief that realistic solutions could be found. In the offline world, support can be provided by members of the victim's close family and social circle.

The circle of peers was considered of particular importance, as it has the power to support the

victim, either by opposing the perpetrator, or by mediating in a positive way, and expressing their support to the victim. Indeed, an interesting suggestion was made for cases where the victims are shy and isolated from their social surroundings. Specifically, it was argued that:

G. "[...] we must try to develop friendships with these people, to incorporate them in our group of friends so that it will be more difficult for them to become targets" (FG4: 597-598).

Results about the online support of victims and on how victims can protect themselves are provided in the online-only Supporting Information File. Prevention was judged to be the most appropriate way to address this phenomenon. In achieving this goal, all factors of socialization play a crucial role. The family's role was considered decisive in bringing up children; adolescents referred to the reproduction of healthy patterns, and the absence of prejudice and negative stereotypes within the family.

B. "The most effective way to deal with something is not to get there" (FG1: 729-730).

However, the role of education for adolescents was also important. Alternative ways of approaching sensitive issues were sought. The duty of all society members to promote healthy standards and mutual respect, as well as the need to be alert for incidents of hate speech, was also mentioned. Individual responsibility to prevent hate speech was stressed. The development of critical competence, the adoption of good practices and healthy attitudes came up as important factors of prevention. A useful finding from the older teenagers pertained to the role of social skills as a protective factor against victimization. The development and maintenance of close relationships could act as a hindrance to perpetrators' plans, because the possible reactions from the victim's surroundings may prevent hate manifestations.

G. [...] "It is prevention to have friends to help you to deal with it" (FG4: 658).

More details and supporting information about the Results are provided in the online-only Supporting Information File.

## Discussion

The present study is an effort to evaluate online hate speech-related perceptions among adolescents in Greece. According to our findings, the majority of the adolescents were unfamiliar with the term “hate speech” and confused it with cyberbullying. Participants stressed the value of the right to freedom of speech, although there was no agreement on its limits. Ethnicity, race, gender, religion, physical weakness, disability, sexual orientation, and appearance were considered as target characteristics of hate, and the victims’ resilience and their socialization as protective behaviors.

Although the examples of hate speech are numerous and they occur every day in both the online and offline worlds, insufficient research has been conducted in this area into the perceptions of adolescents. Adolescents may recognize hate speech when they come across it, but their perceptions regarding the term are not clear, especially among younger participants. They realize that the intention of expressing hate speech is to incite hostility against individuals or groups because of their particular characteristics. Teens revealed that the elements of personality that may attract hatred are primarily related to origin, race and ethnicity, religion, sexual orientation and gender identity, gender, and disability, whereas body characteristics (weight, height, etc.) as well as features of appearance (dressing, hair color, etc.) may also be a stimulus for hate speech. Targeting appearance and looks is an emerging issue for adolescents because of the importance of image during puberty (21, 22). Overlapping and confusion was observed between the concepts of bullying and hate speech, which requires further research, and confirms the need to educate young people to recognize hate speech (9, 23).

Regarding the limits of freedom of speech, a division of opinions was observed. Some participants were in favor of restrictions, whereas others expressed the view that the set of limitations acts as a hindrance to the free exchange of ideas. The differences of opinion between adolescents strongly reflect the divisions in society, state legislation

and international literature. Participants, however, agreed that we ourselves, whose personality has been shaped by family and education, are the right persons for setting limits, on the basis of our personal judgment.

Perpetrators in the offline and online world were described as individuals with personal and family problems. The anonymity of the internet was portrayed as a powerful weapon in their hands. Participants also noted that perpetrators may have been victims in the past, without specifying an act of violence; one idea is more in line with victims’ behavior in terms of cyberbullying (24), and raises questions about the existence of a larger body of peer violence (25).

Interestingly, victims of hate speech were often described by adolescents more as individuals with particular personality traits, rather than people of specific characteristics which differentiate them as minority groups. The victims were depicted as usually introverted, socially isolated, people who differ in their choices and interests. A small minority of participants stated that victims are people who provoke others. The latter is a point to be considered by designers of behavioral prevention programs, as it is a key argument in “legitimizing” hate speech.

As for the observers who witness incidents of hate speech, the most frequently reported attitude was passivity; this may signal “normalization” of hate speech. Certainly there are those who sympathize with the victim, especially if the targeted characteristics are common. Imitating the perpetrator is a reaction of concern; according to adolescents, this occurs when observers identify with common traits in relation to the perpetrator, when they feel fear or threat, but also when the perpetrator has a high status in the community hierarchy.

Finally, the participants stressed the need to support the victims. Advanced methods for online hate speech detection should be developed (26). The social environment and family should support victims and deplore perpetrators’ harmful attitudes. However, the most effective way to deal with the problem is prevention, hopefully integrating problem-focused coping strategies, self-

assertiveness, and media skills (27). By adopting healthy patterns, and through respect for diversity, schools and family can promote empathy and co-existence based on mutual respect and acceptance. Also particularly useful for teachers was the finding that teenagers believe that victimization can be avoided by socialization and forming healthy relationships. Cultivating social skills and enhancing the resilience of children can help them function proactively in the environment.

The volume of published academic papers on hate speech, after an initial growth of interest from 1992 onwards, has increased considerably since 2005 (28) and exponentially since 2011 (29), due to the spread of social media platforms which have transformed public discourse and changed the way people interact and communicate. Nevertheless, few surveys have reflected the perceptions about online hate among adolescents (30) in the last few years and not to such an extent as the present paper. In Greece, the scientific empirical research on online hate speech is limited, although there has been considerable research on cyberbullying. Therefore, this study was undertaken as an initial investigation into this area in terms of adolescents' perspectives on the phenomenon, and the results were part of a comprehensive research program carried out by the SELMA project to achieve a holistic understanding of the online hate speech. These findings provide insights which can help design future relevant surveys, since adolescent perspectives may contribute to a meaningful dialogue in order to address hate speech phenomena. Prevention strategies in the school environment should be considered, in order to help adolescents recognize and potentially combat hate speech online and offline. Additionally, an observatory for monitoring hate speech at school, community and country levels would contribute a great deal to identifying and addressing possible manifestations of this growing phenomenon.

There are several limitations of this research. First of all, the choice of a qualitative study with a limited sample of 36 adolescents limits gener-

alizability, as such a small sample might not be broadly applicable to many different types of people or situations (31). The findings should be further elaborated by other research designs, such as quantitative research methods. Comparative studies with other European and non-European countries would seem of special interest.

Numerous new hypotheses arose from the results of the research which need to be tested and further explored. The vicious circle of hate speech between perpetrator and victim, the association of poor social skills and victimization with hate speech offenders, the relationship between the offender's popularity and bystanders' reactions, appearance and body features as targets of hate speech, as well as hate speech and the conceptual overlap with bullying, are some of the topics to be investigated.

## Conclusion

In conclusion, adolescent perspectives were depicted vividly by the focus group reports. An important finding was that the majority of participants were unfamiliar with the term "hate speech". Additionally, it was highlighted that awareness of what is right and wrong is taught mostly by parents, while the role of education is also important. Regarding people involved in hate speech, the perpetrators in both hate speech and bullying seem to share common characteristics, while the victims were described by the participants as shy, isolated, weak or seemingly weak people. This study was one of the first about adolescents' perceptions of hate speech in Greece. It may contribute to a meaningful dialogue to address the hate speech phenomena. The design of interventions, and the development and delivery of tool kits, hopefully as part of the school curriculum, would help school communities to counter hate speech. Furthermore, an observatory for monitoring hate speech would contribute a great deal at school, community and country level, in identifying and addressing possible manifestations of this growing phenomenon.

**What Is Already Known on This Topic:**

Online hate speech is a phenomenon of growing concern that causes harm all levels as victims experience anxiety, feelings of depression, and fear of actualized online threats in the real world. SELMA (Social and Emotional Learning for Mutual Awareness, <https://hackinghate.eu/>) is a two-year project co-funded by the European Commission, aiming to tackle online hate speech by promoting mutual awareness, tolerance, and respect. The opinions of adolescent students from four European countries (Greece, Germany, the United Kingdom and Denmark) are being evaluated and the processing of these observations is used for the design of the SELMA tool kit.

**What This Study Adds:**

Adolescent perspectives may contribute to a meaningful dialogue in order to address hate speech phenomena. There is a need for prevention strategies in the school environment, so that adolescents will be able to recognize and potentially combat hate speech in the online and offline worlds. Furthermore, an observatory for monitoring hate speech would contribute a great deal at school, community and country levels, in identifying and addressing possible manifestations of this growing phenomenon.

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## Supporting Information File

### Methods

#### *Methodological framework for data analysis*

The data were processed using the thematic analysis method. Two researchers, working independently from each other (M.M, an MSc female high school educator with a background in Psychology, trained in thematic analysis methodology; L.B., a high school educator with a PhD in qualitative research). During the interview, no notes were taken on para-linguistic data as the analysis was focused on the content at the semantic level (1). Thematic analysis is a coding method, which is undertaken using the stages of locating, describing and grouping repetitive thematic motifs. This method was chosen because, in contrast to other qualitative approaches, it gives the researchers the freedom of not committing themselves to a certain ontological or epistemological position, allowing them to substantiate their own theoretical analysis (2).

This study followed Braun & Clark's (2) six stages of thematic analysis. The two researchers worked as data coders and no Qualitative Coding Software was implemented for data coding. During the first stage of the analysis, the researchers became familiar with the data. The second step of the analysis was the "line by line" coding, namely identifying and generating initial codes for each of the transcribed focus groups' data unit. The third stage of the analysis included searching for themes, meaning common patterns using a combination of codes. The major themes were listed as the subjects, and the minor themes as the sub-categories. At this stage, the researchers' aim was to understand, interpret and link the data on the basis of their research plan and epistemological assumptions (3). During the fourth stage of the analysis, subjects were re-examined, themes were redefined, and the coherence of each subject was checked. Some subjects were grouped under wider thematic categories, while others which were segmented became separate topics. The fifth stage concerned the comprehensive, accurate definition

and naming of themes, trying to include all the individual data found during the analysis. A thematic tree representation map of the analysis was generated. The last step was to produce the report and write the findings. In the final analysis, the most vivid, illuminating and representative extract examples were quoted. Each quotation is identified by its codification which includes the focus group number (FG: 1-4), the sex of the respondent (B for boy and G for girl) and the line number of the transcribed data.

### Results

#### **"Major Theme 1: Freedom of Speech"**

Forms of expression: According to participants, expression is not limited to the spoken and written word, but may take various forms. Art, through creative forms, such as painting, music, lyrics, video, dance, photography, and graffiti, provides alternative means of transmitting messages and interacting with others. Other forms of expression are the use of symbols, signals and gestures, as well as political acts, such as voting and demonstrations. Furthermore, the religious expression of faith was mentioned. This could be manifested by symbolic acts, such as women covering their faces with a veil (e.g. niqab).

#### **"Major Theme 2: Hate Speech"**

**Where hate speech is detected:** The respondents unanimously supported the assumption that hate speech is a phenomenon that concerns both the offline and online worlds. Participants reported that:

G. "In social media we face it continuously... there are offensive comments all the time" (FG2: 61-62).

Offending comments were recalled by adolescents from various websites, such as social media, namely Facebook, instagram, twitter, snapchat, webpages of various kinds, applications where everyone can express themselves, such as blogs, chats, posts, and finally YouTube videos and online games. Hate speech can also be expressed in an in-

direct, oblique way, by commenting with “like” or “dislike” under someone’s words.

G. *“Yes, because there are websites where you can add a like or dislike feature to comments. If you choose “dislike” you basically support it negatively. So this may offend or upset you, and it can be indirect because it is not written “ (FG2: 66-68).*

**Differences between offline and online hate speech:** According to the majority of participants, online hate is more severe than offline hate speech. The first and most common reason mentioned was the ease of access to a large number of people on the internet, which contributes to the direct expression and rapid dissemination of users’ views. Consequently, a hate speech incident may spread to many people. Hence, user anonymity is the internet feature that reinforces the spread of online hate speech, and makes it harder to cope with.

G. *“I think there are many more incidents on the internet than in real life, as there are now many applications where you do not have to write your real name or even have a real profile (...) When one does not see the other person face to face, it is easier to insult, since there are no consequences» (FG4: 622-627).*

### “Major Theme 3: People Involved in Hate Speech”

#### **Effects on the victim: feelings and behaviors**

Hate speech was perceived as having an obvious and huge impact on the emotions and behavior of the victims.

B. (...) *“Even if you have confidence, and you do not want to believe it, what others say always affects you “ (FG2: 171-172).*

Targeting makes people experience feelings of sadness and loneliness. Their self-confidence suffers, which results in feelings of inferiority. Their daily routine is characterized by insecurity and the continuing threat of a possible assault. The effects may include the victim’s deliberate isolation from the social and school environment. Some victims might start to struggle to conceal the particular

characteristics that cause their targeting, such as their religious beliefs. It was also pointed out by adolescents that the victim may experience psychological problems, impairment in functioning, frustration in life in general, and even thoughts about and attempts to commit suicide (FG4: 536-537). At this turning point, the vicious circle of violence and hatred might continue, as it was observed that a victim can often become a perpetrator.

**The consequences of observer passivity:** The consequences of observer passivity may lead to the spread and escalation of the phenomenon, which entails even greater insensitivity in the audience. Feelings of insecurity and fear are intensified in teenagers. Anxiety was expressed about tomorrow’s society, which seems to be built on foundations of individualism and erroneous standards.

### “Major Theme 4: Support and Prevention”

**Online support of the victims:** Participants also identified ways to deal with cyber hate speech. A simple, direct and easy way of supporting a target of online hate speech was by using the ‘like’ or ‘dislike’ sign, or reporting someone’s offensive comments.

The prosecution of cybercrime as well as the assistance of support lines was also envisaged as an effective measure to fight hate speech. Participants noted that the protection of browsers should be prioritized by the web developers, and protection arrangements should be in place. Effective reporting and blocking capability was also highlighted.

The victim’s personal responsibility in dealing with hate speech was emphasized. Participants advised the timely and prompt reaction of the victim right after the incident in order to deal directly with the problem, so as to avoid future implications and exacerbation of the problem.

G. *“From the moment it starts, if you let it evolve then it will be even more difficult” (FG2: 194).*

Protection, according to adolescents, could be provided if they share their problems with a trusted person, such as their parents or teachers. Sometimes, it would be useful to speak to the perpetrator directly, to set boundaries, and express

their dissatisfaction to the hateful person, so that the latter will understand that their behavior is not acceptable.

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## Clinical Manifestations and Medical Imaging of Osteogenesis Imperfecta: Fetal Through Adulthood

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### Abstract

The aim of this paper is to describe the varying clinical and imaging manifestations of Osteogenesis Imperfecta (OI) in the fetus, the child, and the adult. OI is a genetic disorder with mutation of Type 1 and non-type 1 collagen genes that results in disruption of multiple collagen based organ systems, most notably bones, often leading to “brittle bones”. Additional features such as blue sclera, dentinogenesis imperfecta, joint and ligamentous hyperlaxity, hearing loss and cardiac defects may be present. Currently, there are at least 30 recognized genetic forms of OI. Given the multiple genes involved, variable genetic inheritance, and the wide range in phenotype, diagnosis can be challenging. While OI may sometimes be diagnosed in the fetus, patients with mild forms of OI may be diagnosed in childhood or even in adulthood. Imaging, including ultrasound, radiography, computed tomography, and magnetic resonance imaging, plays an important role in the diagnoses of OI in the fetus, the child, and the adult. Imaging is also crucial in identifying the many multisystem manifestations of OI. In particular, imaging can help differentiate manifestations of OI from injuries sustained in non-accidental trauma. Age, severity and manner of presentation of OI vary broadly depending on the specific genetic mutation involved, mode of inheritance, and age of the patient. Successful diagnosis of OI hinges on a detailed knowledge of the variable presentation and complications that may be encountered with this disease. **Conclusion.** In conclusion, OI comprises a heterogeneous group of genetic disorders responsible for bone fragility and additional connective tissue disorders, which can result in specific clinical and imaging findings in the fetus, the child, and the adult.

**Key Words:** Osteogenesis Imperfecta ▪ Magnetic Resonance Imaging ▪ Ultrasound.

### Introduction

Osteogenesis imperfecta (OI) is a rare genetic disorder that results in fragile bones (1). The pro-alpha 1 and pro-alpha 2 chains, which make up type 1 collagen, are encoded by the *COL1A1* or the *COL1A2* genes (2). The mutation of these genes results in the various clinical symptoms. Although it has been classically taught that OI encompasses multiple subtypes of a genetic disease that affect type 1 collagen fibers, as the understanding of this disease grows, it is now known that multiple non-type 1 collagen gene alterations exist. As a result of these genetic abnormalities, patients possess weakness in multiple collagen-based organ sys-

tems, most notably bones. The decreased osseous strength is due to a combination of both poor bone mineral density and overall poor quality from abnormal osseous matrix formation (3) which leads to increased risk for fracturing that may occur in utero, postnatal, and beyond into adulthood. In normal bones, stiffness which prevents bending of bone from body weight, toughness which allows energy absorption during impact, and strength which is the load bearing capacity of bone combine to prevent fracture (4, 5). With OI, abnormal bone with low bone mass and increased mineral concentration leads to abnormal bone matrix and microstructure and overall increased fragility and disrupted fracture repair (4, 5).

While OI may sometimes be diagnosed in utero, patients with mild forms of OI may escape diagnosis until childhood or even in adulthood. Imaging plays an important role in the diagnoses of OI in the fetus, the child, and the adult, as well as identifying the many multisystem manifestations of OI. In children, imaging is important in differentiating OI from non-accidental trauma (NAT), which is physical abuse purposefully imposed on an infant or child, also commonly referred to as “child abuse” or “shaken baby syndrome”.

There is a high variability of clinical symptoms associated with OI which vary with subtype, the most common of which are frequent fractures and bone deformities. Other common symptoms include blue sclera, short stature, dentinogenesis imperfecta, and hearing loss. Several current imaging modalities play an important role in the diagnosis and management of patients with OI, and several new imaging methods are on the horizon (6, 7) (Table 1).

Table 1. Imaging of OI.

Modality	Clinical Indications	Advantages	Disadvantages and Limitations
Radiography	<ul style="list-style-type: none"> <li>- Fractures</li> <li>- Bone deformities</li> <li>- Estimate of bone mineral density</li> </ul>	<ul style="list-style-type: none"> <li>- Inexpensive</li> <li>- Widely available</li> </ul>	<ul style="list-style-type: none"> <li>- Ionizing radiation</li> <li>- Low fracture sensitivity in severe osteopenia</li> <li>- Skeletal deformity and fragility may limit positioning</li> </ul>
Dual Energy X-ray Absorptiometry (DXA)	<ul style="list-style-type: none"> <li>- Assessment of bone mineral density</li> </ul>	<ul style="list-style-type: none"> <li>- Relatively widely available</li> </ul>	<ul style="list-style-type: none"> <li>- Ionizing radiation (low)</li> <li>- Relatively expensive</li> <li>- Complicated interpretation with fractures, hardware, bone deformities, and low body height</li> </ul>
Ultrasound	<ul style="list-style-type: none"> <li>- Prenatal assessment</li> </ul>	<ul style="list-style-type: none"> <li>- No ionizing radiation</li> <li>- Portable</li> <li>- Widely available</li> <li>- Relatively inexpensive</li> </ul>	<ul style="list-style-type: none"> <li>- Operator dependent</li> </ul>
Computed Tomography (CT)	<ul style="list-style-type: none"> <li>- Fracture</li> <li>- Bone deformities</li> <li>- Preoperative assessment and planning</li> </ul>	<ul style="list-style-type: none"> <li>-</li> </ul>	<ul style="list-style-type: none"> <li>- Expensive</li> <li>- Ionizing radiation</li> <li>- May not be widely available</li> <li>- Skeletal deformity and fragility may limit positioning</li> </ul>
Magnetic Resonance Imaging (MRI)	<ul style="list-style-type: none"> <li>- Fracture</li> <li>- Bone deformities</li> <li>- Preoperative assessment and planning</li> <li>- Fetal evaluation</li> </ul>	<ul style="list-style-type: none"> <li>- No ionizing radiation</li> <li>- High soft tissue resolution</li> </ul>	<ul style="list-style-type: none"> <li>- Expensive</li> <li>- Long examination time</li> <li>- May be contraindicated in patients with severe claustrophobia</li> <li>- Contraindicated with certain implanted devices</li> <li>- May not be widely available</li> <li>- Skeletal deformity and fragility may limit positioning</li> </ul>
Peripheral Quantitative Computed Tomography (pQCT)	<ul style="list-style-type: none"> <li>- Assessment of bone mineral density, bone microstructure, and bone morphology in the peripheral skeleton</li> </ul>	<ul style="list-style-type: none"> <li>- Rapid image acquisition</li> <li>- Portable</li> <li>- Inexpensive</li> <li>- Allows multiple site assessment</li> </ul>	<ul style="list-style-type: none"> <li>- Ionizing radiation (very low)</li> <li>- Limited availability clinically</li> <li>- May be limited by bone deformity</li> </ul>
High-resolution pQCT (HR-pQCT)	<ul style="list-style-type: none"> <li>- Assessment of bone mineral density, bone microstructure, and bone morphology in the peripheral skeleton</li> </ul>	<ul style="list-style-type: none"> <li>- Rapid image acquisition</li> <li>- Allows multiple site assessment</li> </ul>	<ul style="list-style-type: none"> <li>- Ionizing radiation (very low)</li> <li>- Limited availability clinically</li> <li>- May be limited by bone deformity</li> <li>- Expensive</li> <li>- Not portable</li> </ul>
Slit Beam Digital Radiography	<ul style="list-style-type: none"> <li>- Assessment of skeletal alignment and deformity</li> </ul>	<ul style="list-style-type: none"> <li>- Lower radiation dose than CT and radiographs</li> <li>- 3D reconstruction</li> </ul>	<ul style="list-style-type: none"> <li>- Long acquisition times may have increased motion artifact, especially in children</li> <li>- Skeletal deformity and fragility may limit positioning</li> <li>- Limited availability</li> </ul>
Quantitative Ultrasound (QUS)	<ul style="list-style-type: none"> <li>- Assessment of bone quality and bone mass</li> </ul>	<ul style="list-style-type: none"> <li>- Ultrasound widely available</li> </ul>	<ul style="list-style-type: none"> <li>- Limited data available</li> </ul>

The aim of this paper is to describe the varying clinical and imaging manifestations of OI in the fetus, the child, and the adult. This paper also aims to describe several imaging modalities used in evaluation of patients with OI, including several important recent advancements in imaging.

## OI: Subtypes

At present there are at least 30 recognized genetic forms of OI and their subtype classification has grown beyond the Sillence scheme developed in 1979 where patients were grouped into 4 subtypes based on their disease severity, mild to lethal. It is important to recognize that the increase in numer-

ical value does not correlate with disease severity (3, 8) (Table 2). In 2015 the Nosology Group of the International Skeletal Dysplasia Society added OI subtype V to the 4 subtypes originally described by Sillence (9). The phenotypically based Sillence classification was preserved in the 2019 revision of the Nosology (10).

A more modern approach to OI classification takes into consideration the underlying genetic abnormality (specific gene and role in abnormal collagen synthesis), while still maintaining parts of the Sillence classification system (3) (Table 3).

In the modern classification system of OI, the majority of OI subtypes fall into group A, including the original Sillence subtypes I-IV, and possess

Table 2. Sillence Classification of OI

Type	Clinical severity	Example features	Life expectancy
I	Mild deformity	Mildly short stature or normal height; blue sclera	Full life span.
II	Perinatal lethality	Intrauterine rib and long bone fractures; hypodense skull	Typically stillborn, or death within the first two months of life
III	Severe deformity	Severely short stature/dwarfism; severe spinal scoliosis	Typically full life span. Many develop severe neurological and/or respiratory complications in childhood due to bone weakness and fragility
IV	Moderate deformity	Moderately short stature; mild to moderate scoliosis	Full life span

Table 3. OI Classifications Based on Genetic Mutations While Still Maintaining Some Features of the Sillence Classification

Group	Subtype	Gene(s)	Mechanism
A	I	<i>COL1A1</i> or <i>COL1A2</i>	Defective collagen synthesis, processing, and structure formation
	II	<i>COL1A1</i> or <i>COL1A2</i>	
	III	<i>COL1A1</i> or <i>COL1A2</i>	
	IV	<i>COL1A1</i> or <i>COL1A2</i>	
	XIII	<i>BMP1</i>	
B	VII	<i>CRTAP</i>	Defective post-translational modification of collagen
	VIII	<i>LEPRE1</i>	
	IX	<i>PPB</i>	
	XIV	<i>TMEM38B</i>	
C	X	<i>SERPINH1</i>	Defective collagen folding and/or crosslinking
	XI	<i>FKBP10</i>	
	-	<i>PLOD2</i>	
	-	<i>P4HB</i>	
D	V	<i>IFTM5</i>	Defective bone mineralization
	VI	<i>SERPINF1</i>	
E	XII	<i>SP7</i>	Defective osteoblast differentiation
	XV	<i>WNT1</i>	
	XVI	<i>CREB3L1</i>	

a mutation in the *COL1A1* and *COL1A2* genes resulting in reduced collagen production and poor fiber assembly (3). Nearly all of group A subtypes are inherited in an autosomal dominant fashion, in comparison to the remaining groups where autosomal recessive inheritance predominates (3). Group B mutations result in poor post-translation modification of collagen, resulting in severe subtypes of OI that typically present in infancy (3). Group C patients possess mutations that would normally regulate collagen folding and crosslinking causing moderate to severe forms of OI (3). One syndromic form of OI that falls into Group C is Cole-Carpenter syndrome which in addition to OI includes craniosynostosis, proptosis, hydrocephalus, and abnormal facial features (3, 11). Group D subtypes of OI involve abnormalities in bone mineralization, both increased and decreased (3). Lastly, group E subtypes possess genetic mutations that affect osteoblast differentiation (3). Screening for mutations at these gene locations are useful for diagnosis. Furthermore, genetic testing for the parents may also uncover genetic mutations in an asymptomatic parent.

### OI in Fetus

Ultrasound (US) is the main modality for the in-utero diagnosis of OI, which may be discovered on the routine anatomical survey around 20 weeks of gestation. However, the varied phenotype and severity of

skeletal dysplasia makes it difficult to diagnose accurately with only 65% of suspected OI diagnoses made on prenatal US found to be accurate (12). OI types I and IV are generally mild without many bone fractures, and variable degrees of hearing loss and dentinogenesis imperfecta. Type II is a lethal form and type III is progressive with short stature, dentinogenesis imperfecta, and hearing loss. US has been shown to be helpful in the diagnosis of Type II and deforming type III OI (13). US features of OI include short extremities, bone fractures/increased bone plasticity, and decreased mineralization with decreased echogenicity of the skeletal structures (14) (Figure 1). Less specific findings such as intrauterine growth retardation or hydramnios may also be present. 3 dimensional (3D) rendering US has been shown to help improve diagnosis and disease detection (15) and to

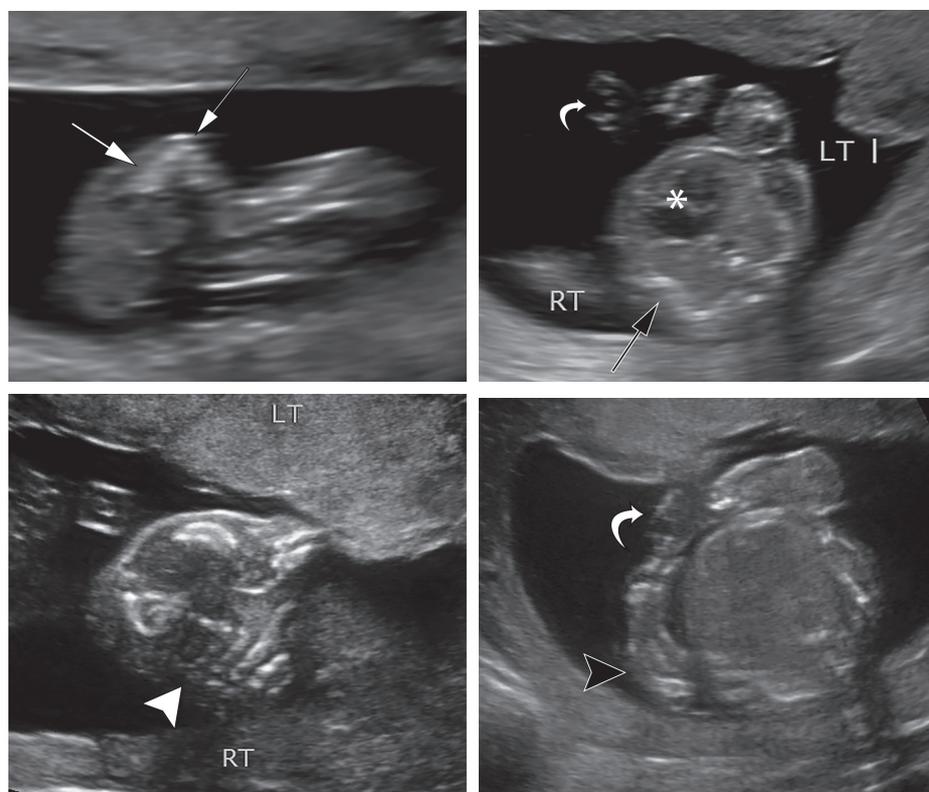


Figure 1. Fetal US images of a 20 week 4 day intrauterine demise secondary to OI. (A) Right femur deformity (white arrow) with bending at the diaphysis indicating fracturing. (B) Multiple right rib fracture deformities (black arrow) in transverse axis (heart denoted by \*, umbilical cord by curved arrow for orientation). (C) Same rib fractures (white arrowhead) in long axis. (D) Right radius/ulna with bending (black arrowhead) at the diaphysis indicating fracturing (foot denoted by curved arrow for orientation).

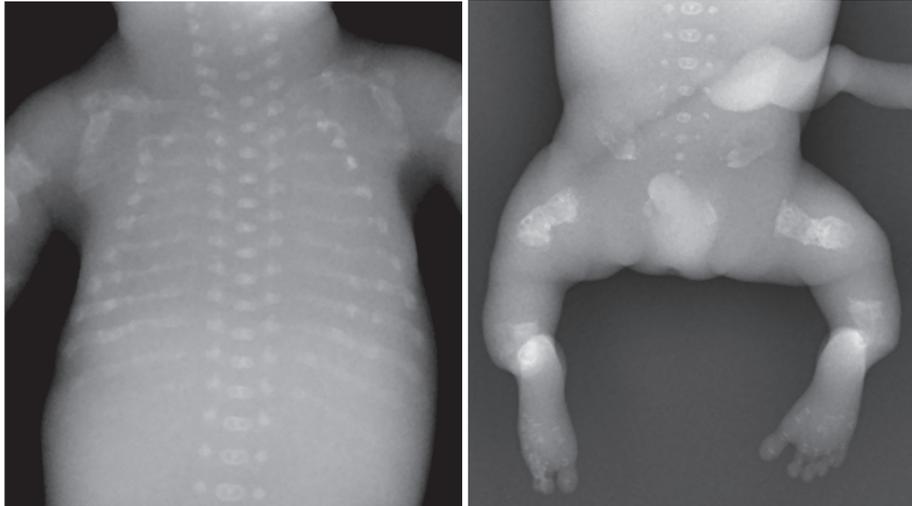


Figure 2. Postmortem radiographs of fetus in Figure 1. Radiographs of the chest (A) and pelvis/lower extremities (B) show multiple rib and long bone fractures.



be superior when used in adjunct with 2D US in the prenatal diagnosis of fetal anomalies (Figure 1). Postmortem radiographs are important adjuncts to confirming and specifying the fetal bone abnormalities in lethal cases of OI (Figure 2).

On prenatal US, OI lethality risk stratification can be performed by multiple means by comparing femur length, abdominal circumference, and chest circumference. Femur length to abdominal circumference ratio of less than 0.16 represents a lethal skeletal dysplasia in 92-96% of cases (16). When this finding is combined with polyhydramnios, the ability to predict lethality can be as high as 100% (16). Chest circumference to abdominal circumference ratio of less than 0.6 represents a lethal skeletal dysplasia in 86.4% of cases (17).

In cases of doubtful diagnosis of OI on prenatal US, low dose computed tomography (CT) with 3D reconstructions can be helpful in assessment of the entire fetal skeleton, performed after 26 weeks of gestation to aid diagnostic accuracy (18) (Figure 3).

The role of magnetic resonance imaging (MRI) is limited but this imaging modality can be useful for assessment of associated abnormalities and the fetal lung volume which can stratify lethality (Figure 4). While MRI has many advantages, such as no

Figure 3. Low dose CT 3D reconstructions of a second trimester fetus of a mother with history of OI. (A, B) Fetal rib (arrowhead) and femoral (arrows) fractures. The mother (C) also has chronic pelvic deformities and a right femoral fracture.

ionizing radiation and high soft tissue resolution, it also has many limitations, such as long examination times, expense, and safety considerations when implanted medical devices are present.

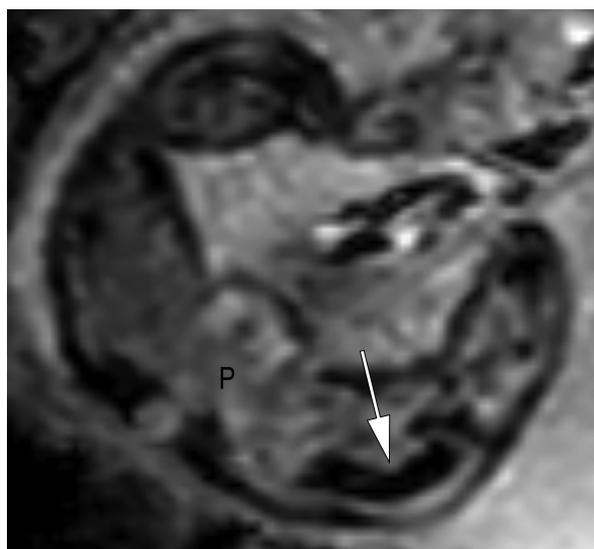


Figure 4. Fetal echo planar MR image of a 31 week 1 day old fetus with OI, showing angulation of the femur (arrow) (pelvis denoted by P for orientation). (Image courtesy of Katherine Epstein, MD)

Regardless of imaging modality used, it is important to look for associated abnormalities that can be seen in OI. Rare anomalies that have been previously described in the literature include microcephaly (19), congenital heart defects (19), anencephaly (20), and encephalocele (21). Given the rarity of the aforementioned neurologic and cardiac abnormalities amongst OI cases, their incidence and order of prevalence is difficult to determine.

### OI in Infancy and Childhood

The clinical presentation of OI in newborns, neonates and children is highly variable in both features and severity. The most common abnormalities include osteoporosis with increased osseous fragility, blue sclera, dentinogenesis imperfecta, and hearing impairment. Other features include ligamentous laxity, hypermobility of the joints, short stature and vascular fragility leading to easy bruising. There is known association of OI with

congenital cataracts (22). The diagnosis is most commonly made at birth, but in the diagnosis of milder forms such as OI type I, can be delayed well past age 4 years (23).

Radiography is the preferred initial modality for the assessment of OI in pediatric patients. The main radiographic features of OI are osteopenia, bone fractures, and bone deformities. The bones may be profoundly osteopenic with cortical thinning and increased lucency at the medullary cavity due to rarefaction of the trabeculae. However, osteopenia is often difficult to accurately diagnose on radiographs, as images may appear normal until ~50% of the bone has been lost (18). Dual energy x-ray absorptiometry (DXA) is a sensitive imaging modality to assess and monitor osteopenia. However, the presence of osseous fractures and deformities, orthopedic hardware, and low body height in OI can make DXA evaluation difficult in patients with OI (24). It is important to remember that osteopenia is not specific for OI and can be seen in variety of metabolic disorders (18).

Multiple fractures are a hallmark of OI, affecting both the axial and appendicular skeleton. Fractures may be caused by minimal trauma but are similar in distribution to those in healthy children, most commonly affecting the diaphysis of the long bones. The callus associated with healing may be hyperplastic, particularly in OI type V (25) (Figure 5). These findings are not specific to OI and can be seen in NAT, more so when there is calcification of a healing subperiosteal hematoma. Hyperplastic osseous calluses can also be seen in cases of spinal dysraphism, bleeding disorders and neurofibromatosis (18). Pseudoarthrosis may develop at the site of healing fractures and bones may become deformed (Figure 6).

Axial skeletal abnormalities in cases of OI include calvarial enlargement, Wormian bones (subset of the small intrasutural ossification centers interposed between the cranial sutures) (Figure 7), delayed closure of the fontanelle, scoliosis, vertebral compression fractures, codfish vertebrae, as well as basilar invagination (invagination of the base of the skull with the top of the C2 vertebra migrated upward which may cause narrowing of

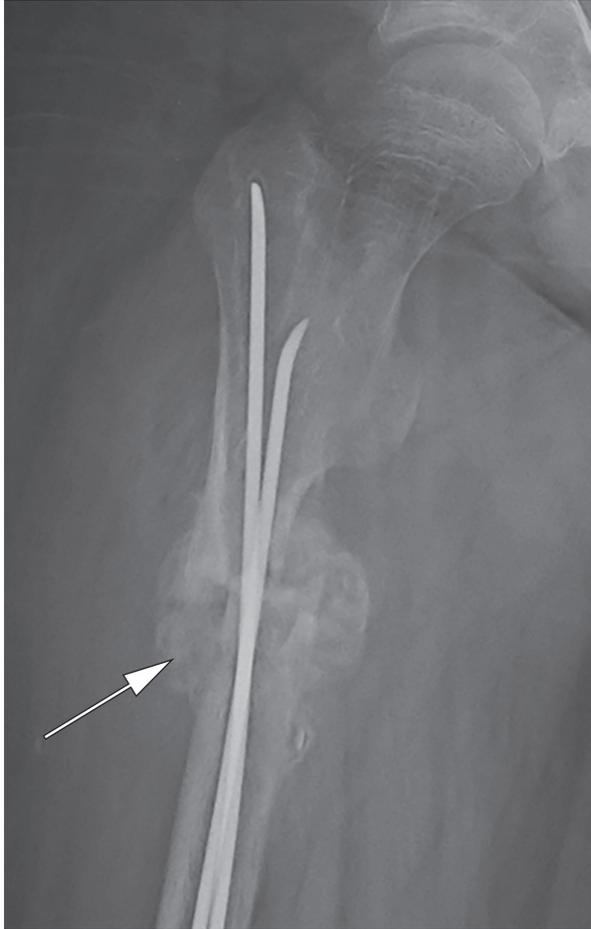


Figure 5. Frontal radiograph of the femur in a 13 year old with OI, demonstrating hyperplastic callus at a mid-femoral fracture, transfixed with two flexible intramedullary nails.

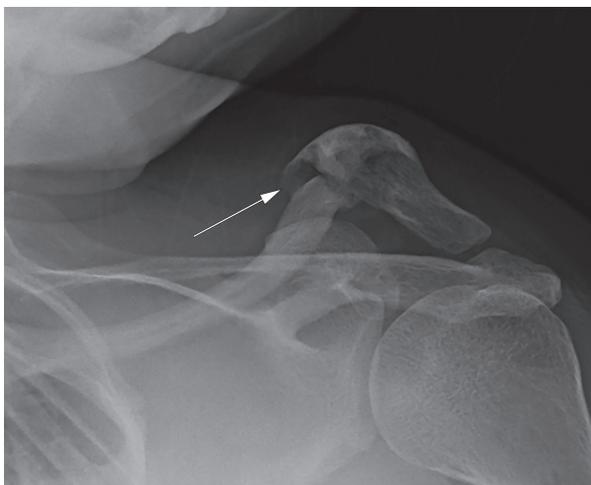


Figure 6. Frontal radiograph of the left clavicle in a 28 year old with OI, with a pseudoarthrosis at the site of prior fracture.

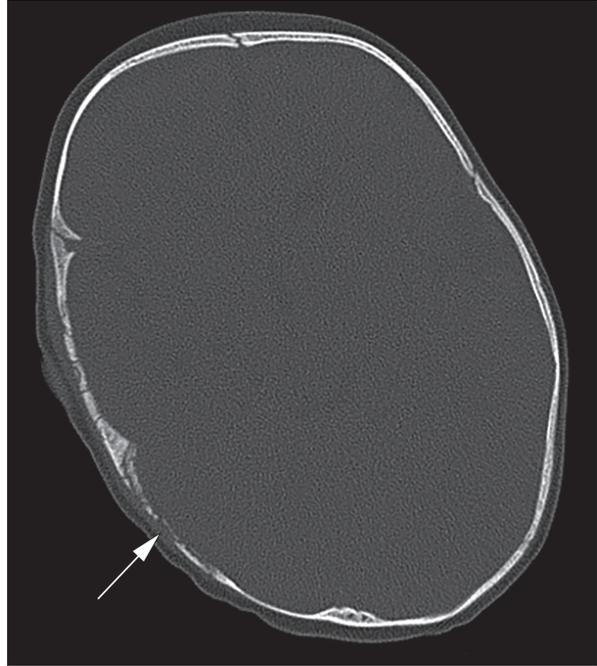


Figure 7. Axial CT image of the head in a 7 month old with OI shows multiple small bones along the right lambdoid suture, consistent with Wormian bones.

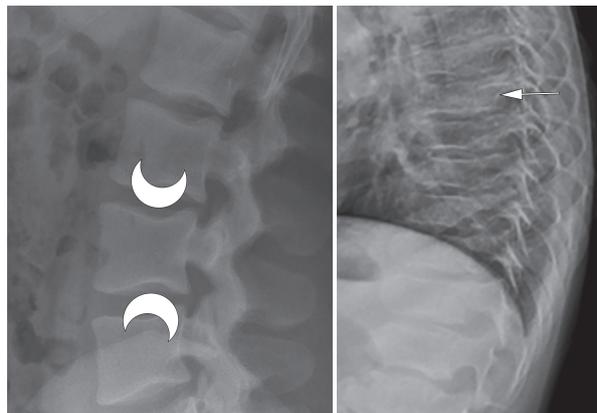


Figure 8. Lateral lumbar spine radiograph in patient 24 year old with OI (A) shows multiple biconcave (codfish) vertebral bodies. A lateral thoracic spine radiograph (B) in a 6 year old with OI shows platyspondyly (multiple flattened vertebral bodies).

the foramen magnum), and platyspondyly (Figure 8, 9). Pectus excavatum or carinatum may be seen, as well as coxa vara (Figure 10). In the appendicular skeleton, bowing and gracile appearance of the long bones is frequent (Figure 11).

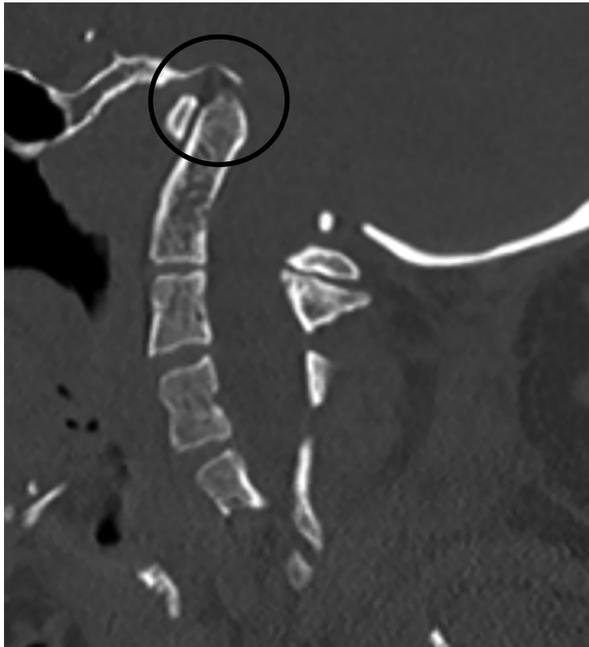


Figure 9. Sagittal CT of the cervical spine in a 34 year old with OI showing basilar invagination with proximal migration of the dens (black circle).

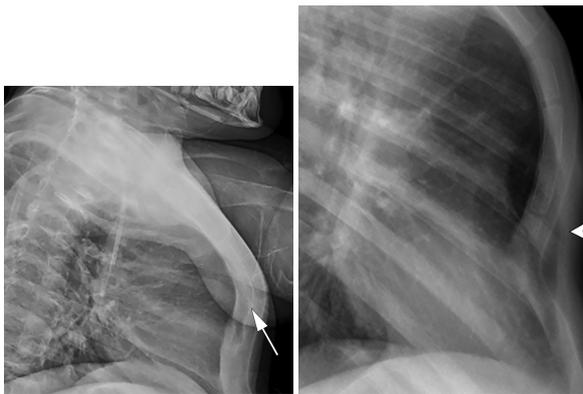


Figure 10. Lateral chest radiographs showing sternum protruding anteriorly (A) in an 8 year old with OI with pectus carinatum and (B) depressed in a 15 year old patient with OI with pectus excavatum.

In younger children, the long bones may demonstrate a “bamboo cane appearance”, where bones are thick and broad with lack of osseous remodeling. Children with type OI may have scalloping at the bone metaphyses and epiphyses with popcorn calcifications, most commonly in OI type III (Figure 12). This tends to occur in the metaphyseal and epiphyseal regions of the knee and may result in leg length discrepancy (26).



Figure 11. Lateral radiograph of the tibia/fibula, showing long bone bowing in a 4 year old with OI.

Cyclic administration of bisphosphonates is often used as treatment for OI. Bisphosphonates can induce the formation of dense metaphyseal bands and occasionally epiphyseal and apophyseal bands, secondary to failure of remodeling of the primary to secondary spongiosa at the physis, creating the “zebra stripe sign” (27-31) (Figure 13). When these lines are present, care should be taken that bone mineralization density is not overestimated on imaging.



Figure 12. Frontal shoulder radiograph of a 14 year old with type 3 OI, showing coarse “popcorn” calcifications within the left proximal humeral metaphysis.

Postnatal CT is usually not necessary, but may be helpful to better assess Wormian bones (Figure 7). Otosclerosis is best evaluated with a temporal bone CT (32). Basilar invagination may be identified on cervical spine CT and MRI (Figure 9).

In a pediatric patient that presents with multiple fractures, there are several differential considerations, including OI, particularly type I and IV, as these patients may have near normal bone mineralization. However, the most common cause of multiple injuries remains NAT (33, 34). There is considerable overlap between fractures that occur due to accidental trauma and NAT and certain fractures have been found to be highly specific for NAT. Metaphyseal corner fractures are thought to be due to shearing of the weak metaphysis in the growing child when the child is shaken and as such are thought to be pathognomonic of NAT (Figure 14). Rib fractures are not particularly common in OI, but they are often seen in NAT, particularly at the posterior ribs, thought to be related to the anteroposterior compression of the rib cage as the child is shaken (22) (Figure 15).

Skull fractures are common in accidental trauma and NAT, but are not particularly common in OI. Additional findings that raise concern for NAT

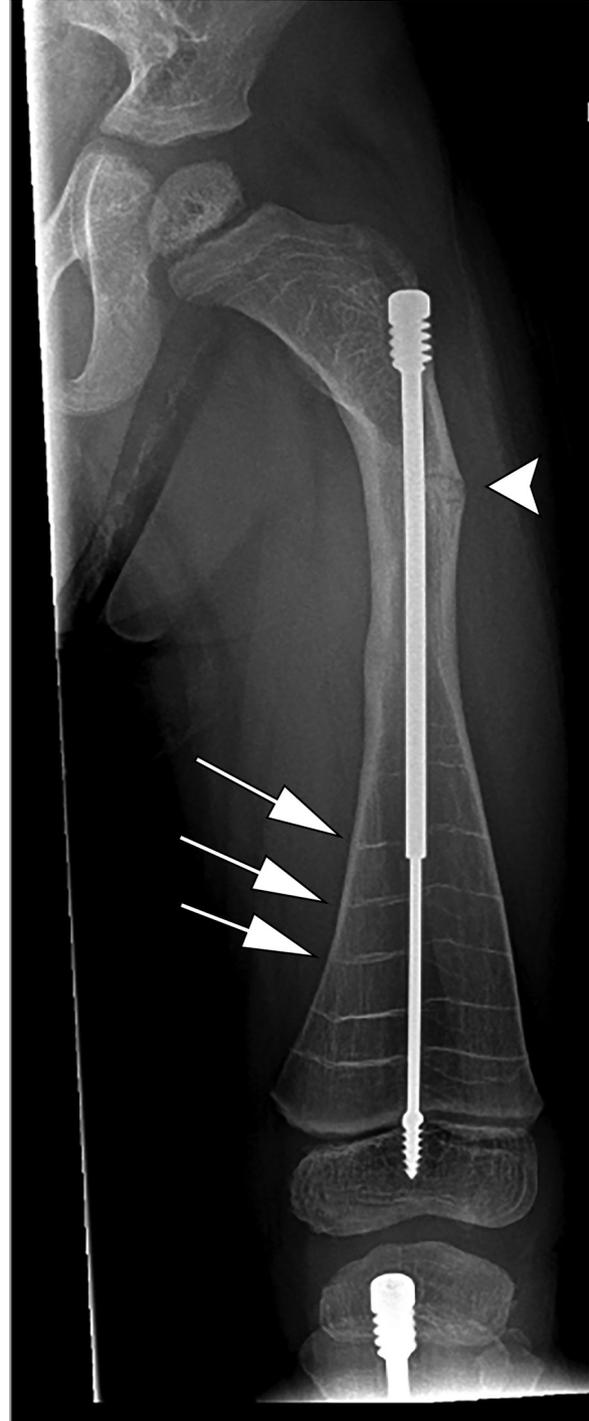


Figure 13. Frontal radiograph of the femur in a 5 year old with Type 4 OI shows an intramedullary nail transfixing the femur, with a healing fracture (arrowhead) of the proximal lateral femoral cortex. Multiple alternating dense (white arrows) and lucent bands are present in the metaphysis (“zebra stripe sign”), presumably due to cyclic bisphosphonate therapy.

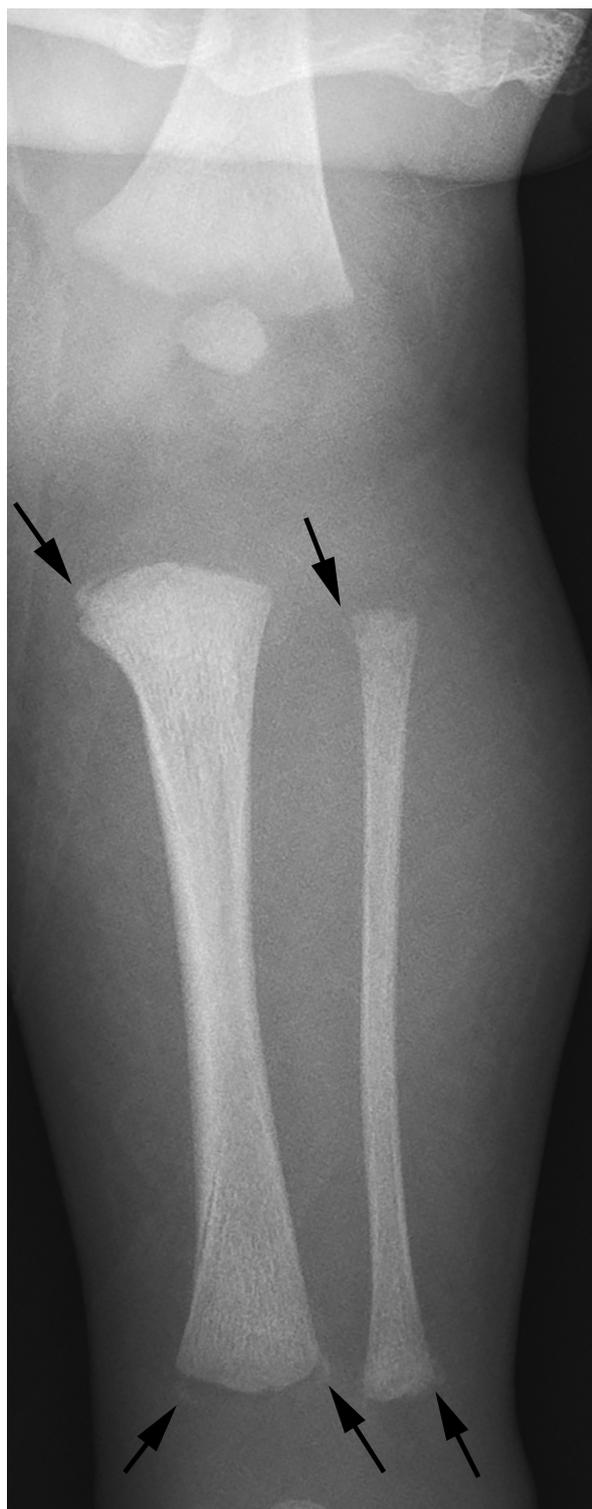


Figure 14. Frontal radiograph of the tibia and fibula in an 11 day old neonate with NAT, showing proximal and distal metaphyseal "corner" fractures (arrows) in the tibia and fibula with extensive soft tissue swelling.



Figure 15. Frontal radiograph of the chest in an 11 day old neonate with NAT, showing posterior rib fractures (arrows).

includes multiple skull fractures or fractures that involve more than one bone or cross sutures, as well as depressed skull fractures. Diastatic sutures are also associated with NAT. Scapular and sternal fractures, as well as distal clavicular fractures are suggestive of NAT and not commonly seen with OI (33). NAT disproportionately affects very young children. In the 1980s it was found that nearly one-third of all cases occurred before 6 months of age, one-third occurred between 6 months and 3 years and one-third occurred in children over the age of three (35).

Other differential considerations when presented with a patient with multiple fractures may include osteopenia of prematurity, osteomalacia, juvenile osteoporosis, hypophosphatemia, Rickets, copper deficiency, scurvy, and Menkes syndrome.

### OI in Adults

Rarely, very mild forms of OI may remain undetected until adulthood and may be diagnosed incidentally following a fracture. OI should be considered in the differential diagnosis for an adult with an unexplained fracture, prior to expected age-related osteoporosis and without any known disease that may lead to osteoporosis. Additional differential considerations for unexplained adult

fractures include Gaucher disease, Marfan syndrome, hypophosphatemia, and various causes of hypogonadism (36).

Recent research has focused on improving the characterization of OI in adulthood, particularly mild forms of OI, which has previously been poorly understood relative to pediatric OI. Increased awareness and continued improved treatment of OI in recent years have contributed to progressively increased life expectancy and quality of life in OI patients.

Radiographs remain the primary modality for diagnosis and follow-up of fractures in adult OI patients. As in children, the primary and least variable symptom of OI in adults is brittle bones. Fracture rates decline with skeletal maturity; however, approximately 25% of OI-related fractures occur in adults (37). In ambulatory adults, fractures of the vertebral bodies, hips, and feet are common, with as many as 50% of fractures involving the spine (37).

Serial radiographs are useful in these patients to evaluate fracture healing, while additional imaging such as CT may be of use if intervention is planned. Manifestations of OI in adults are highly variable, and are not limited to brittle bones and frequent fractures; the multisystem manifestations of OI are often of concern (38).

Fractures in adults with OI may present additional challenges to the orthopedic surgeon relative to the general population. While OI does not prolong fracture healing, OI patients have higher rates of malunion and nonunion, and up to 20% of OI patients experience nonunion of at least one fracture (37). Nonsurgical management of fractures is often preferred. Hip arthroplasties are associated with a higher complication rate in patients with OI, and vertebroplasties are generally contraindicated in treatment of spinal fractures due to high risk of cement extravasation (37). There are several additional musculoskeletal manifestations of OI in adults. These may be diagnosed incidentally on radiographs following a fracture or by MRI for evaluation of musculoskeletal pain. Not infrequently, acetabular protrusio can be seen in adult patients with OI (Figure 16). Osteoarthritis is common,

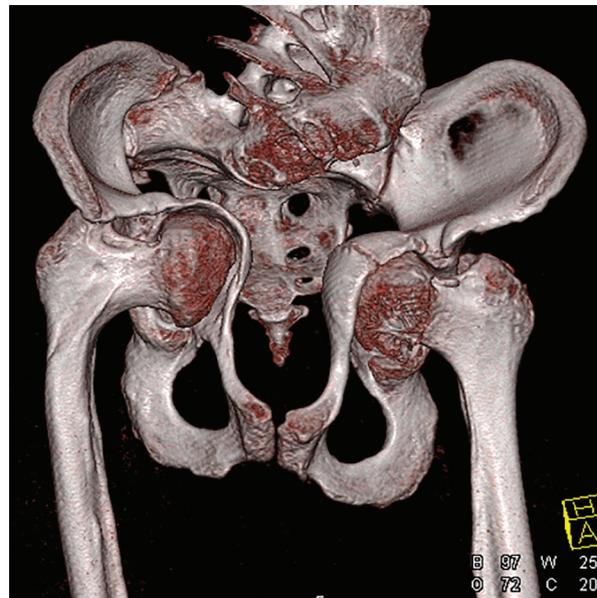


Figure 16. Frontal pelvis radiograph (A) and 3D CT reconstruction (B) of the pelvis in a 45 year old patient with Type 4 OI, demonstrating osteopenia, lumbar scoliosis, and severe bilateral acetabular protrusio.

with nearly half in an online survey of adults by the OI Foundation reporting a formal diagnosis of arthritis (39). Post-traumatic osteoarthritis is also common and the periarticular bone dysplasia and subchondral insufficiency may contribute to rapid progression of osteoarthritis (37). Joint laxity is relatively common, and some patients may benefit from assistive devices originally developed for management of Ehlers-Danlos Syndrome (36). Tendinopathy and tendon rupture may also occur.

This has been less well characterized and overall prevalence is unknown; however, approximately one third of patients in the OI Foundation survey reported prior tendon rupture (39). MRI and diagnostic ultrasound may be useful if tendon pathology is suspected.

Nontraumatic spinal pathologies, including kyphoscoliosis and spondylolisthesis, are more common in adults with OI compared with the general population. Progressive spinal deformity may exacerbate pulmonary dysfunction particularly in more severe forms of OI. Craniocervical junction abnormalities, including basilar invagination, basilar impression, and platybasia, are also seen, more commonly in severe OI. Lateral radiographs of the cervical spine remain most useful in diagnosis of craniocervical abnormalities, while CT may help better evaluate osseous structures (Figure 8, 9).

The most severe craniocervical junction abnormality, basilar impression, typically presents with nonspecific neurological symptoms including headache, vertigo, torticollis, and abnormal reflexes (Figure 9). Rapid diagnosis and treatment are important, as untreated basilar impression may lead to severe neurological consequences including paralysis and death. As with other craniocervical junction abnormalities, radiographs and CT are useful for characterization of osseous structures, while MRI should be considered for better evaluation of neurological structures if basilar impression is suspected.

Dentinogenesis imperfecta is common in patients with OI because part of the dentine of teeth is made up of type 1 collagen resulting in brittle yellow-brown teeth that are at risk of fracturing, decay, and infection (40). Presence of dentinogenesis imperfecta is variable, and the association between dentinogenesis imperfecta and collagen gene mutations is poorly understood. Diagnosis of dentinogenesis imperfecta is often made using clinical and radiographic findings. Dental infection may rarely exacerbate or lead to osteonecrosis of the jaw in patients receiving bisphosphonate therapy.

Hearing loss affects approximately 48-72% of adult OI patients (41). This is most commonly

conductive type with symptoms beginning at the second through fourth decades of life, and later progressing to a mixed type (conductive and sensorineural) (41). CT and MRI of the temporal bone may be of use in evaluating hearing loss in OI to assess for otosclerosis.

Cardiovascular disease is common in adults with OI, often after age 40 and includes aortic and mitral insufficiency, heart failure, and aortic root dilation (42). Hypertension is seen in up to 40% of adults with OI (37) and may be exacerbated by frequent NSAID treatment of musculoskeletal conditions as well as physical inactivity that may be secondary to musculoskeletal deformities.

### **New Horizons in Imaging of Patients with OI**

There have been several important recent advancements in imaging that are useful in evaluating patients with OI, to include peripheral quantitative computed tomography (pQCT), high-resolution peripheral quantitative computed tomography (HR-pQCT), slit-beam digital radiography, and quantitative ultrasound (QUS).

pQCT allows for evaluation of volumetric bone mineral density in the peripheral rather than the axial skeleton, can separately quantify trabecular and cortical volumetric bone mineral density, and has been used in several clinical studies involving OI therapy (43-45). HR-pQCT can further assess bone geometry, volumetric bone mineral density (separately quantifying trabecular and cortical volumetric bone mineral density) and microarchitecture in the peripheral skeleton, and has been used in several clinical studies involving OI therapy (46-53). A slit-beam digital radiography system allows for simultaneous acquisition of tangential images of the entire body with three-dimensional reconstructions, allowing for assessment of skeletal alignment and deformity (54). QUS may have a useful role in the evaluation of patients with OI in the future, particularly in geographical areas where other imaging modalities are not available; however, QUS data is currently scarce. QUS attempts to measure bone quality and bone mass (55, 56).

## Conclusion

OI comprises a heterogeneous group of genetic disorders responsible for bone fragility and additional connective tissue disorders. The osseous hallmarks of this “brittle bone disease” can affect any collagen containing structures resulting in frequent fractures, ligamentous hyperlaxity, and neurologic and cardiovascular abnormalities. Differentiating OI from NAT can cause significant consternation, and correlation with family history and presence of non-skeletal manifestations of OI may aide in diagnosis.

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## Trigeminal Neuralgia and Potential Correlations with Anatomical Variations of the Trigeminal Nerve

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### Abstract

**Objective.** Trigeminal neuralgia is a long-term facial pain syndrome. Our aim was to review the anatomy of the trigeminal nerve and its anatomical relationship with the adjacent structures that may contribute to the pathogenesis of trigeminal neuralgia. **Methods.** Eligible articles were identified by a search of the Medline Embase, Pubmed Cinahl and Google Scholar bibliographical databases. We checked all the references of the relevant reviews and eligible articles that our search retrieved, in order to identify potentially eligible conference abstracts. Titles of interest were further reviewed by abstract. Case reports were excluded. **Results.** Trigeminal neuralgia syndrome seems to be caused by anatomical variations of the trigeminal nerve and its adjacent anatomical structures, mainly through compression. We depict the causes, the pathogenesis, and the clinical manifestations of the syndrome. The classification, diagnostic approach, differential diagnosis, and treatment modalities are also presented and they may be personalized according to the anatomical variations of the trigeminal nerve present, which may lead to trigeminal neuralgia syndrome. **Conclusion.** It is very important to be very careful in cases of new emerging neuralgia and to avoid the term “idiopathic” until proven otherwise by validating the newer and more appropriate tests and diagnostic criteria. Current data are insufficient and future research is needed in order to discover innovative and more effective treatments of trigeminal neuralgia, considering the anatomy and the anatomical variations of the trigeminal nerve.

**Key Words:** Trigeminal Neuralgia ■ Trigeminal Nerve Anatomy ■ Trigeminal Nerve Surgery.

### Introduction

Trigeminal neuralgia is a painful syndrome, which affects 0.07% of the population (1). It occurs mainly in women (60%) and those over the age of 50 (1, 2). The clinical severity of the syndrome is so intense that it may lead some patients to commit suicide (3). The treatment of the disease is pharmacological, while in its complicated forms, surgical treatment can be applied, with varying results and complications. Unexpectedly, effective treatment of the disease has led many scientists and researchers to focus on the pathogenesis of the disease, which still today has not been clearly elucidated.

Our aim was to review the anatomy of the trigeminal nerve and its anatomical relationship with

the adjacent structures that may contribute to the pathogenesis of the trigeminal neuralgia. The correlations have been shown in many studies to be positive, and provide the potential for new therapeutics, and invasive or non-invasive treatment modalities.

### Anatomy and Functions of the Trigeminal Nerve

The trigeminal nerve is the fifth cranial nerve, and contains motor and sensory fibers (mixed nerve). Its course starts from the brain stem, within which all four nuclei are located (principal sensory, spinal trigeminal, mesencephalic, motor) (4). It emerges from the front surface of the pons, consisting of

the thick sensory root and the finer motor root. It passes outward from the posterior cranial fossa, bearing on the upper surface of the apex of the petrous bone in the middle cranial fossa. On the anterior surface of the petrous bone, the sensory root swells and forms the Gasserian ganglion. The Gasserian ganglion occupies the Meckel cavity, which is a dura mater pouch containing cerebrospinal fluid. From the anterior edge of the ganglion the three branches of the trigeminal nerve emerge: the ophthalmic, the maxillary and the mandibular nerve. The ophthalmic nerve (V1) contains only sensory fibers and exits the skull, entering the orbit through the superior orbital fissure. The maxillary nerve (V2) also contains only sensory fibers and exits the skull through the foramen rotundum. The mandibular nerve (V3) contains the sensory and all the motor fibers of the trigeminal nerve and exits the skull through the foramen ovale (4, 5).

The trigeminal nerve and its branches are relatively large, compared to the other cranial nerves, and due to its length and its course towards the face, it is adjacent to various anatomical areas. The most important adjacent anatomical areas are: the superior cerebellar artery (SCA), the posterior vertebral arteries, the facial nerve, the cranial nerve foramina, the teeth, the masticatory muscles, and the brain stem. Anatomical variations, neoplasms or inflammatory processes in these anatomical areas may cause neuralgia (6, 7).

The trigeminal nerve's functions transmit information regarding the sensation of pain, touch, and pressure from the facial skin and mucous membranes. It also serves the movements of the mas-

tatory muscles, the tensor tympani muscle, the tensor veli palatini, the mylohyoid muscle and the anterior belly of the digastric muscle. Moreover, it contains postganglionic parasympathetic fibers derived from four ganglions (otic, pterygopalatine, submandibular and ciliary). Finally, the corneal reflex is mediated by the nasociliary branch of the ophthalmic nerve (V1), only sensing the stimulus on the cornea (8)

### Trigeminal Neuralgia Syndrome

The causes of trigeminal neuralgia syndrome are divided into two categories: primary (idiopathic neuralgia) and secondary (9). Secondary causes include all the causes that may compress the trigeminal nerve or induce its activation, some of which are epidermal cysts, neoplasms, aneurysms and post-herpetic infection, that lead to neuralgia (9, 10). It is important to mention that there is probably a familial form of the disease in 2% of people with the disease, in which a structural change in the base of the skull occurs (11).

The mechanism behind the pathogenesis of trigeminal neuralgia is unknown. The main theories refer to the demyelination of the nerve (12), ectopic impulses due to changes in the  $Ca^{2+}$  channels, central pain mechanisms, and bioresonance (13, 14, 15)

According to the Headache Classification Committee of the International Headache Society (ICHD-3) (16), trigeminal neuralgia syndrome is classified into 2 categories (classical neuralgia and painful neuropathy). There are specific diagnostic criteria from the same society (Table 1). The

Table 1. Diagnostic Criteria According to ICHD-3

1.	3 seizures of unilateral pain + B, C criteria
2.	Distribution of pain in the course of the branches of the trigeminal nerve, without radiation in another area
3.	≥3 criteria from: 1. Recurrent paroxysmal pain lasting from 1 second to 2 minutes. 2. Very high pain intensity 3. Characteristics of pain compatible with those of the syndrome (abrupt, paroxysmal, like getting hit by lightning, like getting stabbed, etc.) 4. Release of pain after analgesic, innocent activity
4.	No clinically obvious neurological deficit
5.	Not compatible with other ICHD-3 criteria

Table 2. Therapeutic Options in Trigeminal Neuralgia Syndrome

Medication	GRADE 1A: Carbamazepine GRADE 1B: Oxycarbazepine GRADE 2C: Baclofen, Lamotrigine Additional drugs: Opioids, Antidepressants, etc.
Surgical treatment	1. Surgical microvascular decompression 2. Treatment with $\gamma$ -knife 3. Transdermal microcompression with balloon 4. Transdermal rhizolysis with glycerol 5. Percutaneous radiofrequency neurolysis of the Gasserian ganglion

characteristic of trigeminal neuralgia syndrome is acute, debilitating, sudden and unilateral pain in the face, where the three branches of the nerve pass (17, 18). The pain may also involve more branches and may be bilateral in 3% of cases (18, 19). There is no specific activity that triggers the pain, and the episodes can last for weeks to months, but the seizures last for seconds to two minutes, reaching rapidly their peak, and seizures are sometimes accompanied by muscle spasms (19).

The diagnosis of trigeminal neuralgia syndrome is based on clinical examination (20) and imaging tests - Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Magnetic Resonance Angiography, and High resolution Brain Magnetic Resonance Imaging) (21). The differential diagnosis of the trigeminal neuralgia must be between four diseases: SUNCT syndrome (Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing), cluster headache, jabs and jolts syndrome, and classic migraine. The treatment of trigeminal neuralgia is mainly pharmaceutical, but in its drug-resistant forms the alternative of surgical treatment might be effective (17, 22) (Table 2).

## Methods

The protocol of this review has been submitted to the Institutional Review Board of Department of Anatomy, National and Kapodistrian University of Athens, Greece, and is available upon request. Eligible articles were identified by search of the

Medline Embase, Pubmed, Cinahl and Google Scholar bibliographical databases for the period from July 2020 to April 2021, due to their detailed articles solely in the field of medicine, and their accessibility, while others such as Scopus, Cochrane, etc were not preferred because they lack this. The study protocol was agreed by all co-authors. The search strategy included the following keywords: trigeminal neuralgia anatomy, causes of trigeminal neuralgia, trigeminal neuralgia surgery and trigeminal nerve anatomical variations.

## Study Selection Criteria

Language restrictions were applied (only articles in English, French and German were considered eligible); two investigators (MA and AP), working independently, searched the literature and extracted data from each eligible study. The criteria of this study selection were: Recent year of publication (2011 until now) and/or of previous years, if the study has plentiful cadaveral material; Abundant references and rich bibliography, and Greek, English, French and German language. Articles that did not state the names of the authors and case reports were excluded. In addition, we checked all the references of the relevant reviews and eligible articles that our search retrieved, so as to identify potentially eligible conference abstracts. Titles of interest were further reviewed by abstract.

## Study Selection

The search strategy retrieved 348 articles, 43 of which were considered eligible. 15 of these are presented in the results of this study and 28 of them were selected as supplements in this literature review. The other articles were excluded (applying exclusion criteria).

## Results

In general, most publications on the relationship between anatomical variations and the occurrence of trigeminal neuralgia focus on the vascular area, and mainly on the superior cerebral artery. There

is a limited number of articles available on other anatomical areas and structures, with varying results. These anatomical areas are the foramen ovale, the Meckel's cave, the pterygospinous process etc. Occasionally the results of the studies were used for a more precise therapeutic option and in others, cadaverals were studied to extract data on the pathogenesis of trigeminal neuralgia.

Bowsher et al., 1997 (23) stated that there are insufficient data to show the relationship between anatomical variants of the trigeminal nerve and the occurrence of neuralgia. Krmpotić-Nemanić et al., 1999 (24) presented the results of a study of 100 skulls with anatomical variations in the pterygospinous process. It is suggested that these variations may be the cause of neuralgia. In research conducted by the University of Nepal Ray et al., 2005 (25) 35 cadaveric skulls were studied. Changes in the shape and size of the foramen ovale were found to compress the trigeminal nerve, and cause pain in the facial area. Buch et al., 2012 (26) reported anatomical variations of the inferior alveolar nerve – a branch of the mandibular nerve - in cadavers from India, which may lead to pain in the mandibular region (including the syndrome of trigeminal neuralgia).

In addition, Munyiri Nderitu et al., 2016 (27) presented how a deep understanding of the precise anatomy of the infraorbital nerve is crucial to avoid iatrogenic injury of the nerve. Forty-two nerves in cadavers were fully examined and described. The appearance and course of the nerve varied, most importantly with the complete absence of the nasal branch in 34.53% of cases, and also the existence of other branches. This parameter is of paramount importance, because resistance to therapy in trigeminal neuralgia syndrome may be attributed to infraorbital nerve variations.

Further, a prospective study by Ding et al., 2016 (28) recruited 108 patients with trigeminal neuralgia. The patients were divided into two groups. This paper dealt with Percutaneous Radiofrequency Thermocoagulation (RFT) of the Gasserian ganglion, which is an effective treatment for primary trigeminal neuralgia. The issues that the scientists wanted to resolve were the high recurrence rate

and technical difficulties in certain patients with foramen ovale (FO) anatomical variations. In the first group, the Hartel anterior approach was used to puncture the FO. In the second group, a percutaneous puncture through a mandibular angle was used to reach the FO. In both groups, procedures were guided by CT imaging and neuronavigation. The success rates, therapeutic effects, complications, and recurrence rates of the two groups were compared. CT and neuronavigation-guided puncture from a mandibular angle through the foramen ovale into the Gasserian ganglion can be safely and effectively used to deliver radiofrequency thermocoagulation for treatment of neuralgia. This method may represent a viable option to treat this syndrome, in addition to the Hartel approach.

Following these, the study by Zdilla et al., 2016 (29) depicted the results of 139 dry human crania. A total of 223 pairs of foramen ovale and trigeminal nerve variations were assessed in relation to compression. The crania were photographed, and the photographs were examined and measured using ImageJ software. The foramen ovale is a crucial anatomical area, because its anatomical variations may cause trigeminal neuralgia, and surgical therapy is mandated. The average angles from the anteromedial-most aspect of the foramen ovale to the anteromedial- and posterolateral-most aspects of the trigeminal impression were  $65^\circ \pm 10.2^\circ$  and  $95^\circ \pm 8.5^\circ$ . From the posterolateral aspect of the foramen ovale, the angles at the anteromedial and posterolateral-most aspects of the trigeminal impression were  $69^\circ \pm 10.3^\circ$  and  $32^\circ \pm 11.2^\circ$ , respectively. The average angles from the centroid of the foramen ovale to the anteromedial- and posterolateral-most aspects of the trigeminal impression were  $47^\circ \pm 11.2^\circ$  and  $83^\circ \pm 9.4^\circ$ , respectively. Paired t tests did not reveal any significant differences in any angles measured between sides.

In addition, Brinzeu et al., 2018 (30) examined 42 patients with trigeminal neuralgia. Imaging examinations showed that there was a variation of the Meckel cavity with an angle of  $86^\circ$  (by nature  $98^\circ$ ,  $P=0.004$ ) and compression of the branches V2 and V3. Medélez-Borbonio et al., 2018 (31) published a retrospective study of 53 patients with tri-

geminal neuralgia. They bilaterally measured the cisternal segment of the trigeminal nerve, the trigeminal-pontine angle and the lateral width of the pontine cistern on the Fiesta MRI sequence. These measurements were very important for the surgical procedure that followed, and an understanding of the etiology of the syndrome. The right trigeminal nerve was affected in 36 patients (67.9%), and the left in 17 (32.1%) patients. The average length of the trigeminal nerve was 9.8mm (range: 4.6–16.8mm) on the affected side, and 10.5mm (range: 5.6–18.4mm) on the unaffected side ( $P=0.02$ ). The average trigeminal-pontine angle was  $12.5^\circ$  (range:  $5.4^\circ$  to  $19.5^\circ$ ) on the affected side, and  $10.2^\circ$  (range:  $5.0^\circ$  to  $30.5^\circ$ ) on the unaffected side ( $P=0.01$ ).

Tsutsumi et al., 2018 (32) studied the anatomy of the trigeminal root. Considerable inter- and intra-individual variability was exhibited that may influence the symptoms of trigeminal neurovascular compression. Thin-sliced, axial T2-weighted imaging, and coronal constructive interference in steady-state (CISS) sequence were performed for a total of 167 patients. On axial T2-weighted imaging, 3 divisions of the main trigeminal sensory root were unequivocally delineated in 36% of the 95 patients. 63% of Meckel's caves were bilaterally adjacent to the petrous portion of the internal carotid artery. On CISS sequence, the course of the main trigeminal sensory root was well delineated in all of the 72 patients. The accessory sensory and motor rootlets were identified in 38% and 56% of 144 sides, respectively. Levels of the main trigeminal roots at the original site and entrance into Meckel's cave, as well the morphology of the original segment of the main trigeminal sensory root were variable. Furthermore, in 24% of sides, three divisions of the main trigeminal sensory root were clearly delineated, arranged in variable manners. In 20% of sides, segments of the superior cerebellar artery had contact with the main trigeminal sensory root and motor rootlets.

The next article, by Dupont et al., 2019 (33), dealt with the simultaneous existence of the ossification of the roof of the porus trigeminus with an ipsilateral duplicated abducens nerve behind the entrance to the Dorello's canal. This anatomical

variant raises the suspicion of a cause-and-effect relationship for trigeminal neuralgia. Additionally, the publication of Elnashar et al., 2019 (34) refers to percutaneous stereotactic radiofrequency rhizotomy, which is necessary before presenting the precise anatomy of the foramen ovale. The third branch of the trigeminal nerve passes through the foramen ovale, and variability in its shape and size can cause nerve compression, resulting in neuralgia. The researchers analyzed 174 skull bases, and found an area loss of an average of  $18.5\% \pm 5.7\%$ .

Another publication from Clearly et al., 2019 (35) presented three patients with drug-resistant trigeminal neuralgia. Magnetic Resonance Imaging was performed showing the absence or hypoplasia of Meckel's cave as the cause of the neuralgia. The  $\gamma$ -knife treatment was successfully selected.

Hardaway et al., 2019 (36) performed a case control study. Brain MRIs of 232 patients were compared with measurements obtained in 100 age-matched and sex-matched healthy controls (control group). The odd ratio (OR) of females not having NVC compared to males was 2.7 (95% CI 1.3–5.5,  $P=0.017$ ). In terms of age, patients younger than 30 years were much less likely to have neurovascular compression (NVC) compared to older patients (OR 4.9, 95% CI 1.3–18.4,  $P=0.017$ ). The posterior fossa volume was significantly smaller in TN patients without NVC compared to those with NVC. Posterior fossa volume in males was larger than posterior fossa volume in females.

Finally, a retrospective analysis published in 2019 by Grigoryan et al., (37) studied 51 patients with trigeminal neuralgia and Cerebellopontine angle (CPA) tumors: 29 meningiomas of the petrous apex, 11 epidermoids, 9 vestibular schwannomas, 1 hemangioma, and 1 cavernoma. After the removal of the tumour and microvascular decompression, all patients were relieved from the pain syndrome.

## Discussion

In this paper, we focused on the relationship between the onset of trigeminal neuralgia and anatomical variations of the fifth cranial nerve. We be-

lieve that precise knowledge about the variations of the trigeminal nerve is “the key” to developing new and revolutionary therapeutic options, which will relieve a large number of patients with neuralgia around the world. The first paper we perused, Bowsher et al., 1997, states that there are insufficient studies to denote a relationship between the occurrence of trigeminal neuralgia and anatomical variants of this nerve. From 1997 until the present day, the massive development of technology in the field of imaging techniques (especially MRI) (38) has provided enormous possibilities for brain imaging, with the result that subsequent researchers have better data to study. When searching the term “trigeminal neuralgia”, it seems that the publication of papers on this subject has increased rapidly. For instance, in Pubmed the number of publications in 1997 about the term “trigeminal neuralgia” was 146, while in 2020 this number increased to 428.

Regarding papers on cadaveric material, they showed that there are significant variations in the anatomy of the areas adjacent to the trigeminal nerve during its course. These variations mainly concern its shape, but in many cases there is even an absence of the anatomical area itself. The anatomical area that has been studied most frequently is the foramen ovale, which has been described to have a variety of shapes such as: “banana-like”, “triangular”, “oval”, “truly oval”, “elongated oval”, “elongated”, “semicircular”, “almond”, “round”, “rounded”, “slit”, “irregular”, “D- shape” and “pear shaped”. It is essential to describe the anatomical variants of the anatomical structures through which the nerve passes. Most of the skulls belonged to adults, while references to skulls of persons <18 years of age are minimal. It is very likely that these anatomical varieties of the shape of the foramen ovale in adults exert pressure on the nerve, resulting in neuralgia.

In terms of patient data, many cases of trigeminal neuralgia syndrome were initially diagnosed as “idiopathic” and the patient did not receive proper treatment from the beginning. The average time from misdiagnosis to receiving proper treatment was about two years. The majority of patients were > 18 years old and female. Patients continued to suffer from the syndrome, and only when more

specialized imaging tests were performed (MRI, MRA) did the neuralgia resolve with surgery. The most common surgical treatment performed on these individuals was microvascular decompression, which has given spectacular results. This is the reason why it is of paramount importance to perform the appropriate imaging examinations early because the diagnostic criteria of trigeminal neuralgia (ICHD-3) (15) do not exclude secondary causes, or the possibility of any anatomical variations of the nerve. According to the European Academy of Neurology, an imaging technique must be performed in order to provide a personalized therapeutic option (39).

As mentioned above, MRI may indicate possible anatomical variations of the trigeminal nerve. In the papers we analyzed, it seems that the anatomical areas through which the trigeminal nerve passes, but also the nerve itself, showed anatomical variations in many cases, with a statistically significant difference in most studies. In fact, Hardaway et al., 2019 (35) examined the anatomical variants of the nerve and the neighboring areas, in relation to age and sex, which produced very interesting results. Women are more likely to develop neuralgia at a younger age compared to men. Men with neuralgia are more likely to have neurovascular compression and to be cured with surgical treatment. Moreover, young patients are much less likely to have neurovascular compression, compared to older patients. Furthermore, the posterior fossa in males is larger than the posterior fossa in females. Thus, men and older patients are more likely to be treated with surgical microvascular decompression.

There are also many studies presenting interesting case reports of trigeminal neuralgia. First of all, Zimering et al., 2017 (40) depicted a case of trigeminal neuralgia. A 52-year-old man came for a preoperative MRI, which showed lesions close to Meckel’s cave. He was considered a coroner and a biopsy was sent for histological examination, in which no mitoses were seen, but normal brain tissue. This is the only case with ectopic tissue that caused nerve compression and the corresponding symptoms. Sundararajan et al., 2018 (41) present-

ed a case report of a male patient with classic trigeminal neuralgia in the V3 branch (mandibular nerve). On MRI, followed by a diagnostic protocol, there were no anatomical variations of the brain vessels, but hypoplasia of Meckel's cave. In addition, no examination showed any disease that may be related to neuralgia syndrome. The treatment was surgical. In Peris-Celda et al., 2019 (42), pre-operative MRI was performed on a female patient with trigeminal neuralgia syndrome of branches V2 and V3. An enlarged Meckel's cave and a loop of the cerebral artery were found. The next study by Hirata et al., 2019 (43) presented the case of a 46-year-old man with trigeminal neuralgia, in whom computed tomography was performed which showed bone hyperplasia in the area of the left cerebellopontine cistern, resulting in compression of the left trigeminal nerve. The patient underwent surgery (microvascular decompression) and the neuralgia disappeared completely.

Finally, it is very important to be very careful in cases of new emerging neuralgia and to avoid the term "idiopathic" until proven otherwise by validating the newer and more appropriate tests and diagnostic criteria.

## Conclusion

The occurrence of trigeminal neuralgia correlates with anatomical variations of the trigeminal nerve and the adjacent anatomical areas and structures, mainly through compression. The enormous development of technology in the field of medicine, especially in terms of imaging and surgical techniques, has changed the therapeutic options for trigeminal neuralgia. However, more research is necessary to address this issue in order to discover innovative and more effective treatment modalities to ameliorate the severity of this disease.

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## A Case of Otomycosis Associated With a Sugar-Loaded Traditional Medicine Solution and Other Factors

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### Abstract

**Objective.** The aim of this case report is to illustrate how multiple co-existing factors can contribute to otomycosis and to highlight possible new etiologies for this common condition. **Case Report.** We report the case of a woman with otomycosis in which a) several factors could have played an additive, contributing role, and b) with all other clinical parameters being equal (*ceteris paribus*) before and after otomycosis-specific treatment, a home-made, sugar-loaded medicinal solution could also have contributed to its pathogenesis. **Conclusion.** Our case highlights that traditional medicines must be used with caution since they might cause side-effects and that history-taking must include enquiry about their use. This case also highlights that a *ceteris paribus* approach can be useful when interpreting case reports, which lack the methodological robustness of case-control or interventional studies.

**Key Words:** Otomycosis ■ Corticosteroids ■ Psoriasis ■ Fungal Otitis Externa ■ Case Report.

### Introduction

Otomycosis is a common superficial fungal infection of the external auditory meatus that may present with various non-specific otologic manifestations such as aural fullness, pruritus, conductive hearing loss, and otorrhea (1). Occasionally, otomycosis may even cause perforations of the tympanic membrane (2). The most common causative organisms are *Aspergillus niger* and *A. tubingensis*, even though other fungi including *Candida* species (such as *Candida Auris*) (especially in children), *Mucor* species, *Rhizopus* species, *Scopulariopsis* species, *Alaromyces purpurogenus*, *Naganishia albida*, *Filobasidium magnum*, and *Saksenaeva vasiformis* have also been observed (1, 3).

Here we describe the case of a woman who presented with otomycosis in which a) several factors could have played an additive, contributing role, and b) with all other clinical parameters being equal (*ceteris paribus*) before and after otomycosis-specific treatment, a home-made, sugar-loaded medicinal solution could have potentially contributed to its pathogenesis. Presenting this case allows us to: a) discuss factors that raise clinical suspicion for otomycosis and highlight that clinicians should be always aware of all potential risk and protective factors for otomycosis, b) present a hypothesis on a potential underlying cause, and c) remind practitioners that traditional medicines must be used with caution since they can result in adverse events, and, in doing so, emphasize that

enquiry about their use must be included when history taking (4).

The aim of this case report is to illustrate how multiple co-existing factors can contribute to otomycosis and to highlight possible new etiologies for this common condition.

### Case Presentation

A 66-year-old woman of European ancestry presented to a private ear, nose, and throat (ENT) practice describing an intense feeling of heaviness and blockage in the ears. She had a past medical history of *a)* mild psoriasis in the forearm and the elbow, *b)* Hashimoto's thyroiditis treated with levothyroxine, *c)* chronic diffuse alopecia, *d)* occasional osteoarthritic pain, and *e)* diphtheritis during childhood. She also had mild skin and ear psoriasis, which only affected the entrance to the external auditory meatus and not the canal itself, as well as recurrent episodes of excessive cerumen (earwax) and cerumen impaction requiring micro-suction by an ENT doctor.

Several weeks prior to presentation, she had been involved in restoring some furniture, which involved significant exposure to dust. Over the last three months, she had also experienced a relapse in skin and ear psoriasis, which was ascribed to anxiety and treated with topical corticosteroids in the form of ointment that was applied to the concha of the external auditory canal. Moreover, she had for some time been washing her hair at least twice a day with a home-made sugar-loaded medicinal solution made according to a regional traditional medicine recipe (home-made aloe vera solution mixed with crystal sugar and plain water) to treat her alopecia.

On examination, ear endoscopy revealed unilateral otomycosis of the external auditory canal in the right ear, with features entirely typical for the disease; namely, there was accumulation of debris containing dark-colored hyphae, mild erythema of the skin of the ear canal, and a small amount of watery discharge. However, the auricles were not affected. Fungal cultures or fungal potassium hydroxide stains were not performed taking into

account both the patient's request and because the laboratory findings would not have affected treatment. Therefore, the patient was prescribed a two-week course of topical anti-fungal containing acetic acid, clotrimazole, licorice, essential oils, allantoin, and glycerol, and she was instructed to discontinue the sugar-loaded medicinal solution.

There were no other physical examination findings of note. On follow-up two weeks later, her ear symptoms and endoscopic features of otomycosis had resolved despite continuing with her furniture restorations. Although she continued to apply topical corticosteroids for her skin and ear psoriasis, she had discontinued using the traditional medicinal solution remedy. Even though not used to treat her otomycosis at that time, microsuction (ear toileting) was recommended to the patient if and when she felt the presence of earwax.

### Discussion

Here we present a case of otomycosis in which several factors may have contributed to its pathogenesis including: *a)* ear psoriasis, given that topical corticosteroids used for ear canal psoriasis are a risk factor for otomycosis (1); *b)* exposure to dust, which alongside its associated mycobiome (5) is another risk factor for otomycosis, especially in female patients undertaking housework (6), with our patient reported being in a particularly dusty environment prior to presentation; *c)* excessive cerumen; and, *d)* local humidity in the ear canal due to repeated hair washing in the moist environment of the shower, especially if not followed by adequate hair drying (1). We postulate that extensive hair washing (at least twice a day in this case) could have played a major role in the *ceteris paribus* sense (i.e., all factors being equal) because: *a)* despite the continued application of topical corticosteroids for ear psoriasis and continuing her house restorations after the otomycosis, there was no recurrence of otomycosis; *b)* according to the patient, the home-made solution contained a copious amount of sugar (described as *sweet* and *sticky*); and *c)* the otomycosis resolved after application of that solution was stopped. As a result, the

otomycosis may have, at least in part, been caused by the sugar-loaded solution. Indeed, systematically high glucose levels (such as in uncontrolled type 2 diabetes mellitus) are associated with fungal infections, as are locally high glucose concentrations such as in the bladder after treatment with SGLT2 inhibitors (7), which increase the risk of genital infections. Therefore, this home-made, sugar-loaded extract could have contributed to the patient's acute otomycosis, either through the effects of glucose in the solution or through contamination of the ear with fungi present in the non-sterile, home-made medicinal product.

Of note, even in the presence of other ear comorbidities such as ear psoriasis, a single dose of the antifungal clotrimazole is efficacious and cost-effective for otomycosis (8). Traditional medicines must be used with caution since they can result in adverse events (9), and enquiry about their use must be included when history taking. Since case reports lack the rigor of a case-control or interventional methodology, the *ceteris paribus* (i.e., all other factors being equal) approach is useful in their interpretation. From the patient's perspective, she felt reassured by the lack of recurrence of otomycosis and the explanation of the range of factors that might have played a role. She was therefore able to make adjustments to her lifestyle and daily tasks to mitigate against the risk of recurrence.

### Limitations of Case Study

Our case study has limitations: *a*) it is a single case report of a frequent pathology caused by multiple risk factors which are, however, combined in this case; *b*) a formal microbiological diagnosis was not made; and *c*) the duration of follow-up was relatively short.

### Conclusion

To our best knowledge, this is the first reported case of otomycosis in which a sugar-loaded medicinal solution could have in part contributed to the pathogenesis. Our case highlights that traditional medicines must be used with caution since they

could potentially result in adverse events, and enquiry about their use must be included when history taking. This case also highlights that a *ceteris paribus* approach can be useful when interpreting case reports, which lack the methodological robustness of case-control or interventional studies.

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

*Otomycosis is a frequent disease encountered in ENT practice. To date, several risk factors for otomycosis have been identified including dust exposure, humidity, and topical corticosteroid use. However, there have not been any reports of the combined presence of risk factors or the contributing role of sugar-rich solutions.*

#### What This Study Adds:

*This study presents an intriguing example of otomycosis where several factors may have contributed to the disease pathogenesis. We also speculate that a home-made, sugar-loaded medicinal solution may have contributed, in part, to its pathogenesis by analogy with infections in other body systems. This case report also illustrates that a *ceteris paribus* approach can be useful when interpreting case reports.*

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

**Informed Consent:** Informed consent has been obtained from the patient for the publication of this case report.

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## Large Congenital Juvenile Xanthogranuloma in a Two-Month-Old Girl, a Case of Non-Langerhans Cell Histiocytosis

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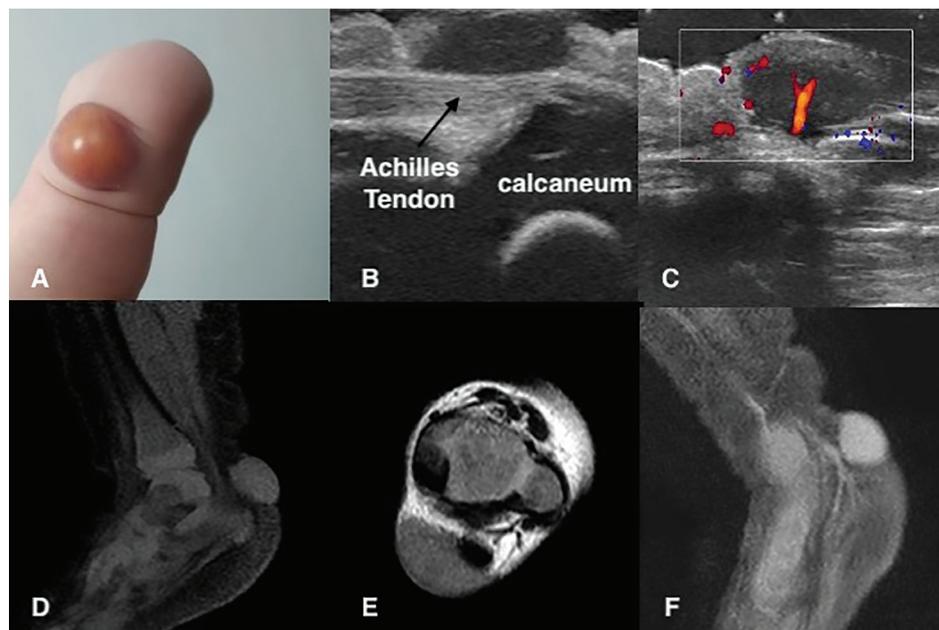
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A two-month-old girl presented to the pediatric surgery department with an asymptomatic, solitary, supra-calcaneal mass, which had almost doubled in size since her birth. Upon clinical examination it appeared large, shiny, and orange-yellow, with well-defined erythematous borders (Panel A). Ultrasound (US) examination revealed a large (20 mm) hypoechoic well-circumscribed oval mass within the subcutaneous tissue, without disruption of the dermis or infiltration of the adjacent

Achilles tendon. Minor vascular flow was detected within the mass by Color doppler evaluation (Panels B and C). MRI revealed a mass with an intermediate signal on T1-weighted images (Panel D), low signal on T2-weighted images (Panel E), and mild enhancement (Panel F).

Imaging features were atypical and thus the differential diagnosis was broad, including fibrous hamartoma of infancy, myofibroma, tendon-sheath fibroma, juvenile xanthogranuloma and neurofibromatosis.

Juvenile xanthogranuloma (JXG) was diagnosed by histopathology. Juvenile xanthogranuloma (JXG) is a form of non-Langerhans cell histiocytosis (1) affecting children within the first two years of life. It can also be congenital. Its incidence is unknown, but it has a higher frequency in males (ratio: 1.4:1) (1, 2). Its exact pathophysiological mechanism



is poorly understood. JXG lesions may be cutaneous or extracutaneous with systemic involvement (1, 2). Involvement of the central nervous system with fatal outcome has also been reported (3). In our case, abdominal-US excluded systemic manifestations. Cutaneous lesions most frequently involve the head and neck, the trunk and, less frequently, the limbs (2). They are generally self-involuting and usually treatment is not necessary (1). The majority of patients undergo a diagnostic surgical excision, and no recurrent case is known in the literature (2). The common US appearance includes a well-defined hypoechoic solitary mass, without vascular flow. On MRI, JXG typically appears isointense to hyperintense on T1, and isointense to hypointense on T2-weighted images (4). Clinical and radiological features may vary, and biopsy may be needed (1). Pediatricians, pediatric surgeons and radiologists should be aware of this pathological entity, and be able to differentiate it from other soft-tissue tumors. Abdominal-US can detect possible systemic involvement, and a biopsy will confirm the diagnosis.

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

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

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## Hysterosalpingogram after Two Deliveries within Twenty-Seven Days

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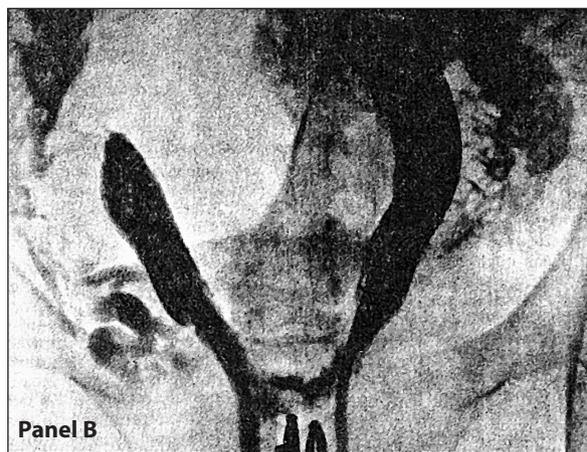
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### To the Editor

We would like to increase the visibility of an interesting hysterosalpingogram published in the article “Rare manner of birth in a twin pregnancy” written by Jovanović and Petrović published in *Acta Medica Saliniana* in 1972 (1). The authors also published a feedback on the aforementioned paper (2). A 36-year-old multipara was admitted to hospital in 1972, seventeen days after she gave birth to the second newborn. Two deliveries were twenty-seven days apart and both newborns were mature and healthy (Panel A). Her pregnancy, as well as the deliveries, was not under the medical supervision. According to the patient’s calculation, the first newborn was delivered on time. The newborns were of different sexes, first newborn being female. The hysterosalpingography was performed seventeen days after the second delivery and the hysterosalpingogram (Panel B) shows a double uterus as well as a septate uterine cervix with two cervical channels, each connected to a separate uterus. This is consistent with uterus didelphys, a type of paramesonephric (Müllerian) duct anomaly (3). The difference in size of the uterine cavities is evident and is in accordance with the data that deliveries happened twenty-seven days apart, so the involutory changes of the uterus were at different stages when diagnostics were performed. The woman and both babies were discharged from hospital healthy and stable.



**Authors’ Contributions:** Both the authors contributed equally to this article.

**Conflict of Interest:** Authors declare that HT is a member of the Editorial Team of the *Acta Medica Academica*. There are no other conflicts of interest to disclose.

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## The Influence of Different Risk Factors on COVID-19 Outcomes in Adult Patients - An Observational-Descriptive Study

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### Abstract

**Objective.** The aim of our study was to investigate the predictors of morbidity (age, gender, smoking habits, obesity and the presence of chronic diseases) and COVID-19 outcomes. **Subjects and Methods.** The research was an observational descriptive study, conducted at The Family Medicine Education Center, The Primary Health Care Center, Banja Luka, in the period from 26<sup>th</sup> June to 31<sup>st</sup> December 2020. During the research period, seven family medicine teams followed their patients with COVID-19, and recorded possible predictors for morbidity and their influence on the disease outcome. **Results.** The study included 934 patients, 46.90% of whom were male. The majority of subjects were non-smokers and overweight. Diabetes was found in 5.57% patients, hypertension in 29.44%, chronic respiratory diseases in 5.25%, cancer in 4.39% patients. In the observed sample, 29.23% subjects contracted pneumonia, 18.52% were hospitalized, while 19 (2.03%) patients with severe clinical features had a fatal outcome. Multivariable regression analysis showed a high risk of pneumonia in male patients [OR=2.45, 95% CI (1.73-3.46)], elderly [OR= 1.07, 95% CI (1.06-1.09)] and obese patients with Body Mass Index  $\geq 30.0$  kg/m<sup>2</sup> [OR=2.55, 95% CI (1.73-3.77)]. Male gender [OR=2.19, 95% CI (1.11-4.31)], older age [OR=1.08, 95% CI (1.05-1.11)] and hypertension [OR=2.51, 95% CI (1.06-5.91)] were the most important predictors for the development of severe clinical features in COVID 19. The statistically significant predictors of mortality were male gender [OR=7.16, 95% CI (1.56-32.86)] and older age [OR=1.12, 95% CI (1.06-1.18)]. **Conclusion.** Being familiar with the predictors of morbidity and poor outcome in COVID-19 is helpful for carrying out preventive measures, early diagnosis and treatment of risk groups of patients.

**Key Words:** COVID-19 ■ Risk Factors ■ Comorbidity.

### Introduction

The pandemic caused by Severe Acute Respiratory Syndrome Coronavirus -2 (SarsCoV-2 virus) started in December 2019 in the Chinese city Wuhan, and gradually spread to countries around the world (1). This new coronavirus causes the disease Corona Virus Disease 2019 (COVID-19) (2). The World Health Organization (WHO) declared this outbreak a global pandemic on 11<sup>th</sup> March 2020 due to the rapid increase in the number of cases all around the world (3). The symptoms are mild in the majority of infected persons but a small number of infected persons can develop severe clinical

features, with severe pneumonia, or potentially Acute Respiratory Distress Syndrome (ARDS), or other organ failure can occur, and the disease can have a fatal outcome (4).

At the beginning of the pandemic it was not known what the potential risk groups for COVID-19 were, nor what risk groups of patients would develop severe or potentially life threatening forms of the disease. As the pandemic spread, researchers worldwide identified the persons at higher risk for the infection and for developing severe or potentially life threatening forms of the disease. For instance, Alqahtani at al. reported that patients with chronic obstructive pulmonary

disease (COPD) were at higher risk of developing severe clinical features and a high mortality rate compared to patients without COPD (5). Also smokers and former smokers were at higher risk of developing COVID-19 complications and had a higher mortality rate (5).

A meta-analysis that investigated the prevalence and risk factors associated with COVID-19 mortality reported a significant correlation between mortality and older age (> 65 years), male gender, patients treated in Intensive Care Units (ICU), obesity, hypertension, diabetes, cardiovascular diseases and cancer (6). Diabetic patients with COVID-19 pneumonia had worse treatment outcomes that manifest as increased mortality, severe clinical features, more frequent occurrence of ARDS, and disease progression (7). Patients with hypertension and COVID-19 pneumonia have worse treatment outcomes overall. Pranata et al. found in their research that patients with hypertension had a higher mortality rate, severe forms of COVID-19, more frequent ICU admission, and more frequent disease progression (8). The presence of cardiovascular and cerebrovascular diseases is also related to worse COVID-19 outcome (9).

The studies reported that patients with cancer were more likely to contract COVID 19, and had more severe forms of the disease and higher mortality (10). The results of a large number of studies showed a strong correlation between morbidity and poor treatment outcome in overweight or obese persons that contracted COVID-19 (11, 12).

The aim of our study was to investigate the influence of age, gender, smoking habits, obesity and the presence of chronic diseases (diabetes, hypertension, chronic respiratory diseases, cancer) in adult patients, on the severity of COVID-19 clinical features and outcomes.

## Subjects and Methods

The research was an observational descriptive study, conducted at The Family Medicine Education Center, The Primary Health Care Center, Banja Luka. The patients were included in the period from 26<sup>th</sup> June to 30<sup>st</sup> November 2020 and all

patients were followed up for one month. During the follow-up, data on disease severity, pneumonia and death were collected. During the research period, seven family medicine teams followed their patients with COVID-19. Each physician registered patients infected with virus SarsCoV-2. For further follow-up and analysis, only patients with COVID-19 confirmed by PCR (polymerase chain reaction) were taken into account. PCR test was administrated to almost all symptomatic patients. Laboratory testing was performed in two microbiological laboratories: at the Clinical Centre of the Republic of Srpska or in the Public Health Institute of the Republic of Srpska.

## Subjects

The study included 934 patients with COVID-19. All the subjects were examined for the first time at The Outpatient Department for Acute Respiratory Diseases, The Primary Health Care Center, Banja Luka. The data from those examinations were recorded in electronic medical records, so that they are available to the subjects' family physicians. On the basis of all the available data for each subject, the severity of clinical features was estimated (mild, moderate and severe). The estimation of the severity of clinical features was performed according to the recommendations from "The Manual for Treating the Infection Caused by the Novel Coronavirus", published by The Faculty of Medicine in Banja Luka.

According to the severity of clinical features, the subjects were classified into three groups using the following criteria:

- Mild cases: They have mild clinical features of uncomplicated infection. Possible symptoms are mild fever, headache, nasal congestion, malaise, loss of smell and taste, and myalgia.
- Moderate cases: Symptoms such as high or long-term fever, weakness, malaise, shortness of breath, cough, chest x-ray showing signs of incipient pneumonia. The patient does not need supplemental oxygen therapy.
- Severe cases: The patients have bilateral pneumonia with at least one of the following signs: severe dyspnea, tachypnea with respiration rate

>30/minute, respiratory failure or the necessity for supplemental oxygen therapy (SaO<sub>2</sub> on room air is <90%), or other organ failure (13).

The majority of patients with pneumonia included in the study, had bilateral pneumonia, confirmed by lung X-ray or low-dose chest CT findings. All our patients with fatal outcome, died in hospital. Family doctors had discharge from the hospital in which the first diagnosis was COVID-19, as a cause of death.

### **Measuring**

For the purpose of the study, the following data from electronic medical records were used:

- Data about confirmed diagnosis of pneumonia, hospitalization and fatal outcome (all-cause mortality)
- Additional parameters: age, gender, Body Mass Index (BMI), smoking status and the presence of chronic diseases (diabetes mellitus, chronic respiratory diseases, hypertension, cancer).

In estimating the severity of clinical features, other medical documentation was also used: specialist medical reports, hospital discharge summaries, low-dose chest CT findings, laboratory findings.

In relation to the BMI levels, all the patients were divided into three groups: patients with BMI < 25.0 kg/m<sup>2</sup> i.e. patients with ideal body weight; patients with BMI from 25.0 to 29.9 kg/m<sup>2</sup> i.e. the group of pre-obese patients; and patients with BMI ≥30.0 kg/m<sup>2</sup> i.e. the group of obese persons.

In relation to smoking status, patients were divided into groups of smokers, non-smokers and ex-smokers. Smokers are defined as persons who consume tobacco or tobacco products every day. Ex-smokers are defined as people who have not smoked for at least 6 months or longer (6). In statistical data processing, ex-smokers and non-smokers were classified into one group and viewed as non-smokers compared to current smokers.

### **Ethical Statement**

The written consent of the director and the Ethics Committee of the Primary Health Care Cen-

ter (Number: 01-592-1, 18.06.2020.), Banja Luka was obtained for conducting this research. The research was conducted in accordance with the Declaration of Helsinki.

### **Statistical Analysis**

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) Version 25. Descriptive statistics were presented as the mean plus standard deviation, or median plus interquartile range, based on the distribution determined by the Kolmogorov-Smirnov test. The difference in means was evaluated by the Student t-test and ANOVA in the case of normal distribution, or by the Mann Whitney U test in the case of non-normal distribution. The independent predictors of the severity of clinical features and mortality were identified using univariable and multivariable logistic regression analysis. In the analytical methods applied, the level of significance was P<0.05.

### **Results**

Out of the total of 934 patients with COVID-19 included in this study, 46.90% were male. The average age of patients with mild clinical features was 40.22±15.23 years, while the average age of patients with severe clinical features was 65.40±11.82 years. The majority of patients included in our study, 675 (72.27%), were non-smokers. In relation to BMI, the smallest number of patients (18.95%) were obese with BMI ≥30.0 kg/m<sup>2</sup>. In our group of subjects, 133 patients were health care professionals, and they mostly had mild clinical features. Among our subjects, in relation to the comorbidities present, there were 5.57% patients with diabetes, 29.44% patients with hypertension, 5.25% patients with chronic respiratory diseases (asthma, chronic obstructive lung disease), and 4.39% patients with cancer.

In the observed sample of patients, 29.23% subjects contracted pneumonia, 18.52% subjects were hospitalized, while 19 (2.03%) subjects with severe clinical features had fatal outcomes (Table 1).

Table 1. The Characteristics of Patients with COVID 19

Variable	Clinical features			P <sup>†</sup>	Total N (%)
	Mild N (%)	Moderate N (%)	Severe N (%)		
<b>Gender</b>					
Male	250 (38.94)	151 (62.92)	37 (71.15)	<0.001	438 (46.90)
Female	392 (61.06)	89 (37.08)	15 (28.85)		496 (53.10)
Total	642 (100)	240 (100)	52 (100)		934 (100)
Age ( $\bar{x} \pm SD$ )	40.22±15.23	54.90±13.48	65.40±11.82	<0.001	-
<b>Smoking status</b>					
Smoker	128 (19.94)	31 (12.92)	8 (15.39)	0.001	167 (17.88)
Non-smoker	463 (72.12)	180 (75.00)	32 (61.53)		675 (72.27)
Former smoker	51 (7.94)	29 (12.08)	12 (23.08)		92 (9.85)
Total	642 (100)	240 (100)	52 (100)		934 (100)
<b>BMI<sup>‡</sup></b>					
<25	314 (48.91)	44 (18.33)	8 (15.38)	<0.001	366 (39.19)
25-30	253 (39.41)	116 (48.33)	22 (42.31)		391 (41.86)
≥30	75 (11.68)	80 (33.34)	22 (42.31)		177 (18.95)
Total	642 (100)	240 (100)	52 (100)		934 (100)
<b>Healthcare professionals</b>					
Yes	106 (16.51)	26 (10.83)	1 (1.92)	0.003	133 (14.24)
No	536 (83.49)	214 (89.17)	51 (98.08)		801 (85.76)
Total	642 (100)	240 (100)	52 (100)		934 (100)
<b>Diabetes</b>					
Yes	17 (26.48)	27 (11.25)	8 (15.39)	<0.001	52 (5.57)
No	625 (73.52)	213 (88.75)	44 (84.61)		882 (94.43)
Total	642 (100)	240 (100)	52 (100)		934 (100)
<b>Hypertension</b>					
Yes	120 (18.69)	113 (47.08)	42 (80.77)	<0.001	275 (29.44)
No	522 (81.31)	127 (52.92)	10 (19.23)		659 (70.56)
Total	642 (100)	240 (100)	52 (100)		934 (100)
<b>Asthma, COPD<sup>§</sup></b>					
Yes	27 (4.21)	17 (7.08)	5 (9.62)	0.081	49 (5.25)
No	615 (95.79)	223 (92.92)	47 (90.38)		885 (94.75)
Total	642 (100)	240 (100)	52 (100)		934 (100)
<b>Cancer</b>					
Yes	25 (38.94)	10 (4.17)	6 (11.54)	0.034	41 (4.39)
No	617 (61.06)	230 (95.83)	46 (88.46)		893 (95.61)
Total	642 (100)	240 (100)	52 (100)		934 (100)
<b>Pneumonia</b>					
Yes	6 (0.94)	215 (89.58)	52 (100)	<0.001	273 (29.23)
No	636 (99.06)	25 (10.42)	0 (0)		661 (70.77)
Total	642 (100)	240 (100)	52 (100)		934 (100)
<b>Hospitalization</b>					
Yes	7 (1.09)	114 (47.50)	52 (100)	<0.001	173 (18.52)
No	635 (98.91)	126 (52.50)	0 (0)		761 (81.48)
Total	642 (100)	240 (100)	52 (100)		934 (100)
<b>Fatal outcome</b>					
Yes	0 (0)	0 (0)	19 (36.54)	<0.001	19 (2.03)
No	642 (100)	240 (100)	33 (63.46)		915 (97.97)
Total	642 (100)	240 (100)	52 (100)		934 (100)

†One-Way ANOVA; ‡Body Mass Index; §Chronic Obstructive Pulmonary Disease.

Table 2. The Predictors for Pneumonia Onset in COVID 19 Patients

Variable	Logistic regression			
	Univariable		Multivariable	
	OR (95% CI)*	P†	OR (95% CI)*	P†
Male vs. Female	2.70 (2.02-3.62)	<0.001	2.45 (1.73-3.46)	<0.001
Age (years)	1.08 (1.06-1.10)	<0.001	1.07 (1.06-1.09)	<0.001
Smoker vs. Former smoker + Never smoker	0.64 (0.43-0.95)	0.027	0.69 (0.44-1.08)	0.101
BMI‡ ≥30 vs. BMI<30	4.13 (2.93-5.80)	<0.001	2.55 (1.73-3.77)	<0.001
Health care workers vs. Non-health care workers	0.46 (0.29-0.74)	0.001	0.72 (0.43-1.23)	0.230
Diabetes (Yes vs. No)	3.59 (2.03-6.34)	<0.001	0.81 (0.41-1.60)	0.550
Hypertension (Yes vs. No)	4.86 (3.58-6.60)	<0.001	1.02 (0.67-1.55)	0.937
Asthma, COPD§ (Yes vs. No)	1.88 (1.05-3.38)	0.034	1.39 (0.68-2.87)	0.371
Cancer (Yes vs. No)	1.42 (0.74-2.73)	0.292	-	-

\*Odds ratio (95% Confidence interval); †Statistically significant at P<0.05; ‡Body Mass Index; §Chronic Obstructive Pulmonary Disease.

In our study, the factors that contributed to the onset of pneumonia in patients with COVID-19 were analyzed. Therefore, the univariable regression analysis showed that male gender [OR=2.70, 95% CI (2.02-3.62)], older age [OR=1.08, 95% CI (1.06-1.10)], non-smokers [OR=0.64, 95% CI (0.43-0.95)], obesity with BMI ≥30.0 kg/m<sup>2</sup> [OR=4.13, 95% CI (2.93-5.80)], non-health care profession [OR=0.46, 95% CI (0.29-0.74)], diabetes [OR=3.59, 95% CI (2.03-6.34)], hypertension [OR=4.86, 95% CI (3.58-6.60)] and pulmonary diseases [OR=1.88, 95% CI (1.05-3.38)] were risk factors for the occurrence of pneumonia in COVID-19 (Table 2). The multivariable regression analysis showed that male patients [OR=2.45, 95% CI (1.73-3.46)], older patients [OR=1.07, 95% CI (1.06-1.09)] and obese patients with BMI ≥30.0 kg/m<sup>2</sup> [OR=2.55, 95% CI (1.73-3.77)] (Table 2) had a high risk for pneumonia.

In our sample of 934 patients with COVID-19, the predictors of the development of severe clinical features were analyzed (Table 3). The univariable regression analysis showed that the predictors of severe clinical features of COVID-19 were male gender [OR=2.96, 95% CI (1.60-5.47)], older age [OR=1.10, 95% CI (1.07-1.13)], obesity with BMI ≥30.0 kg/m<sup>2</sup> [OR= 3.44, 95% CI (1.93-6.12)], non-health care profession [OR=0.11, 95% CI (0.06-0.81)], presence of diabetes [OR=3.46, 95%

CI (1.54-7.80)], hypertension [OR=11.69, 95% CI (5.77-23.69)] and cancer [OR=3.16, 95% CI (1.26-7.89)]. The predictors of severe clinical features were analyzed using multivariable regression analysis which showed that male gender [OR=2.19, 95% CI (1.11-4.31)], older age [OR=1.08, 95% CI (1.05-1.11)] and hypertension [OR=2.51, 95% CI (1.06-5.91)] were the most important predictors of the development of severe clinical features in COVID-19 in our group of subjects (Table 3).

Out of the 934 patients included, 19 (2.03%) had fatal outcomes. The predictors of all-cause mortality were analyzed using univariable and multivariable logistic regression analysis (Table 4). The univariable regression analysis showed that the statistically significant predictors of all-cause mortality were: male gender [OR=9.97, 95% CI (2.29-43.42)], older age [OR=1.15, 95% CI (1.10-1.20)], the presence of hypertension [OR=46.09, 95% CI (6.12-347.01)] and cancer [OR=4.33, 95% CI (1.21-15.49)]. The multivariable logistic regression analysis showed that the statistically significant predictors of all-cause mortality were male gender [OR=7.16, 95% CI (1.56-32.86)] and older age [OR=1.12, 95% CI (1.06-1.18)] (Table 4).

No multicollinearity was found in Tables 1 to 3, in which a tolerance score ranged from 0.630 to 0.967 and a variance inflation factor ranged from 1.034 to 1.607.

Table 3. The Predictors of Severe Clinical Features

Variable	Logistic regression			
	Univariable		Multivariable	
	OR (95% CI)*	P†	OR (95% CI)*	P†
Male vs. Female	2.96 (1.60-5.47)	0.001	2.19 (1.11-4.31)	0.023
Age (years)	1.10 (1.07-1.13)	<0.001	1.08 (1.05-1.11)	<0.001
Smoker vs. Former smoker + Never smoker	0.83 (0.38-1.79)	0.629	-	-
BMI‡ ≥30 vs. BMI‡ <30	3.44 (1.93-6.12)	<0.001	1.85 (0.97-3.52)	0.062
Health care workers vs. Non-health care workers	0.11 (0.06-0.81)	0.030	0.25 (0.03-1.88)	0.177
Diabetes (Yes vs. No)	3.46 (1.54-7.80)	0.003	0.72 (0.29-1.78)	0.477
Hypertension (Yes vs. No)	11.69 (5.77-23.69)	<0.001	2.51 (1.06-5.91)	0.036
Asthma, COPD§ (Yes vs. No)	2.03 (0.77-5.35)	0.154	-	-
Cancer (Yes vs. No)	3.16 (1.26-7.89)	0.014	1.45 (0.51-4.11)	0.487

\*Odds ratio (95% Confidence interval); †Statistically significant at P<0.05; ‡Body Mass Index; §Chronic Obstructive Pulmonary Disease.

Table 4. The Predictors of Mortality in COVID 19 Patients

Variable	Logistic regression			
	Univariable		Multivariable	
	OR (95% CI)*	P†	OR (95% CI)*	P†
Male vs. Female	9.97 (2.29-43.42)	0.002	7.16 (1.56-32.86)	0.011
Age (years)	1.15 (1.10-1.20)	<0.001	1.12 (1.06-1.18)	<0.001
Smoker vs. Former smoker + Never smoker	1.23 (0.40-3.76)	0.716	-	-
BMI‡ ≥30 vs. BMI‡ <30	1.14 (0.38-3.49)	0.813	-	-
Health care workers vs. Non-health care workers	0.02 (0.00)	0.989	-	-
Diabetes (Yes vs. No)	3.31 (0.93-11.76)	0.064	0.48 (0.12-1.97)	0.309
Hypertension (Yes vs. No)	46.09 (6.12-347.01)	<0.001	6.43 (0.77-54.01)	0.087
Asthma, COPD§ (Yes vs. No)	1.00 (0.13-7.67)	0.997	-	-
Cancer (Yes vs. No)	4.33 (1.21-15.49)	0.024	1.94 (0.45-8.33)	0.374

\*Odds ratio (95% Confidence interval); †Statistically significant at P<0.05; ‡Body Mass Index; §Chronic Obstructive Pulmonary Disease.

## Discussion

The results of our study showed that the majority of patients with COVID-19 were female, non-smokers and overweight patients. The severity of clinical features increased with age, therefore the majority of patients with severe clinical features were older than 65 years. The multivariable regression analysis identified male gender, older age and obesity (with BMI ≥30.0 kg/m<sup>2</sup>) as the main predictors for pneumonia onset; male gender, older age and comorbidity hypertension as the main predictors for severe clinical features onset, while

the most important predictors of all-cause mortality were male gender and older age.

Regarding gender, the results of other studies have shown that both genders can develop the disease almost equally, however, the clinical features and outcome of the disease were worse in male patients (14). Although our study showed that in the sample of subjects with more female patients, the male patients had more severe clinical features and higher mortality rate compared to the female patients. The authors explain the differences in the severity of the clinical features and mortality between the male and female patients by the differ-

ences in the expression of angiotensin-converting enzyme-2 and increased immune responses (15).

SarsCov-2 virus infection has a considerably greater health impact on the elderly (>65 years). The elderly have worse disease prognosis, and the outcome of the disease is worse in patients with more comorbidities (16). The results of our study were similar to those published in other studies (17). Therefore, our older subjects also had statistically significantly more pneumonia present, severe clinical features and high all-cause mortality compared to younger subjects. Although the majority of authors have reported that smoking is a considerable risk factor for severe clinical features in COVID-19, the data from different studies are contradictory. Some authors found that smoking has a considerable impact on the development of the severe clinical features and poor outcomes of COVID-19 (18, 19). In our study, the majority of patients were non-smokers, and no statistically significant influence of smoking on the onset of severe clinical features and pneumonia, or increased mortality in active smokers was verified. Özdemir et al. report in their study that being a non-smoker is an independent risk factor for the development of pneumonia, which is not in accordance with the results of our study (20). Lippi et al. reported in their meta-analysis that active smoking is not associated with severity of coronavirus disease 2019 (21).

The majority of investigators report that almost all age groups can contract COVID-19, but severe clinical features develop in older patients, and in patients with cardiovascular comorbidities and chronic respiratory diseases (22). However, numerous studies have stressed the important role of obesity in poor disease outcome, including fatal outcomes in obese patients (23). Obesity is related to poor disease outcome through several mechanisms, but the most emphasized is the influence of chronic inflammation, oxidative stress and impaired immune response in these patients (24). Our study, using univariable regressive analysis, showed that obesity with BMI  $\geq 30$  kg/m<sup>2</sup>, is a statistically significant predictor of severe clinical forms that include the onset of pneumonia, but not for fatal outcomes of the disease. Pongpirul et al. found that

obesity was independent risk factor for COVID-19 pneumonia, what is in accordance with the results of our study (25). If obesity is related to other risk factors, such as smoking (26) or diabetes (27), the risk of development of severe clinical features and fatal outcomes increases even more.

Numerous investigators have shown that diabetes is significantly related to the development of severe clinical features, and increases the possibility of fatal outcome in patients with COVID-19 (28). In our sample of subjects, 5.57% had diabetes as a comorbidity. The results obtained using univariable regressive analysis in our patients showed that diabetes is a predictor of the onset of pneumonia and severe clinical features, but this was not confirmed using multivariable regressive analysis. Interestingly enough, the odds ratio changed direction and went from “predictor” in univariate regression (Table 3) to “protector” in multivariate regression. This may be due to potential confounders which were not assessed by our analysis.

The majority of authors indicate that chronic respiratory diseases (Asthma, Chronic Obstructive Pulmonary Disease) are predictors of severe clinical features in COVID-19 (29), while other studies (30) found that chronic respiratory diseases are not predictors of severe clinical forms, hospitalization in ICU or fatal outcome due to SarsCov-2 infection. Our study showed that asthma and COPD are not predictors for the onset of pneumonia and development of severe clinical features with fatal outcome in patients, using multivariable regressive analyses.

Patients with hypertension are at greater risk for SarsCov-2 virus infection and severe clinical features (8), and these patients, when they contract COVID-19, are at greater risk of a fatal outcome. Similar results were confirmed in our study. We found that hypertension was a predictor for development of severe clinical features in patients with COVID-19.

The majority of authors report that patients with cancer are at greater risk of contracting COVID-19, with the explanation that their immune system is weakened due to the underlying disease and the aggressive treatment they are receiving,

and they are susceptible to severe forms of the disease (31, 32, 6). However, the results of a meta-analysis (Wang et al.) showed that the independent risk factors related to COVID-19 were hypertension, diabetes, chronic obstructive pulmonary disease, cardiovascular and cerebrovascular diseases, while no correlation was found between an increased risk for the disease among patients with liver disease, kidney disease and cancer (33). The results of our study are similar to the results of Wang's study and showed that the presence of cancer is not associated with higher odds of severe clinical features and all-cause mortality.

### **Limitation of the Study**

In conducting this study, we did not examine the patients personally, but the data used in the study were obtained from the existing medical documentation. We included in the study patients, registered by seven family medicine teams in the city of Banja Luka, Bosnia and Herzegovina. Consequently, we cannot be sure that the results are representative for the whole country. Most patients from the urban area were included in the study. We did not examine possible differences between patients from urban and rural areas. Due to observational nature of the study, potential confounding variables could not be excluded. The aim of the study was to assess independent predictors of pneumonia, severe clinical feature as well as all-cause mortality. Therefore, the strength of the association (odds ratio) could not be interpreted because it is possible that some of them do not represent a total effect rather than a partial effect, i.e. an effect that does not go through the mediators.

### **Conclusion**

Our study indicated the important predictors of COVID-19 morbidity, and also the predictors for the development of pneumonia, or severe clinical features and mortality. It appeared that older age, male gender and obesity were predictors for the onset of severe clinical features and mortality in patients with COVID-19, but regarding smoking

habits, no evidence was found to support a connection. In relation to comorbidities present, hypertension appeared to be an important predictor for the development of severe clinical features.

#### **What is Already Known on This Topic:**

*COVID19 is a new and poorly known disease. Furthermore, risk factors contributing to COVID- 19 morbidity, severe clinical forms of the disease and mortality are poorly known.*

#### **What This Study Adds:**

*This study identified frequent risk factors in the observed population of patients with COVID-19 at The Primary Health Care Center, Banja Luka.*

**Authors' Contributions:** All authors contributed equally to the article.

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

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## Forms and Frequency of Sanctions against General Practitioners and Family Medicine Specialists in Macedonia

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### Abstract

**Objective.** The goal of this study is to evaluate the reasons for sanctioning and the types of sanctions used on general medicine primary healthcare practitioners (GM-PHPs) in the Republic of Macedonia. **Materials and Method.** This is a cross-sectional study for which we used an anonymous survey. This survey was distributed in a printed and electronic form to GM-PHPs in different parts of Macedonia and 438 of them responded. We used the SPSS statistical program to process the quantitative data. **Results.** The GM-PHPs' sex was not associated with the sanctioning in the univariable analysis, but it was in the multivariable. GM-PHPs with  $\geq 30$  years of experience have 8.7 times higher odds to be sanctioned than those with  $\leq 5$  years of experience. GM-PHPs that worked in the hospital or  $\leq 19$  km from the nearest hospital were significantly more frequently sanctioned. The most common three reasons for sanctioning were: "Financial consumption of prescriptions and referrals above the agreed amount", "Higher rate of sick leaves and/or unjustified sick leaves" and "Unrealized preventative goals or education". "Financial sanction by scale" was the most common type of sanction - 49.8% of participants. GM-PHPs who followed the guidelines, but were exposed to violence by patients or their family/companion were sanctioned significantly more frequently. **Conclusions.** In our sample, we can observe that in the univariable analysis age, years of experience, family medicine speciality, the distance of the workplace from the nearest hospital and violence are associated with sanctioning. In the multivariable analysis: sex, years of experience, the distance of the workplace from the nearest hospital and violence are associated with sanctioning. The majority of sanctions were financial sanctions (84.5%).

**Key Words:** Sanctions ■ Primary Healthcare ■ Family Medicine ■ Financial Control ■ General Practitioners.

### Introduction

The Republic of Macedonia, after becoming independent in 1991, underwent thorough reforms in the healthcare system. Previously, in the Socialist Federal Republic of Yugoslavia (SFRY), the healthcare system was state-owned. What made the Yugoslavian healthcare system unique in Eastern Europe was the implementation of Andrija Štampar's ideas in the 1920s. According to Štampar's model, the healthcare system had community-oriented primary health care and was funded from compulsory social insurance contributions (1–3). This model became a national policy after World

War II, however, the organizational and financing models at the primary level have changed in the independent countries after the breakup of Yugoslavia (1, 3). After Macedonia became independent, in the period from 1991 to 2005, there was an intensive transformation of primary health care from public to private. In this process, the Ministry of Health (MoH) and the Health Insurance Fund (HIF) of the Republic of Macedonia were involved, and through them the users of the health services as well as the public health institutions from the primary health care. Primary healthcare practitioners (PHPs) working in public health care were required to open private practices and enter

into a contract with the HIF on a capital model. Privatization was completed in 2007 (4–8). Despite the fact that we have gone through these changes, what has remained the same, and at the same time a problem for other countries that were previously part of the SFRY, is the system of regulation which is through sanctions.

To clarify the description of the organisation of primary health care, we constructed a diagram showing the interconnections between the bodies involved in that system (Figure 1). MoH assesses the organizational set-up of the institutions in the system and the need for restructuring processes and/or the establishment of new institutions and activities and monitors the efficiency of the HIF. Primary health care consists of five separate activities: general medicine, occupational medicine, child/pediatric health care (0-6 years), school medicine (pupils and young people aged 7 to 19) and women's health care (obstetrics and gynaecology) (5, 9). General medicine primary healthcare practitioners (GM-PHPs) in Macedonia consist of general practitioners (GPs) and family medicine

specialists (FMSs). GPs are physicians that finished 6 years of integrated studies in general medicine. The family medicine speciality is relatively new, being introduced and implemented in the programs for specialization and additional education on the Medical faculty of the University Ss. Cyril and Methodius in Skopje in 2009. The studies last 3 years and are self-funded (9, 10).

The GM-PHPs are paid by the HIF for their services: 70% of the monthly fee is the basic capitation that depends on the number and age of the insured and 30% of the monthly fee is meeting the goals depending on the amount of achievement. According to the law, GM-PHPs provide general medical services, prescription of drugs, issuance of referrals for specialist outpatient services, issuance of referrals for hospital treatment, issuance of sick leaves lasting up to 7 days or up to 15 days only after a recommendation from a specialist doctor (11–13). The MoH controls and regulates the work of health workers in primary health care through the State Health and Sanitary Inspectorate and the HIF. The control performed by the HIF in the

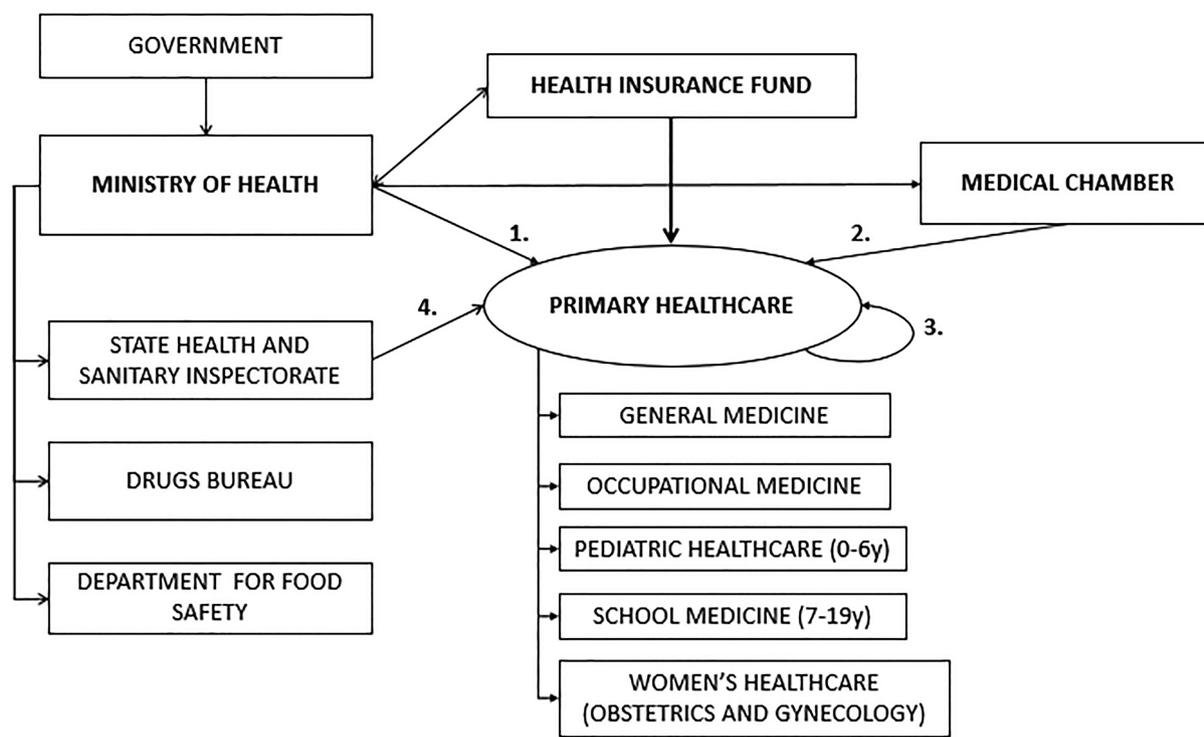


Figure 1. Regulatory Bodies responsible for controlling the work of primary healthcare practitioners.

health institution at the primary level is regulated through Article 31 of the contract that the primary healthcare institutions conclude with the HIF. The health institution is obliged at any time to provide the authorized persons for control of the Fund with insight and control in their entire operation (11, 12). The HIF controls the GM-PHPs on the following: prescription of medication and orthopaedic aids, casts and supports according to the HIF guidelines, achieving preventative goals, attending specific medical education, issuing referrals and sick leaves according to the HIF guidelines, delivering computer and paper documentation as well as other administrative work. They also review purchase reports for the medication and their expiration dates as well as the availability of mandatory ampule medication. The HIF obliges GM-PHPs to send monthly and yearly financial reports. Based on the capitation points they determine a certain financial amount the GM-PHPs can spend for certain medications in one health institution (11, 12).

There are four types of supervision over the work of PHPs in general (Figure 1) (13, 14):

1. Supervision over the legality of the work – performed by the MoH, as regular supervision in

accordance with the annual program and as needed or at the proposal of the HIF, the relevant chamber, state body, association and citizen.

2. Supervision over the professional work - performed by the Medical, Dental and Pharmaceutical Chamber in accordance with the annual plan.
3. Internal supervision over the professional work - performed by the director of the institution.
4. Inspection supervision - performed by the State Sanitary and Health Inspectorate.

According to Article 182 of the Law on Health Care of the Republic of Macedonia, the healthcare professional can be sanctioned with a public admonition, financial sanction and termination of employment depending on the severity of the violation – disciplinary misconduct (minor violation) and disciplinary offence (major violation) (13, 14). If the GM-PHP violates some of the provisions of the contract he has concluded with the HIF, according to Article 35 he pays a contractual penalty or receives an admonition. Depending on the type of violation, there are different sanctions: admonition before a contractual penalty, a contractual

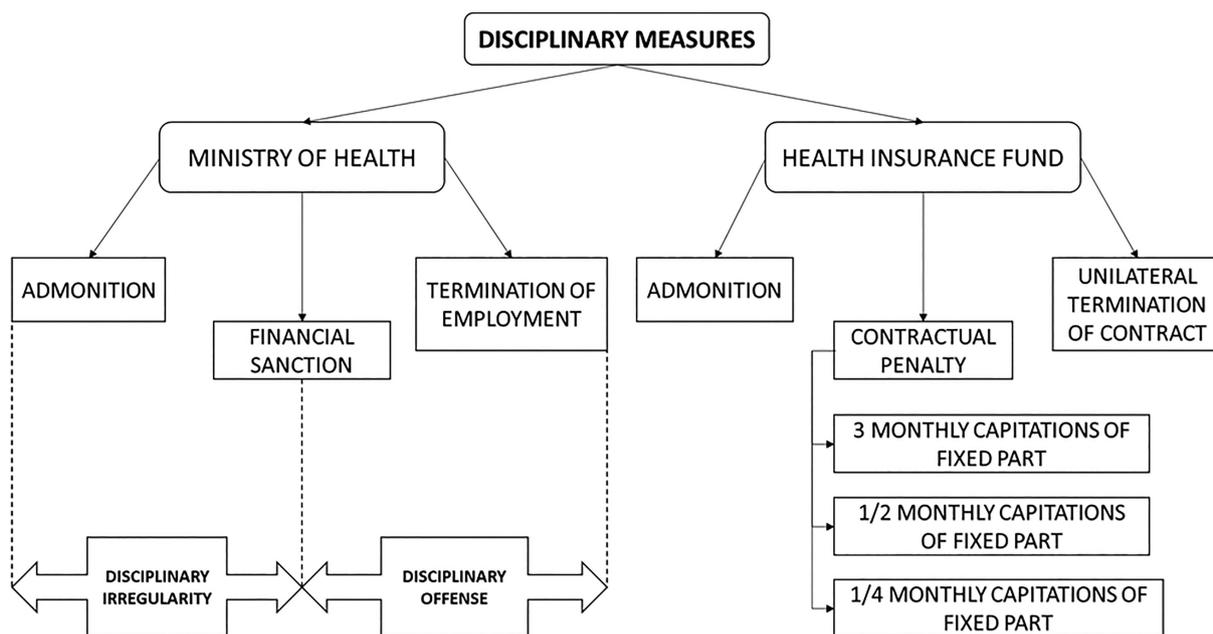


Figure 2. Disciplinary measures taken by the Ministry of Health and the Health Insurance Fund.

penalty in the amount of 3 monthly capitations of fixed part, a contractual penalty in the amount of ½ monthly capitations of fixed part and contractual penalty in the amount of ¼ monthly capitations of fixed part. There is also a possibility of unilateral termination of the contract (Figure 2) (11–13).

Currently, in Macedonia, there are no financial incentives for the good performance of GM-PHPs. The only undertaken stimulating measure is a special financing scale for GM-PHPs that work in rural areas and have less than 1800 capitation points. This tool was used to stimulate physicians to work in less populated areas (11). The different types of sanctions are the only form of regulation.

The aim of this study is to describe the types of sanctions, the reasons for sanctioning as well as the relationship between sanctioning and various demographic factors among GM-PHPs which include general practitioners (GPs) and family medicine specialists (FMSs). Additionally, we also want to see whether GM-PHPs experienced violence by patients or their relatives if they followed the HIF guidelines, and if there is a relationship between sanctions and violence by the patient and/or their family/companion when the GM-PHPs followed the HIF guidelines.

## Materials and Methods

### *Study Design, Study Population, Timeframe and Data Collection*

This study is cross-sectional and it was conducted in the form of a survey. The survey was compiled by the Association of General Practitioners and Physicians of Family Medicine of Southeast Europe (AGP/FM SEE) and additionally adapted for Macedonia.

Our target population was GM-PHPs – specifically GPs and FMSs. The survey was anonymous, randomly distributed in printed and electronic form in the period between November 2017 and March 2018. The survey was distributed with the help of the Center of Family Medicine and the Association of Residents and Young Physicians of Macedonia. We distributed 202 surveys in printed

form to GM-PHPs through the Center of Family Medicine, of which 197 were answered. The electronic survey was shared on an online platform of the Association of Residents and Young Physicians of Macedonia that is used by GM-PHPs. The electronic survey was filled by 241 GM-PHPs. In total, we received 438 filled surveys.

### *Survey*

The survey contained 6 multiple-choice, 5 dichotomous and 1 mixed question. The data collected for descriptive statistics included: sex, age, family medicine speciality, years of experience working in primary health care, population count in the area of the workplace and its distance from the nearest hospital. Questions about sanctioning included: whether they have ever been sanctioned, the type of sanction and whether their salary has been reduced due to the sanction. There were also questions about whether physicians that followed the HIF guidelines, experienced pressure or violence by their patients or the patients' family/companions, and if so, what type of violence it was (verbal, physical or both). The mixed question was about the reason for sanctioning, where participants could choose one or more from the listed reasons or add their own option if it wasn't available.

### *Statistical Analysis*

We used the SPSS statistical program to process the data. Categorical variables were represented by distribution frequencies. In order to test the differences between the compared variables, we used non-parametric tests (Chi-Square Test) and binary logistic regression. We considered the  $P < 0.05$  values to be statistically significant.

## Results

### *Descriptive Statistics*

A total of 438 GM-PHPs from the Republic of Macedonia participated in our research. According to sex structure, 76.7% (336) were women and

Table 1. Sociodemographic Variables

Variable	N (%)
<b>Gender</b>	
Female	336 (76.7)
Male	102 (23.3)
<b>Type of practitioner</b>	
General practitioner	292 (66.7)
Family medicine specialist	146 (33.3)
<b>Age</b>	
25 – 29	63 (14.4)
30 – 39	139 (31.7)
40 – 49	113 (25.8)
50 – 59	92 (21.0)
≥ 60	31 (7.1)
<b>Years of experience</b>	
≤ 5	86 (19.6)
6 – 9	77 (17.6)
10 – 19	152 (34.7)
20 – 29	81 (18.5)
≥ 30	42 (9.6)
<b>Population count in the area of workplace</b>	
≤ 19,999	110 (25.1)
20,000 – 49,999	102 (23.3)
50,000 – 99,999	106 (24.2)
100,000 – 499,999	56 (12.8)
≥500,000	64 (14.6)
<b>Distance of the workplace from the nearest hospital</b>	
The workplace is part of the hospital	131 (29.9)
≤19 km	244 (55.7)
20 – 49 km	54 (12.3)
≥50 km	9 (2.1)

Sanctions, Violence and Reasons for Sanctioning

23.3% (102) were men. Out of the 438 participants, only 33.3% (146) were specialists in family medicine. In terms of age, the age group from 30 to 39 years dominates - 31.7% (139). Subsequently, according to the years of experience, the majority have 10-19 years of experience - 34.7% (152). Most of the doctors who participated in the study work in less populated areas - 25.1% (110) work in places with a population of less than 20,000, and 24.2% (106) participants in places with a population of 50,000 to 100,000. The workplace for most

Table 2. Sanctions and Violence

Variable	N (%)
<b>Sanctioned</b>	
Yes	302 (68.9)
No	136 (31.1)
<b>Type of sanction</b>	
Admonition	40 (13.2)
Admonition before termination	3 (1.0)
Financial sanction by scale	218 (72.2)
Financial sanction by damage	37 (12.3)
Unanswered	4 (1.3)
<b>Reduction of salary because of sanction</b>	
Yes	35 (11.6)
No	262 (86.7)
Unanswered	5 (1.7)
<b>Violence by the patient and/or their family/companion</b>	
Yes	321 (73.3)
No	110 (25.1)
Unanswered	7 (1.6)
<b>Type of violence</b>	
Verbal	305 (95.0)
Verbal and physical	16 (5.0)

participants is ≤19 km from the nearest hospital - 55.7% (244) (Table 1).

Out of the 438 participants, 68.9% (302) were sanctioned. According to the type of sanction, 84.5% were financial sanctions, with the dominion of financial sanction by scale (72.2%). Only 13.2% got admonition and 1% got admonition before termination. Most of the participants didn't have their salary reduced by the director of the primary healthcare institution due to the sanction by the HIF. If participants followed the HIF's guidelines, they were a lot more likely to experience pressure or violence by their patients or their family/companions. The type of violence in most cases was verbal (95%), and rarely both verbal and physical (5%) (Table 2).

There were 414 selected and/or added responses from the survey about the reasons for sanctioning. They were categorized in the groups shown in Table 3. The most common reason selected was "Financial consumption of prescriptions/referrals

Table 3. Frequency Table for Variable: Reasons for Sanctioning

Reasons for sanctioning	N (%)
Financial consumption of prescriptions/referrals above the agreed amount	119 (28.7)
Higher rate of sick leaves and/or unjustified sick leaves	91 (22.0)
Unrealized preventative goals or education	86 (20.8)
Prescribing medication outside of the HIF guidelines	48 (11.6)
Incomplete or not timely updated documentation	28 (6.8)
Lack of ampule medication or expired medication	10 (2.4)
Prescribing orthopaedic aids, casts and supports outside of the HIF guidelines	7 (1.7)
Giving referrals outside of the HIF guidelines for diagnosis	5 (1.2)
Secondary or tertiary healthcare practitioners' error	5 (1.2)
Others	15 (3.6)
Total	414 (100)

above the agreed amount”, followed by “Higher rate of sick leaves and/or unjustified sick leaves” and “Unrealized preventative goals or education”. Out of the 28 in the category “Incomplete or not timely updated documentation”, 18 were due to mistakes or omissions in paper documentation and 5 were about omissions in the electronic health record. In the category “Lack of ampule medication or expired medication”, 8 were for the lack of the ampule medication (medication in liquid form) which is mandatory according to HIF and 2 were for expired glucose solutions. The category “Secondary or tertiary healthcare practitioners' error” consists of doctors who wrote that they were sanctioned because the specialists' report contained the wrong diagnosis or a medication that couldn't be prescribed by the GP or FMS for a certain diagnosis. The category “Others” contains reasons that weren't specified or that couldn't be grouped (singular different violations).

### ***Relationship of Different Variables with Sanctions***

For the univariable analysis, a chi-square test was done to examine the relationship between sanctioning and various variables. The sex of GM-PHPs was not associated with the sanctioning by the HIF ( $P=0.2$ ), although men were sanctioned by 6.8%

more. Physicians' age had a significant association with HIF's sanctioning ( $P<0.001$ ). Sanctioning of the GM-PHPs by HIF was associated significantly with their working experience ( $P<0.001$ ). GM-PHPs having the least experience, i.e. having the length of the service years of 5 years and shorter, were sanctioned more rarely than the doctors with longer working experience - 38.4% (33/86). The variable type of practitioner had a statistically significant association with sanctioning. FMSs were sanctioned by the HIF more frequently than the GPs - 76% (111/146) vs 59.9% (175/292),  $P=0.001$  (Table 4). In this study, it was not proved that the sanction of the GM-PHPs by HIF depended significantly on the population count in the area of the workplace ( $P=0.231$ ). The distance to the workplace from the nearest hospital had a significant association with the sanctions of GM-PHPs ( $P=0.005$ ) (Table 4). Violence from the patient and/or their family/companion had a statistically significant association with sanctioning ( $P<0.001$ ). GM-PHPs who have followed the HIF guidelines and have been subjected to violence by the patient and/or their family were more often sanctioned than physicians who have not experienced it. (Table 4).

After the univariable analysis, a binary logistic regression was performed to ascertain the effects of sex, type of practitioner, years of experience, the distance of workplace from the nearest hospital and violence by the patient and/or their fam-

Table 4. Overview: Differences in Sanctioning Against Physicians by Sociodemographic Variables

Variable	Value	Sanctioned		UA*	MA†	OR (95% CI)
		Yes N (%)	No N (%)	P	P	
Gender	Female	214 (63.7)	122 (36.3)	0.200	0.03	0.541 (0.311-0.941)
	Male	72 (70.6)	30 (29.4)			
Type of practitioner	FMS‡	111 (76.0)	35 (24.0)	<0.001	0.121	1.494 (0.899-2.484)
	GP§	175 (59.9)	117 (40.1)			
Age	25-29	23 (36.5)	40 (63.5)	<0.001	-	-
	30-39	95 (68.3)	44 (31.7)			
	40-49	80 (70.8)	33 (29.2)			
	50-59	59 (64.1)	33 (35.9)			
	≥ 60	29 (93.5)	2 (6.5)			
Years of experience	≤ 5	33 (38.4)	53 (61.6)	<0.001	-	-
	6-9	50 (64.9)	27 (35.1)			
	10-19	113 (74.3)	39 (25.7)			
	20-29	56 (69.1)	25 (30.9)			
	≥ 30	34 (81.0)	8 (19.0)			
Population count in the area of workplace	≤19.999	72(65.5)	38(34.5)	0.231	-	-
	20.000 – 49.999	63(61.8)	39(38.2)			
	50.000 – 99.999	63(59.4)	43(40.6)			
	100.000 – 499.999	41(73.2)	15(26.8)			
	≥500.000	47(73.4)	17(26.6)			
Distance of the workplace from the nearest hospital	Workplace¶	89 (67.9)	42 (32.1)	0.005	-	-
	≤19 km	168 (68.9)	76 (31.1)			
	20 – 49 km	24 (44.4)	30 (55.6)			
	≥50 km	5 (55.6)	4 (44.4)			
Violence by the patient and/or their family/companion	Yes	232 (72.3)	89 (27.7)	<0.001	<0.001	2.710 (1.659-4.429)
	No	52 (47.3)	58 (52.7)			

\*Univariable analysis (Chi-square test); †Multivariable analysis (Logistic regression); ‡Family medicine specialist; §General practitioner; ¶The workplace is part of the hospital.

ily/companion on the likelihood that participants are sanctioned. The logistic regression model was statistically significant,  $\chi^2=80.614$ ,  $P<0.001$ . The model explained 23.6% (Nagelkerke  $R^2$ ) of the variance in sanctioning and correctly classified 74.0% of cases. While in the univariable analysis sex was insignificant, in the multivariable analysis we observed that females were less likely to be sanctioned than males. When other variables were taken into account, the type of practitioner was not associated with sanctioning. Age was shown to be a confounding factor and thus it wasn't included in the multivariable analysis. Increasing years of experience was associated with an increased odds

ratio for sanctioning. GM-PHPs with 30 or more years of experience have 8.7 times higher odds to be sanctioned than those with 5 or fewer years of experience. Distance of the workplace from the nearest hospital and Violence by the patient and/or their family/companion remain significant both in the univariable and multivariable analysis. GM-PHPs that experienced violence by their patient and/or the patient's family/companion have 2.71 times higher odds to be sanctioned than those that didn't experience violence, when sex, type of practitioner, years of experience and distance of the workplace from the nearest hospital are taken into consideration.

## Discussion

We wanted to investigate the problem from several angles, so we explored several factors. Firstly, the relationship between sanctions and the demographic factors: sex, age, type of practitioner, years of experience, population number in the workplace and the location of the workplace in relation to the nearest hospital. We considered that these factors may affect the penal policy by the inspection. Secondly, we wanted to see whether GM-PHPs that followed the HIF guidelines experienced violence by patients or their family/companion and if there is a relationship between sanctions and violence by the patient and/or their family/companion. Thirdly, and most importantly, we described the types of sanctions and the reasons for sanctioning.

In 2017 the total number of GM-PHPs (both GPs and FMSs) in Macedonia was 1577, which is 0.86 doctors per 1000 insured (15). Our research covered 438 GM-PHPs, which is 27.8% of the total number of registered GM-PHPs at that time. With a 95% confidence level, our sample is representative with a margin error of 3.98%. A cross-sectional study in the UK has shown that female GPs were the least likely to receive sanctions compared with their male colleagues (16). Since general medicine in Macedonia was predominated by women (17), we thought the same might occur, but even so, there wasn't any association between sex and sanctions in the univariable analysis. However, in the multivariable analysis, it was shown that female GM-PHPs were less likely to be sanctioned than their male colleagues. This means that sex is not significant by itself, however when we include the type of practitioner, years of experience, the distance of the workplace from the nearest hospital and violence by the patient and/or their family/companion it gains significance.

On the other hand, we concluded that there is an association between age and sanctions. Older GM-PHPs were sanctioned significantly more than younger GM-PHPs. We need to take into consideration the phrasing of the question in our survey "Have you ever been sanctioned by the HIF?" which automatically gives younger age

groups less chance for being sanctioned since they have worked for a shorter period of time and thus haven't been exposed to a lot of regulation and inspections during their work. With the multivariable analysis, we excluded age since it showed a correlation with years of experience and we only kept years of experience in the model. In both the univariable and multivariable analyses, doctors with the least experience were sanctioned significantly more rarely.

A paramount question that arose from the univariable analysis is: Why are FMSs sanctioned significantly more than GPs? We would assume that since they are specialists in this field that they had more training and education and subsequently would be less sanctioned. When we included other variables in the model we see that this effect was a result of an influence of another variable.

Whether the area of the workplace is urban or rural, it didn't associate with the sanctions. But interestingly enough, the location of the workplace in relation to the nearest hospital did. Doctors with workplaces in the hospital or  $\leq 19$  km from it were significantly more sanctioned. Are these doctors more prone to mistakes and why, or do the inspectors target these workplaces more often? Further research is needed to find an answer.

The frightening fact is that 73.3% of the GM-PHPs were exposed to violence by their patients if they followed the HIF guidelines and refused to step out of them. This implies that either our patient population isn't well informed and educated about the functioning of the primary healthcare system and their rights and obligations as a patient or the system isn't adequately organized to fulfil the needs of said patients. In the WHO Primary healthcare report about Macedonia, respondents reported patients' general distrust towards primary health care, with about 20–30% of patients requesting the PHP to hospitalize them. This also influenced referral rates (9). Our quantitative data shows that the GM-PHPs who experience more violence after following the guidelines are also significantly more sanctioned than those who don't. Additional research is needed to conclude whether sanctioning happens because doctors give in un-

der the pressure and violence by their patients and go against HIF guidelines, or the irregularities during their work for which they are sanctioned make their patients unsatisfied with the care and they resort to violence. In 2016, Healthgrouper researched 240 PHPs and determined that 75% of the participants have faced various forms of violence. The majority of doctors (60%) said that the reasons for the attacks were due to dissatisfaction with the health system as a whole. In terms of the type of violence, they determined that 90% were verbal, and only 10% physical violence. In terms of location, 73% happened in the workplace, and less than 2% outside of the workplace (18). We can observe that this is an ongoing problem from the past, with numbers being consistent, suggesting a need for new policies to be applied to assure the safety of the PHPs and the improvement of the quality and organization of primary health care and subsequently reducing both violence and sanctioning.

Concerning the type of sanctions, we can see that the financial sanctions predominate admonitions, with financial sanctions by scale with 72.2%. According to a study by Healthgrouper in 2012, 44% of the physicians who participated in the study confirmed that they were sanctioned by the HIF the previous year, and sanctions vary and range up to 25% of the total amount of capitation for more prescriptions, passive patients, and deletion of patients' information while transferring the insured patients from one workplace to another. Many doctors believed that their income has been unfairly reduced and that their capitation is often reduced (19). Comparing to this study we see a rise of 24.9% in sanctioning, and the most common reason for sanctioning remains the same - exceeding the permitted number of prescriptions/referrals. However, only 11.6% of the doctors had their salary additionally reduced by the director of the primary healthcare institution due to their sanction.

The most common reasons for sanctioning are closely connected to the change of the system with the privatization and introducing limitations to prescribing medicine, issuing referrals and sick

leaves and realizing the preventative goals and education. We need to determine what is the reason for exceeding these limitations and whether it is justifiable to increase the number of prescriptions and referrals one physician can give. Consumption of prescription drugs at the expense of the HIF in the period from 2008 to 2017 shows a continuous increase, with ATC C group drugs being the most consumed drugs. The top 5 prescribed drugs were: ACE inhibitors, anxiolytics, beta-blocking agents, blood glucose-lowering drugs and drugs for peptic ulcer and gastro-oesophageal reflux (20). The increasing trend of prescription drugs consumption continued in the period from 2017 to 2019, with ATC C group drugs still being the most consumed. On the other hand, there was a 1.4% decrease compared to 2018 in the prescribing of antibiotics (21). The fact that the highest prescription consumption is for drugs that are used for chronic diseases gives rise to the question about the structure of the patient population of GM-PHPs who got sanctioned for "Financial consumption of prescriptions/referrals above the agreed amount". Since different GM-PHPs can have various populations of patients, it is logical that a physician with a larger portion of chronic registered patients will spend more prescriptions and/or referrals per month, than a physician with a majority of healthy young registered patients. Further research needs to be done to determine whether GM-PHPs with a higher number of registered chronic patients are sanctioned more for exceeding the prescription limit.

PHPs who mostly work in solo practices (68%) have a relatively high number of registered patients, usually 2000-4000 per practice, although regional differences exist. In the WHO Primary healthcare report about Macedonia, respondents claimed that they cannot refuse to register a new patient in their practice and that employing a new PHP in the practice is too complicated. With so many patients and administration, they didn't have much time left to examine the patient who is then referred to a specialist. It was concluded that the considerable number of registered patients partly explained the high rate of referrals to secondary health care. Another reason is the inability of PHPs

to prescribe certain medicines without a report of a specialist's opinion, such as insulin, statins, levothyroxine, oral and nasal corticosteroids; or order specific diagnostic tests, such as endoscopies, MRI or CT scans (9). The high referral rate is a symptom of low responsiveness of primary health care, generating safety concerns and bottlenecks in secondary health care.

In the Republic of Macedonia, an Electronic Health Card is used since 2006 and an electronic health information system called "Moj Termin" (literally translated as My Appointment) is used since 2013 (5, 9). The Electronic Health Card contains the patient's personal data and provides access to the patient's health data that is stored in a centralized database (5). "Moj Termin" is used to create an electronic health record, introducing new work processes such as electronic referrals, prescriptions and examination appointments that ensure good communication between primary, secondary and tertiary health care. This system reduces administrative work and increases quality service (22). Even with the introduction of the electronic health system, GM-PHPs are still obligated to record data both in paper and electronic forms which doubles the time spent on administrative work and the chances of making mistakes. Although there were only 28 responses for "Incomplete or not timely updated documentation", it is of importance to note that the majority were due to omissions or mistakes in paper documentation. Studies showed that the use of electronic systems reduces medical errors compared with paper-based methods (23). Taking all of this into consideration, it is questionable why the HIF still obliges GM-PHPs to record paper documentation.

Understanding and evaluating the system of organization and regulation in primary healthcare of a low-income, post-socialist country such as Macedonia is beneficial especially to the countries that have mainly public primary healthcare and are planning to transition into a completely private primary healthcare or a private-public partnership. Studies comparing pre- and post-privatization outcomes tended to find worse health system performance associated with rapid and extensive

healthcare privatization initiatives (24). Our study sheds a bit of light on the healthcare regulatory system in Macedonia and the controls GM-PHPs face, but also raises a lot of questions that need to be answered in further research in order to constructively recommend improvements of said system.

## Conclusion

With this study, we observed that in the univariable analysis age, years of experience, family medicine speciality, the distance of the workplace from the nearest hospital and violence are associated with sanctioning. In the multivariable analysis, we observed that: sex, years of experience, the distance of the workplace from the nearest hospital and violence are associated with sanctioning of the GM-PHPs in Macedonia. The most common reasons for sanctioning were the ones that were related to the change of the system with the privatization of primary healthcare. The types of sanctions were mostly financial and rarely admonitions. This study raised a lot of questions about the functionality of the regulatory systems in Macedonia, the effectiveness of the defined disciplinary measures and the quality of care GM-PHPs provide. Further research is needed to determine whether the dysfunctionality of the policies is due to disorganization of the regulatory bodies, lack of experience and education of the physicians or a mix of both.

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### What Is Already Known on This Topic:

*In the Republic of Macedonia, the quality and effectiveness of the work of GM-PHPs are regulated by the Health Insurance Fund and the Ministry of Health through a system of sanctions. The sanctions used are admonition, financial sanction and termination of contract/employment. Previous studies on this topic about this country are scarce.*

### What This Study Adds:

*In our sample of 438 GM-PHPs, with a multivariable analysis, we can observe that sex, years of experience, the distance of the workplace from the nearest hospital and violence are associated with sanctioning. The majority of sanctions were financial sanctions (84.5%). The most common reasons for sanctioning were: "Financial consumption of prescriptions/referrals above the agreed amount", followed by "Higher rate of sick leaves and/or unjustified sick leaves" and "Unrealized preventative goals or education".*

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## The Frequency and Form of Controls by HIIS over Primary Health Care Physicians in Slovenia

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### Abstract

**Objective.** The aim of this study was to evaluate the pattern of controls and sanctions by the Health Insurance Institute (HIIS) over primary healthcare practitioners (PHCPs) in Slovenia, the reasons for sanctions and the violence against PHCPs if they followed the HIIS rules. **Materials and Methods.** We performed analyses using survey data from a cross-sectional study, across public health centres and individual contractors in which 1,458 PHCPs were invited to answer a questionnaire anonymously via an online system used to collect data for the Slovenian Medical Chamber and the Association of General Practice/Family Medicine of South-East Europe. Quantitative data were presented by descriptive statistics and analysed using Pearson's chi-squared test. **Results.** Responses were obtained from 462 female and 138 male PHCPs. Of the total number of 600 participants, 430 were family medicine specialists. 263 (43.8%) responded that they have been sanctioned for various reasons. PHCPs that are more likely to be sanctioned include family medicine specialists and individual contractors. PHCPs working in areas smaller than 20,000 inhabitants were sanctioned in a bigger proportion than their counterparts. Monetary penalties levied against those working at health centres were usually covered by the health centre. Family medicine specialists, more often than other PHCPs experienced violence from patients or patients' relatives if they followed HIIS rules. **Conclusion.** Family medicine specialists are sanctioned more frequently than other PHCPs, individual contractors are sanctioned more frequently than public healthcare PHCPs and PHCPs in working area with a population less than 20,000 are more frequently sanctioned than those working in an area with a bigger population count.

**Key Words:** Primary Health Care ■ Insurance ■ Prescription Controls ■ Sanctions ■ Violence at Work.

### Introduction

The World Health Organization has identified four key functions needed for the health system to function: stewardship, resource creation, funding and service delivery. Stewardship means oversight of the system's basic functions and includes management, information transmission, coordination and monitoring of the system at various levels (1). The quality of the healthcare system depends on the successful integration of these four functions, and this integration depends on the quality control of the healthcare system.

In the countries of the European Union there are different types of health care systems and different regulatory bodies within those systems. Three different systems have been defined: the Beveridge model, the Bismarck model and the mixed model. Countries that use the Beveridge model have financing that is predominantly through taxes, provide universal health coverage and the government regulates what physicians can do and charge for their services (e.g. Cyprus, Denmark, Finland, Ireland, Italy, Latvia, Malta, Portugal, Spain, Sweden and United Kingdom). In contrast to that, in the countries that use the Bismarck model the funding is granted through compulsory social se-

curity contributions by employers and employees (e.g. Belgium, Estonia, France, Germany, Lithuania, Luxembourg, Netherlands, Poland, Czech Republic, Romania, Slovakia, Slovenia and Hungary). Countries that use the mixed model have significant funding from voluntary insurance or upfront payments (e.g. Croatia, Greece, Austria, Bulgaria) (2-4).

In the countries organized by the Bismarck model health insurance funds usually have some role in regulation of the work of physicians. For example, in Romania the Ministry of Health (MoH) and the National Health Insurance House (NHIH) together develop an annual national framework contract that contains the rights of the insured population and the conditions for all providers including primary healthcare practitioners (PHCPs). Based on this document they routinely monitor medical files, mandatory licensing, feedback on services and utilization of NHIH listed resources and drugs (5). In Slovakia, Health Care Surveillance Authority (HCSA), professional chambers and self-governing regions monitor and enforce responsibilities that were previously set by the MoH. HCSA is a regulatory body that also supervises the Insurance funds, is involved in quality management and has the power to impose sanctions (6). Germany, on the other hand has a more complex system with regulatory bodies on the federal, state and corporatist level. The individual states implement the federal legislation and supervise the public health services, as well as the regional medical associations, the regional associations of physicians that work with statutory health insurance (SHI) and the insurance funds. The regional associations of SHI physicians have a supervisory and regulatory role over the health services that have been defined by law and in contracts with the insurance funds (7).

The healthcare system in Slovenia is also based on the Bismarck model, additionally with an accent on primary healthcare gatekeeping. Primary healthcare (PHC) service provision is under the jurisdiction of the municipalities, which are responsible for health policy development at the local level and are also the owners of community-level

PHC centres. In Slovenia, there are 65 healthcare centres that deliver PHC at 459 locations. Healthcare workers at publicly-owned health centres are salaried public servants. PHC is organised through a coexistence of predominantly public health centres as an exclusive form of health centres and individual contractors, or concessionaires (8). The number of individual contractors has increased since Slovenian independence in 1991. This now encompasses 30% of PHC providers (family physicians, paediatricians and gynaecologists) (9). Quality of care at the PHC level is formally a priority, but the legislation to ensure quality in this area is proceeding very slowly. There are formal instruments for assessing quality, such as obligatory certification of physicians every 7 years through collecting credits, voluntary certification and accreditation and mandatory licensing of physicians and nurses, but PHC quality has not yet been systematically assessed by quality indicators (10).

In Slovenia regulation is conducted by the MoH, Health Inspectorate, Health Insurance Institute (HIIS) and The Medical Chamber of Slovenia. Supervision of compliance with the Patients' Rights Act is exercised by the MoH. Slovenia's Health Inspectorate's authority is limited exclusively to the competence of the offence authority. The Medical Chamber of Slovenia carries out professional supervision (11). The HIIS has control over prescribing, proper identification of sick leave, allocation of ambulance transport in accordance with HIIS rules and dispensing and charging for medicinal products. These controls are detailed in the HIIS Rules on Controls and Supervisions. Supervision is carried out using data from the HIIS records on issued and billed medicines, documents for exercising the right to medicines and other available documentation (12). HIIS supervises the work of the PHCPs and if they detect that their rules aren't followed a report is issued to the MoH to ask for an administrative control. According to the severity of the breach, two types of sanctions are given: a warning, and a fine. Fines can be covered by the institution, partially by the PHCP or fully by the PHCP. If the breach is too severe, the PHCP undergoes

another type of control, which is internal control that might result with licence revoking (11).

Patients also have to understand the limitations and rules to which PHCPs need to adhere, since it has been shown that lack of understanding the health system, expectation gaps, limited medical services and low education were a part of the reasons for violence against healthcare workers (13, 14). This is important because violence against healthcare workers is frequent and it has negative effects on the mental and physical health of the healthcare practitioners, the quality of healthcare delivery and the organization as a whole (15-18).

This study is the first to investigate the frequency and forms of HIIS controls faced by PHCPs and especially over family medicine specialists. We wanted to see whether there is a relationship between different sociodemographic factors and sanctions of PHCPs, what are the reasons for sanctions and whether PHCPs experienced violence from patients or their relatives if they followed the HIIS rules.

## Materials and Methods

### *Study Design, Timeframe, Data Collection and Study Population*

The design is retrospective and cross-sectional. The study was carried out by anonymous online questionnaire containing 13 different questions ranging from multiple choice to essay questions. The questionnaire was adapted from a standardized questionnaire made by the Association of General Practice/Family Medicine of South-East Europe (AGP/FM SEE). Every single practitioner had his own anonymous internet protocol address (IP), from which he or she was able to participate only once. The survey took roughly 20 minutes to fill out.

In the first phase a pilot survey was sent to 30 participants in December 2017 in order to improve the quality of the survey. In the second phase, in January 2018, the official survey was distributed in

electronical form to all the PHCPs registered with the Medical Chamber of Slovenia. In Slovenia, regulation is conducted by the Health Insurance Institute (HIIS), Health Inspectorate, Ministry of Health and The Medical Chamber of Slovenia.

Data collection was concluded at the end of March 2018. Participants were medical professionals registered with the Medical Chamber, with or without PHC specialisation. The number of total registered family physicians in 2017 was 1,362, the number of GPs was 256, the number of gynaecologists was 463 and the number of paediatricians was 851 (19). Filters were added to distinguish those working as PHCPs from those working in secondary, tertiary healthcare or other institutions. Additional filters to remove retired PHCPs were added. After this process of filtering, a total of 1,458 PHCPs were approached.

The research methodology was presented and discussed at two meetings of the European General Practice Research Network in Sarajevo (2018) and Tampere, Finland (2019).

### *Questionnaire*

The questionnaire consisted of 13 questions: seven single-select multiple-choice, four dichotomous, one mixed (multi-select multiple choice question used for reasons of sanctioning) and one mandatory essay question. We collected the following socio-demographic characteristics: sex, age, professional education status, years of experience in the field of primary healthcare, distance from the workplace, practice environment and the employment status (individual contractor or public healthcare). Questions about sanctioning consisted of: whether they have ever been sanctioned, the type of the sanction, the reason for sanctions and the responsible body for the payment of the sanction. There were also questions about whether physicians experienced violence from their patients or the patients' relatives if they followed the HIIS rules, and if so, what type of violence it was (verbal, physical or both).

### **Ethical Approval**

The content and ethics of the research was confirmed at the nineteenth session of the Executive Board of the Medical Chamber on November 16th, 2017, Decision no. 270/19/2017 (20).

### **Statistical Analysis**

We used the statistical software SPSS Statistics 22. Values of  $P < 0.05$  we considered statistically significant. Quantitative data were presented by descriptive statistics and analysed using Pearson's chi-squared test.

## **Results**

### **Descriptive Statistics**

Our study covered 600 PHCPs in Slovenia. In Table 1 the sociodemographic characteristics of the participants are shown. It has to be noted that, regarding specialty, the questionnaire contained only a question whether they are specialists of family medicine or not. This is why no other specialties are shown in the table.

From all of the participants, 263 (43.8%) received sanctions in either the form of a fine or a warning. Table 2 summarizes this, as well as the type of sanction the PHCPs received. The responsible body for the payment of the sanction is divided into several categories: healthcare administration, which means the institution covers the fine, personally: partially and up to total – which means the PHCPs partially pay for the fine or for the total amount accordingly. From the 263 sanctioned, only 150 (57%) answered this question and 113 (43%) left it blank. The numbers shown under this variable in Table 2 are from those that answered. Participants were also asked whether they were exposed to violence from their patients or their patients' relatives if they complied with HIIS rules. These data, together with the type of violence is also shown in Table 2.

Table 1. Sociodemographic Characteristics of Respondents

Variable	N (%)
<b>Sex</b>	
Female	462 (77.0)
Male	138 (23.0)
<b>Family medicine specialist</b>	
Yes	430 (71.6)
No	170 (28.3)
<b>Age structure</b>	
25–29	1 (0.2)
30–39	89 (14.8)
40–49	165 (27.5)
50–59	238 (39.6)
≥60	107 (17.8)
<b>Years of practice</b>	
0–10	67 (11.1)
11–15	85 (14.1)
16–20	75 (12.5)
21–30	204 (34.0)
≥31	169 (28.1)
<b>Employment status</b>	
Individual contractor	175 (29.1)
Public healthcare	425 (70.8)
<b>Population in work area</b>	
<20,000	206 (34.3)
20,000–49,999	164 (27.3)
50,000–99,999	58 (9.6)
100,000–499,999	138 (12.7)
≥500,000–999,999	34 (5.6)
<b>Distance from nearest hospital</b>	
Workspace is part of hospital	223 (37.1)
<20 km	161 (26.8)
20–49 km	180 (30.0)
≥50–99 km	36 (6.0)

Table 2. Sanctions and Violence Experienced Working as a PHCP

Variable	N (%)
<b>Ever Sanctioned</b>	
Warned	56 (9.3)
Fined	207 (34.5)
Not Sanctioned	337 (56.1)

Type of sanction	
Warning	55 (21.0)
Warning before termination of agreement	1 (0.1)
Monetary amount based on damages caused	92 (34.8)
Monetary amount on fixed scale	115 (44.0)
Responsible body for payment of sanction*	
Health centre administration	118 (78.7)
Personally: partially	20 (13.3)
Personally: up to total	12 (8)
Victim of violence at work	
Yes	464 (77.3)
No	136 (22.7)
Type of violence	
Physical	1 (0.2)
Verbal	441 (95.0)
Physical and verbal	22 (4.7)

PHCP=Primary healthcare practitioners; \*Missing answers 113.

### *Reasons for Controls and Sanctions*

When looking at the results for the reasons for controls and sanctions, it should be taken into consideration that this was a mixed question. Participants could select more options from the ones listed below and additionally add their own answer if their option wasn't listed. It was not an obligatory question and some participants chose more reasons for their sanctioning, while others didn't choose at all. That means from the 263 sanctioned, 207 gave answers to this question and some selected more reasons which at the end summed as 263. This is why the number of responses isn't same as the number of participants who selected that they had been sanctioned. Even though the number of sanctioned PHCPs and the number of selected answers to this question have the same value-263, they do not correspond to the number of participants that answered this question – 207.

From the answers received, the reasons were grouped in the categories shown in Table 3. The most common reason was "Prescribing drugs not in accordance with HIIS rules", which includes: prescribing drugs above the agreed financial amount, prescribing medication while the patient

was hospitalised in a secondary or tertiary institution, prescribing drugs in a dosage not in accordance with HIIS rules, unnecessary prescribing of more drugs with the same effect and prescribing drugs that aren't covered by the HIIS as they were. The second most common reason was "Prescribing technical or orthopaedic devices not in accordance with HIIS rules", from which adult diapers were most commonly prescribed against HIIS rules. From the 50 who got sanctioned for excessive sick leave and/or unjustified sick leave, 8 commented that the reason was giving sick leaves to mothers who had hospitalized children. In the category "Incomplete or not timely updated documentation", 12 specified that the reason was inconsistency between the paper and electronic forms.

Table 3. Reasons for Sanctions

Reasons for sanctions	Frequency (%)*
Prescribing drugs not in accordance with HIIS rules	68 (25.9)
Prescribing technical or orthopaedic devices not in accordance with HIIS rules	65 (24.7)
Excessive sick leave and/or unjustified sick leave	50 (19)
Issuing transportation orders without following HIIS rules on diagnosis and/or distance	32 (12.2)
Incomplete or not timely updated documentation	26 (9.9)
Issuing referrals not in accordance with HIIS rules	10 (3.8)
Home care order costs and/or justification for issuing	9 (3.4)
Other	3 (1.1)
Total	263 (100)

HIIS=Health Insurance Institute; \*Represents the percent of a choice from all the choices selected by all the participants who answered the question.

### *Sanctions and Violence against PHCPs in Relation to Sociodemographic Variables*

Table 4 shows the relationship between sanctions and sociodemographic variables, as well as the relationship between exposure to violence and the sociodemographic variables.

Table 4. Sanctions and Violence against Physicians by Sociodemographic Variables

Variable	Value	Sanctions			Violence		
		Yes	No	P	Yes	No	P
		N (%)	N (%)		N (%)	N (%)	
Sex	Male	81 (30.8)	57 (16.9)	<0.001	101 (21.8)	37 (27.2)	0.185
	Female	182 (69.2)	280 (83.1)		363 (78.2)	99 (72.8)	
Age (years)	25–39	26 (9.9)	64 (19.0)	<0.001	75 (16.2)	15 (11.0)	0.05
	40–49	57 (21.7)	108 (32.0)		133 (28.7)	32 (23.5)	
	50–59	124 (47.1)	114 (33.8)		181 (39.0)	57 (41.9)	
	60–69	56 (21.3)	51 (15.1)		75 (16.2)	32 (23.5)	
Family med. specialist	Yes	202 (76.8)	228 (67.7)	0.008	354 (76.3)	76 (55.9)	<0.001
	No	61 (23.2)	109 (32.3)		110 (23.7)	60 (44.1)	
Years of practice	0–10	16 (6.1)	51 (15.1)	<0.001	57 (12.3)	10 (7.4)	0.231
	11–15	31 (11.8)	54 (16.0)		71 (15.3)	14 (10.3)	
	16–20	24 (9.1)	51 (15.1)		57 (12.3)	18 (13.2)	
	21–30	103 (39.2)	101 (30.0)		153 (33.0)	51 (37.5)	
	>30	89 (33.8)	80 (23.7)		126 (27.2)	43 (31.6)	
Population in work area	≤ 19,999	119 (45.2)	87 (25.8)	0.003	157 (33.8)	49 (36.0)	0.728
	20,000–49,999	72 (27.4)	92 (27.3)		128 (27.6)	36 (26.5)	
	50,000–99,999	19 (7.2)	39 (11.6)		48 (10.3)	10 (7.4)	
	≥100,000	53 (20.2)	119 (35.3)		131 (28.2)	41 (30.1)	
Employment status	Individual contractor	120 (45.6)	55 (16.3)	0.001	129 (27.8)	46 (33.8)	0.174
	Public healthcare	143 (54.4)	282 (83.7)		335 (72.2)	90 (66.2)	

Male PHCPs, were more often sanctioned than their female colleagues ( $P < 0.001$ ). Family medicine specialists were more frequently sanctioned in comparison with others ( $P = 0.008$ ). PHCPs working in sparsely populated areas (less than 20,000 inhabitants) were sanctioned in bigger proportion than their counterparts working in urban centres. Individual contractors were sanctioned statistically significantly more frequently compared to PHCPs employed at public health centres.

We did not find any relationship between violence and the practitioner's sex ( $P = 0.185$ ). Family medicine specialists, more often than other PHCPs experienced violence from patients or patients' relatives if they followed HIIS rules ( $P < 0.001$ ). There was also significant relationship between violence and PHCP's age ( $P = 0.05$ ). In all age groups, the majority of PHCPs were exposed to violence, with a difference in the proportions between individual groups (83.3%, 80.3%, 76.1% and 70.1% for the age groups from the youngest to the oldest doctors).

## Discussion

This paper analyses the problem of HIIS controls and sanctions of PHCPs on one hand, and PHCPs' exposure to patient violence provoked by upholding the HIIS insurance standards on the other. Multiple factors affected the study's outcome.

In the last 50 years there has been rapid "feminisation" of general practice (21). From the beginning of the new millennium there has been a sharp decrease in medical graduates drawn to the field of general practice. Reasons such as finding the job interesting, likely job satisfaction, aptitudes, likely ability to be successful in a chosen specialty, opportunities, compatibility with domestic and social life, material and intellectual rewards and personal aspirations about how best to contribute to serving patients play a vital role (22). In our study we concluded that sex of the PHCPs was associated with being sanctioned, with the male PHCPs being more often sanctioned than their female

colleagues. Some studies find possible explanations for this in the fact that female PHCPs self-report fewer hours of work than their male peers, are younger, have fewer patient encounters and deliver fewer services, and write fewer prescriptions, but spend longer with their patients during a contact and deal with more separate presenting problems in one visit (23-26). The results of the study showed that there is no relationship between violence and the PHCPs sex. While violence against healthcare workers in general was not associated with sex (15, 27), a systematic review showed that women working in primary care or general hospitals were less likely to be exposed to physical violence than men (15). Other studies showed that women PHCPs experienced more verbal violence and stalking (28, 29).

Age and years of practice also showed association with sanctions, with older PHCPs being sanctioned more often than the younger colleagues ( $P < 0.001$  and  $P < 0.001$ ). Here, we have to take into consideration how the question was formulated: "Have you ever been sanctioned by the HIIS?". Since the question covers their whole career, the chance of those with a longer career to be sanctioned is higher. Additionally, the questionnaire lacked a question to determine the total number of sanctions one PHCP got in their career and whether PHCPs got one sanction for multiple breaches or multiple sanctions over the years for different singular breaches. In our study there was a significant relationship between violence and PHCP's age. A meta-analysis showed that healthcare workers that were younger, exposed to shift work and worked longer hours had a higher risk of experiencing any type of violence (15).

The results showed that family medicine specialists were more frequently sanctioned than other PHCPs ( $P = 0.008$ ) and are more often victims of violence from patients and patients' relatives if they follow the HIIS rules ( $P < 0.001$ ). Slovenia is a country with a long tradition of family medicine specialist training. Even as part of Yugoslavia, specialist training in GP/FM started as early as 1961, first in Zagreb, Croatia, at the Andrija Štampar School of Public Health, and 1 year later in Lju-

bljana (30). A new model for vocational training in family medicine was established in 2002, following the recommendations of the European Union of General Practitioners (UEMO). According to the new program, which lasts four years, trainees spend half of their training in a hospital setting and half in general practice, where they are supervised by a trainer in practice (31). Currently family medicine specialty is obligatory, but due to historical reasons, we have 4 types of practitioners of general medicine: a) young doctors who pass their 2-year internship and final exam; b) general practitioners already practicing (some have no specialist training and completed part of their training during residency); c) physicians with no internship (from the old Yugoslav educational system, with a 1-year residency and "state professional" exam), working in general practice for many years, but who have never been vocationally trained; d) physicians who have not yet practiced GP/FM (employed in institutes, pharmaceutical companies, etc., only statistically regarded as GPs) (31). Regarding the results, further research is needed to determine the underlying reasons for why family medicine specialists are more frequently sanctioned than other PHCPs and why they experience more violence from patients and patients' relatives than other PHCPs. It is also interesting to research in the future whether this violence from the patients, influences PHCPs to go against HIIS rules. Patients need to be aware of the fact that family physicians do not limit their rights and that the majority of the decisions in regards to diagnosing and treatment depend on health insurances' regulations (32).

The population count in the work area was also associated with sanctions, but not with violence. In other studies, however, urban settings were shown to be significantly positively associated with violence (15, 27, 28). In Slovenia, the biggest region- Central Slovenian Region (Osrednjoslovenska), has 537,893 inhabitants, and the biggest municipality - Ljubljana has 279,631 inhabitants (33). Even though the municipality with the highest number of inhabitants is 269,631, the questionnaire included the category  $\geq 500,000$ –999,999, because this survey was made in accordance with

AGP/FM SEE member states who have bigger populations. It has to be noted that in our study there were 34 PHCPs who chose the category  $\geq 500,000$ –999,999. This raises the question about how participants understood the term “workplace area” and selected the category - by municipality or region. As there are no regions below the population of 50,000, we assume that those answers were meant as municipalities, consequently marking population below 20,000 as rural.

Regarding employment status, individual contractors were significantly more sanctioned than PHCPs working in public healthcare, but there was no difference in the experience of violence. This is contrary to the findings of Berendes et al. in which they concluded that the private sector is performing better in drug availability and aspects of delivery of care, including responsiveness and effort, and possibly being more client orientated (34). Another perspective to look at in future research is whether the frequency of control from the HIIS is the same in the public and private sector and whether individual contractors are more often targeted for evaluations.

Large amounts of health care funds are spent on medicines, and this number has been increasing in the last decades in Slovenia - from 384\$/capita in 2002 to 546\$/capita in 2018 (35). Because of this, policy makers are searching for different strategies to control the costs of medicines while providing patients with the medicine they need. They can do this in two different ways - by introducing educational policies or regulatory policies. Educational policies include laws, rules and regulations that require medicine prescribers to get certain types of information, education or feedback about their prescribing behavior. Regulatory policies, on the other hand, include laws, rules and regulations regarding who can prescribe medicines, what type of medicines they can prescribe and how much they can prescribe. Usually, prescribers are monitored to make sure they follow these policies (36). A review covering studies from the UK, Germany and Ireland concluded that drug budgets for physicians in private practice can limit drug expenditure (per item and per patient) by limiting the

volume of prescribed drugs, increasing the use of generic drugs or both (37). In Slovenia, even though there is a combination of educational and regulatory policies controlled by the HIIS, in our study we still see that the most common reason for sanctioning is “Prescribing drugs not in accordance with HIIS rules”. Maybe a bigger accent on educational policies could reduce these numbers in the future.

In Slovenia, out-of-pocket payments are still relatively low as most health services and medicines are covered by compulsory and complementary health insurance schemes (38). So, another option might be increasing co-payments and out-of-pocket payments as a way of reducing the prescription of drugs above the agreed amount. A systematic review concluded that cap and co-payment policies may reduce the use of medicines and reduce medicine expenditures for health insurers. However, they may also reduce the use of life-sustaining medicines or medicines that are important in treating chronic, including symptomatic, conditions and, consequently, could increase the use of healthcare services. Fixed co-payment with a ceiling and tiered fixed co-payment may be less likely to reduce the use of essential medicines or to increase the use of healthcare services (39).

Physician density in Slovenia is 3.09/1,000 population and is among the lowest in Europe (40). In 2014, the number of PHCPs still lagged behind most EU countries (41), leading to problems of access and over-referrals to specialist care in some parts of the country (42). Our study, on the other hand, showed that issuing referrals not in accordance with HIIS rules wasn't a very common reason for sanctioning.

Having an electronic health record (EHR) is strongly empirically associated with the workflow, policy, communication and cultural practices recommended for safe patient care in ambulatory settings. Even medication safety had a statistically significant and positive relationship to full EHR adoption (43). Another study showed that the use of an electronic system was associated with a reduction in medical errors, compared with the paper-based method (44). EHR also result in

a positive financial return on investment to the health care organization (45). In Slovenia, PHCPs record information about patients both in paper and electronic form. Around 10% of the reasons for sanctions are due to discrepancies between paper and electronic form, most often than not missing information in paper form which was already registered in electronic form. Different computer programs exist in Slovenia for medical records. The most commonly used program is “Hipokrat”. None of the programs allow the user to leave a “must- field” empty before proceeding to the next step, thus missing or forgetting to file a critical information is impossible. Since the implementation of the health insurance card, in which personal data, previous and ongoing therapy, history of prescribed medical devices and type of insurance are recorded we find paper form to be redundant, if there is further investment in the content of the health insurance card (46). Adding the needed information which is within the paper form to the EHR form, will help us achieve faster, less error prone recorded medical history, carried by the patient and at the same time real time copy will exist at the hands of the chosen PHCP database servers.

The strength of the study is that it is the first one to research the control of HIIS on PHCPs in Slovenia. It opens a lot of new questions about the regulatory system and the policies of sanctioning and gives space for formulating new hypotheses about additional research that could help in optimizing the system. The sample size of PHCPs was also satisfactory and the distribution of the survey through the Medical Chamber of Slovenia helped avoiding selection bias. With all the information given in this study, we think it is very easy for future researchers to optimize the survey and conduct further research.

This study has several weaknesses and most of them are connected to the formulation of certain questions. The first weakness is that we do not know the exact number of the subgroups of gynecologists and pediatricians within the group of PHCPs, because the question asked only if they are family medicine specialists or not. The second one is the question about sanctions: “Have you

ever been sanctioned by the HIIS?”, which limited gathering data about how many times PHCPs were sanctioned throughout their career. The third one is the question: “Have you ever experienced violence from the patient or patients’ relatives if you followed HIIS rules?”, which also limited gathering data about how many times PHCPs experienced violence. Finding research about Slovenia for comparison was also very hard, since our study is the first one to explore the issue.

## Conclusion

Shortcomings were observed from PHCPs regarding the adherence to HIIS rules and limitations. Family medicine specialists were sanctioned more frequently than other PHCPs, individual contractors were sanctioned more frequently than public healthcare PHCPs and PHCPs in working area with a population less than 20,000 were more frequently sanctioned than those working in an area with a bigger population count. The three most common reasons for sanctions were: “Prescribing drugs not in accordance with HIIS rules”, “Prescribing technical or orthopaedic devices not in accordance with HIIS rules” and “Excessive sick leave and/or unjustified sick leave“. Family medicine specialists were more often victims of violence from patients and patients’ relatives if they followed the HIIS rules. Age was also associated with violence from patients and patients’ relatives if PHCPs followed the HIIS rules. We believe that the future lies in partnership between PHCPs, patients and the HIIS, which could lead to strengthening the PHC provision and a more efficient healthcare system overall.

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### What Is Already Known on This Topic:

*Slovenia has a gatekeeper system comprised of public and private PHC. The Health Insurance Institute (HIIS), Health Inspectorate and Ministry of Health are responsible for following and regulating the work of PHCPs in Slovenia. These regulatory bodies use measures such as warnings and financial fines to control and improve the work of PHCPs. PHCPs regardless of control often experienced violence in their workplace.*

### What This Study Adds:

*Our study on the sample of 600 PHCPs showed that the sanctioning of PHCPs in Slovenia is significantly related with age, sex, years of prac-*

*tice, specialty of family medicine, workplace and employment status. Most PHCPs were exposed to verbal violence which was significantly associated with family medicine specialty and age. All this information should be taken into consideration in order to change and modernize the system of monitoring and control.*

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## Langerhans Cell Histiocytosis in a Three-Year-Old Girl in Bosnia and Herzegovina

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### Abstract

**Objective.** To present a rare disease, and to point out that clinical manifestations treated for a long period of time without an adequate response to therapy may be a manifestation of a rare disease. **Case report.** We present the case of a 3-year-old girl who had been drinking a large amount of water for the previous ten days with frequent urination, and who experienced the worsening of symptoms of scalp dermatitis that had been treated for a year without success. Physical examination revealed a maculopapular rash on the scalp, neck and both ear shells, and exophthalmos of the right eye with periorbital edema. Magnetic resonance imaging of the orbits showed extensive lesions of the skull bones. Further diagnostic evaluation revealed similar lesions in other bone structures. Biopsy of the affected region, microscopic and immunohistochemical analysis led to diagnosis of Langerhans cell histiocytosis. **Conclusion.** Langerhans cell histiocytosis mostly occurs in the first three years of life. The incidence is 4-5 patients per million children under 15 years of life. The clinical presentation is highly variable, and can range from isolated, self-healing skin and bone lesions to life-threatening multisystem diseases. Due to the diverse clinical picture, that is often unrecognized, these patients are often referred to other specialists, resulting in the treatment of individual symptoms rather than the underlying disease.

**Key Words:** Langerhans-Cell ▪ Child ▪ Dermatitis ▪ Exophthalmos ▪ Rare Disease.

## Introduction

Histiocytoses are a rare and heterogeneous group of diseases characterized by pathological accumulation and multiplication of cells of the monocyte-macrophage system in tissues. The World Health Organization divides histiocyte diseases into dendritic cell diseases, macrophages, and histiocyte malignancies. The Langerhans cell (LC) is a bone marrow-derived mononuclear cell, belonging to the dendritic cell family. Factors that play a role in the etiology and pathophysiology are: infections (especially viral), immune system cell dysfunction, neoplastic mechanisms, genetic factors, race/ethnicity, and a combination of these causes (1, 2). We present a case of a rare disease from initial symptoms to diagnosis.

## Case Presentation

A three-year-old girl had been brought to the pediatrician in primary health care. For the previous ten days she had been drinking a large amount of water which was accompanied by frequent urination. Her scalp dermatitis had been treated unsuccessfully for the previous year, and the symptoms were deteriorating. At the physical examination there were changes on the scalp, neck and both ear shells, in the form of erythema, papules and crusts, with odor (Figure 1). There was evident proptosis of the right eye, with periorbital edema and divergent strabismus. The general condition of the child was good. Laboratory results were normal, except for mild anemia (Hgb 10.3g/dl, Hct 32%, MCV 60 fl). Due to suspicion of a retrobulbar tumor mass an ophthalmologist was consulted and rec-

ommended urgent magnetic resonance imaging (MRI) of the orbit.

Examination of the child's medical records indicated that child was born healthy. At the age of two, changes began on her scalp and she was referred to a dermatologist. The dermatologist treated her under the diagnoses of Seborrheic dermatitis, Eczematous dermatitis and Tinea capitis, but the lesions persisted.

Two months after the scalp lesions appeared, she presented for an examination with a petechial rash. Laboratory results showed thrombocytopenia (PLT  $70 \times 10^9/L$ ). She was examined by a hemato-oncologist, treated on an outpatient basis with vitamin C, and her platelet count returned to normal within 7 days. She had not been examined by a pediatrician in the previous six months, but she visited a dermatologist in a private practice. MRI of the orbit showed extensive lesions of the skull bones, corresponding to the lesions usually seen with Langerhans cell histiocytosis (Figure 2).

The diagnostic evaluation continued in the hemato-oncology department. Osteolytic lesions were also found on the bones of the pelvis, femur and humerus (Figure 3).

After femoral bone biopsy, the pathohistological, microscopic and immunohistochemical findings confirmed the diagnosis of Langerhans cell histiocytosis. Chemotherapy started according to the protocol.



Figure 1. Scalp skin involvement.

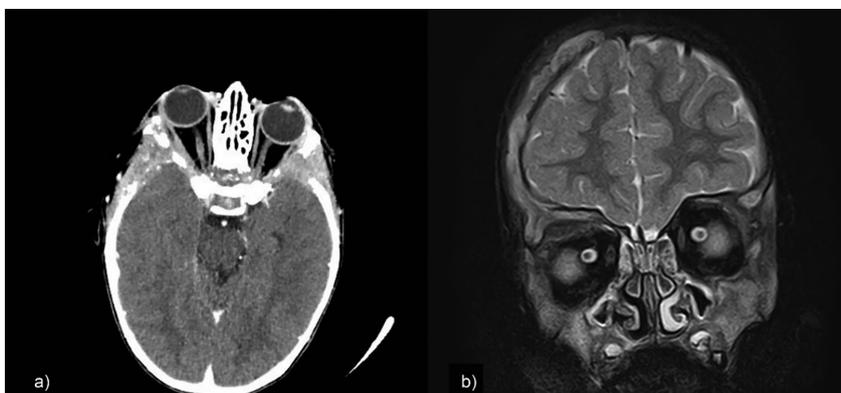


Figure 2. a) CE-CT axial scan revealed the presence of osteolytic lesions in the skull, causing right-side proptosis; b) Coronal T2w MRI scan indicates the involvement of the right orbital roof, along with the rest of the frontal bone with isointense osteolytic lesions.



Figure 3. X-ray representation of the osteolytic lesions in the left iliac bone and metaphysis of the right femur.

## Discussion

Langerhans cell histiocytosis (LCH) can occur at any age, but the incidence is highest in the first three years of life. The current classification differentiates between the single system disease (SS-LCH) and the multisystem disease (MS-LCH). MS-LCH is defined as the involvement of two or more organs or organ systems. The following organ systems are classified as risk organs, and their involvement indicates a worse prognosis: the spleen, liver, hematopoietic system, and lungs. SS-LCH includes the involvement of one of the following systems (unifocal or multifocal involvement): bones, skin, lymph node, lungs, central nervous system or other (thyroid, thymus) (3-5). The most commonly affected organ in LCH is bone, where changes are present in 80% of cases (61% in the skull). It manifests as a tumor mass, sometimes accompanied by pain and swelling (6, 7). The time from the onset of bone lesion symptoms to the diagnosis of LCH varies, ranging from 1.5 to 4 months, according to a study in Japan. However, there are cases where the changes lasted more than 6 months (8, 9).

Skin lesions occur in 40% of cases, and they are the first manifestation of the disease in 80% of patients. They have different clinical manifestations, from varicella-like changes, seborrheic eczema, or macular rash. The time from the appearance of clinical symptoms of skin lesions to diagnostic biopsy is at least 3 months, in some cases more than 2 years. The final LCH diagnosis is based on histological and immunophenotypic examination of the tissue. Treatment depends on the severity of the disease and the number of organs affected (10, 11, 5).

## Conclusion

The aim of this paper is to present LCH as a rare disease, and to indicate the time needed from the initial symptoms to the establishment of the final diagnosis through review of other studies. The clinical presentation is highly variable and can

range from isolated, self-healing skin and bone lesions, to a life-threatening multisystem disease. Due to the diversity of the clinical features in this disease, patients are often referred to other specialists (dermatologist, orthopedist, ear, nose and throat specialist or pediatric dentist), which results in the treatment of individual symptoms rather than the underlying disease. Cooperation among specialties is important for early establishment of the correct diagnosis. The prognosis is better in older children in whom the disease is limited to the skin and bones, while children with an affected liver, spleen and bone marrow have a poorer prognosis. Making the right diagnosis in a short period of time is a significant challenge for physicians, and considerably influences the prognosis of the disease and the quality of life of the patient.

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### What Is Already Known on This Topic:

*LCH is a rare disease, with unexplained etiology and unpredictable clinical course. It is most often manifested by changes in the bones and skin, in the form of a single systemic disease. In young children, skin changes often progress to the multisystem form. Patients with unifocal disease generally have a good prognosis. Patients with multifocal LCH have a variable prognosis, depending on how quickly the disease continues to progress and the patient's response to treatment.*

### What This Study Adds:

*Only a few cases of LCH in children have been described in BH, but more detailed studies on this disease have not been published. We present the first case of a three-year-old girl where the disease began with changes on the skin, but the diagnosis was set after a multifocal form had developed, with exophthalmos, diabetes insipidus, infiltration of the skull bones, and lesions in other bone structures. From this case we see that bone changes require radiological evaluation. The clinical presentation of LCH with skin lesions should lead to a straightforward diagnosis. A biopsy of a typical skin lesion would be the way to confirm the clinical suspicion and avoid delay in management. For physicians in primary health care it is very important to have information about rare cases in order to be able to establish a diagnosis more quickly and ensure a better prognosis for the patient.*

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## Rosalie Sattler-Feuerstein: An Austro-Hungarian Official Female Physician in Bosnia and Herzegovina, 1914–1919

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### Abstract

This short biography traces the life and medical activities of Rosalie Sattler, née Feuerstein (1883–19??), who was employed as an official female physician at the Austro-Hungarian (AH) provincial public health department in Sarajevo from 1914–1919. Born in 1883 into a Jewish middle-class family in Chernivtsi (then Czernowitz), Ukraine, in Bukovina, the easternmost province in Austria, Feuerstein moved to Vienna in 1904 to study medicine. After earning her MD from Vienna University in 1909, she started her career as an assistant physician at the Kaiser Franz Josef Hospital in Vienna. In spring 1912, Feuerstein moved to Sarajevo to work as an intern at the local provincial hospital (Landeskrankenhaus). In the same year, she married AH district physician Moritz Sattler (1873–1927) in Vienna. In 1914, Sattler-Feuerstein successfully applied to be an AH official female physician in Bosnia. She was an employee of the provincial public health department in Sarajevo and never functioned as an official female physician in the sense of the relevant AH service ordinance. After the collapse of the monarchy, Sattler-Feuerstein continued to be employed as an official female physician of the Kingdom of Serbs, Croats, and Slovenes. She resigned from service in 1919 and established herself as a private general practitioner in Sarajevo with her husband, who had also resigned as an official physician and started to practice privately at that point. Widowed in 1927, she left Sarajevo for an unknown destination, likely in 1938–1939, and vanished from historical records. **Conclusion.** Rosalie Sattler-Feuerstein (1883–19??) came to Bosnia as the eighth AH official female physician and worked as an employee of the AH provincial public health department in Sarajevo from 1914–1919, after which she practiced as a private physician in Sarajevo for more than 25 years.

**Key Words:** Bosnia and Herzegovina 1878–1918 ■ Official Female Physicians ■ Rosalie Sattler-Feuerstein ■ Sarajevo.

### Introduction

After Austro-Hungarian (AH) troops occupied the Ottoman province of Bosnia and Herzegovina (BH) in 1878–1879, the AH administration took unusual measures to transform the rural “backward” country into a “future province” of the dual monarchy. Among these measures was the recruitment of women physicians, particularly for the treatment of the female Muslim population in the context of widespread endemic syphilis. Though female physicians were not permitted in the Austro-Hungarian Empire (AHE) in 1890, joint minister of finance and BH governor Benjamin de Kallay was a staunch supporter of the use of state-employed

women doctors to contribute to the modernization and hygienization of Bosnia’s “rural” population (1). Six women physicians were employed in BH starting in 1890–1902, and they practiced in the social-medical framework of “women’s doctors for women” with de Kallay’s approval. Most of these women had a personal background in the AHE or Congress Poland, and all had acquired their diplomas in Switzerland or France.

The “Bosnian” institution of AH official female physicians was an essential step toward the admission of women to medical studies at domestic universities in the AHE in 1895 (Hungary) and 1899 (Austria). After de Kallay’s death in 1903, the AH administration changed its recruitment policies

for female health officers to work toward a long-term goal of exclusively employing female physicians with domestic diplomas. Accordingly, the positions in Banja Luka and Travnik were never officially advertised, and provisory officials Gisela Rosenfeld Januszewska (Banja Luka) (2) and Rosa Einhorn Bloch (Travnik) (3), both of whom had obtained Swiss diplomas, were urged as married women to practice as private physicians with official functions. After the position in Tuzla was advertised in 1897

in the AHE and filled by Jadwiga Olszewska (4), the next advertisement to recruit an official female physician for Bosnia was not published until 1918 (5). Nevertheless, Kornelija Rakić (Bihać) was employed in 1908 because she was a young woman physician from Vojvodina who had obtained a Hungarian diploma; therefore, she perfectly fit the desired profile (6). The AH public health department in Sarajevo also appointed Rosalie Sattler-Feuerstein, a young Austrian physician with a MD from Vienna University, as the eighth AH official female physician, although she did not practice in her actual function until after the AHE collapse.

Rosalie Sattler-Feuerstein's life and professional activities in Bosnia are the subject of this review. The latter topic is reliant on the sparse sources from Sattler-Feuerstein's medical studies in Vienna and her short career as an official female physician in AH and in the Kingdom of Serbs, Croats, and Slovenes.

### Rosalie Sattler-Feuerstein's Short Biography

A detailed biography of Rosalie (also Rosalia) Sattler-Feuerstein's is not yet available (7). She is briefly mentioned in Ctibor Nečas' collective biography of the AH female health officers in BH as the AH female health official in BH who never took



Picture 1. Czernowitz. From the period when Rosalie Feuerstein was born.

office (8). A grey literature research report by Barbara Martin (2017) based on Sattler-Feuerstein's personnel file as an AH official female physician reveals little more, but adds the fact that she remained an official physician in the service of the SHS-State in 1918 and the Kingdom of Serbs, Croats, and Slovenes in 1919 (9). She practiced as a private physician in Sarajevo starting in 1920 and left the city in 1938 or 1939; the circumstances, place, and time of her death proved untraceable (9). Rosalie Feuerstein was born on August 10, 1883, in Chernivtsi (then Czernowitz) (Picture 1), located in today's Western Ukraine the capital of Austria's easternmost province, Bukovina.<sup>1</sup>

She was the only child of Abraham Feuerstein, a local cloth merchant, and his wife Anna, née Zellermayer.<sup>2</sup> Rosalie likely attended a "lycée", a six-year higher education institution for girls in the AHE that did not qualify the female graduates for university entrance (10). Feuerstein decided to study medicine, so she registered as a private pupil at the (boys') "imperial-royal I. state gymnasium"

<sup>1</sup>"Feuerstein Rosalie", Czernowitz Birth Records, vol. VIII, p. 254, Record No. 358. [cited 2021 Jul 9]. Available from: <https://czernowitz.geneasearch.net/index.php>.

<sup>2</sup>Archiv der Israelitischen Kultusgemeinde Wien (IKG), Trauungsbuch Wien-Alsergrund 68, No. 9.



Picture 2. The Pathological-Anatomical-Institute of the University of Vienna at the time when Rosalie Feuerstein started studying there.

in Czernowitz<sup>3</sup> and passed her qualification for the university entrance exam (“matura”) in July 1904 at age 21.<sup>4</sup> In summer 1904, Feuerstein moved to Vienna and enrolled at the Medical Faculty of Vienna University<sup>5</sup> (Picture 2) as one of just 33 female students of medicine (11).

Women were first admitted to medical studies in Austria in 1899; however, the opportunities for girls to acquire the qualification for university entrance were still extremely limited. The number of female medicine students remained low but started to increase in 1910 (11). Most female medicine students in Vienna, including Feuerstein, came

<sup>3</sup>The number of female private pupils was comparatively high at the I. state-gymnasium Czernowitz because of the preference of the Jewish middle class for female academic education (see Wurzer, K.k. I. Staatsgymnasium in Czernowitz, p. 44). Rosa Welt, mariée Straus (1856–1938), the “first” (German) Austrian female physician at the fin-de-siècle, was the first girl in the AHE to pass her “matura” exam in 1873. The University of Vienna refused to accept her even as an “extraordinary student”; therefore, she moved to Berne, where she was awarded her MD in 1878. Welt worked as an activist for women’s academic education in Vienna and eventually emigrated to the United States in 1882 and Palestine in 1919.

<sup>4</sup>The “Czernowitz Imperial-Royal I. State Gymnasium” Graduates 1850–1913, p 16/80; <http://hauser.de/data/GraduatesAZNumbers.pdf> [accessed July 17, 2016].

<sup>5</sup>Rosalie Feuerstein’s registration forms from winter semester 1904–1905 to summer semester 1909, University of Vienna. University Archive, Nationale von Frauen, Medizinische Fakultät 1902–1921 (registration forms of women, medical faculty, 1902–1921), partly available online, <https://phaidra.univie.ac.at/o:950466>.

from the eastern provinces of Austria, due to the liberal Jewish middle-class preference in Galicia and Bukovina for female academic endeavours, including medical education (11–13). Feuerstein completed her medical studies in five years (Picture 3). She passed her third and final doctoral viva (Rigorosum) at Vienna University on December 16, 1909,<sup>6</sup> and was awarded her MD on December 23<sup>7</sup> (Picture 4).

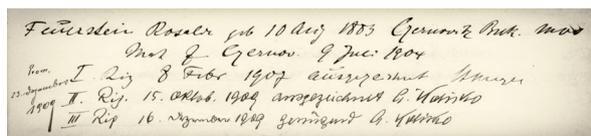
N:o	Abteilung	Name	Geburtsort	Datum	Anmerkung
110		Desjours Waldwede	Bodenstadt	11.8.1880	
111	phil.	Reinert	Wien	1887	
112	med.	Feuerstein	Galizien	1887	
113	phil.	Reinert	Wien	1887	
114		Siegl	Wien	1887	
115		Klein u. Pisko	Wien	1887	

Picture 3. Rosalie Feuerstein’s listing in the “Index of Women Graduated at Vienna University, 1897–1923”. Source: University Archive, Rectorate Archive and Student’s Evidence, M 36/1, s.p. (<http://phaidra.univie.ac.at/o:104996>). With the permission of the University of Vienna Library and Archives.

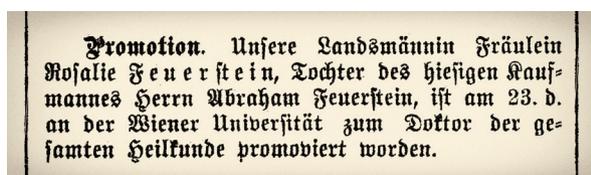
At that point, female physicians were still sufficiently rare in Austria that the Daily Press in Bukovina noted that “our compatriot, Miss Rosalie Feuerstein, daughter of our local merchant Abraham Feuerstein” had received her medical doctorate at Vienna University (14) (Picture 5).

<sup>6</sup>The medical curriculum at AH universities did not require students to submit a thesis but did require them to take three comprehensive “rigorous” examinations known as “Rigorosa”.

<sup>7</sup>“Rosalie Feuerstein”, University of Vienna, University Archive, Doctoral viva records (Rigorosenprotokoll) Med No 4, 1903–1930, p. 136.



Picture 4. Rosalie Feuerstein's entry in the Doctoral Viva Records of Vienna University. Source: University Archive, Doctoral Viva Records (Rigoroosenprotokolle), 1903-1923. With the permission of the University of Vienna Library and Archives.



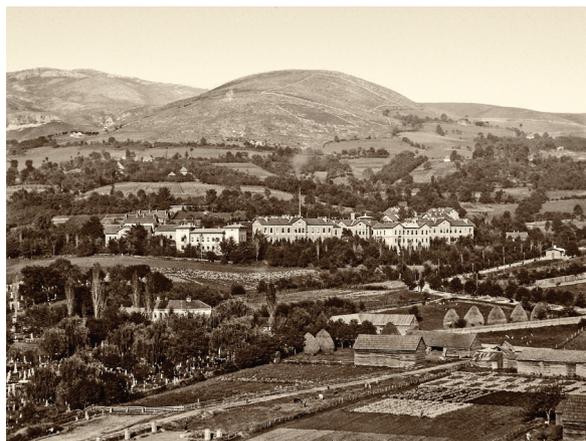
Picture 5. Notification in a local Bukovina newspaper concerning the graduation of "our compatriot Rosalie Feuerstein, daughter of our merchant Abraham Feuerstein as a medical doctor". Source: Bukowinaer Post. 1909, December 25; p. 5.

Feuerstein commenced her career as an "aspirant" at the "imperial-royal" Kaiser Franz Josef Hospital (today "Klinik Favoriten") in the tenth district of Vienna on December 27, 1909 (8). In April 1910, she was employed as an assistant physician ("Sekundärärztin") at the clinic specializing in epidemiology, which was established in 1891. This hospital was particularly notorious for antisemitism. At the time, the hospital management had constructed palliassed walls in all recreation rooms for the medical personnel to keep Jewish and "Aryan" physicians apart (15). In 1912, Feuerstein left Vienna for Bosnia, where she began an internship at the provincial hospital ("Landeskrankenhaus"); in Sarajevo on May 1, 1912 (9) (Picture 6).

Once employed as an assistant physician at the provincial hospital in July 1912, she asked the provincial government to approve her marriage to Moritz<sup>8</sup> Sattler (1872–1927), an AH district physician from the Czech lands who had recently been appointed "physician of the police department" ("Polizeiarzt") in Sarajevo (9).<sup>9</sup> It is probable that

<sup>8</sup>"Moritz" is the German spelling of the name; alternate spellings are "Moriz" and "Moric".

<sup>9</sup>Moritz Sattler, born on December 17, 1872 in Kozolupy, a village next to Plzen in the Czech lands, completed his medical studies at Prague University on July 18, 1898 (Archive of

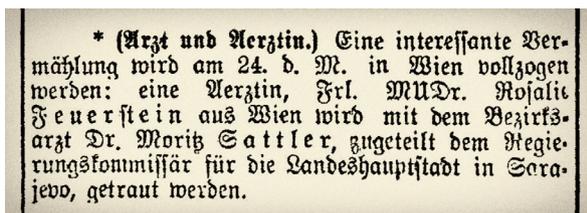


Picture 6. The Provincial Hospital ("Landeskrankenhaus") in Sarajevo at the time when Rosalie Feuerstein started working there. With the permission of the University the National Museum of Bosnia and Herzegovina.

Feuerstein and Sattler had known each other for a long time and that Sattler had arranged Feuerstein's internship in Sarajevo as a first step toward her future employment as an official female physician in BH. Moritz Sattler and Rosalie Feuerstein

the Charles University, collection Registry books of the German University in Prague, inventory No. 2, Registry book of doctors of the German Charles-Ferdinand University in Prague/German University in Prague (1892–1904), p. 191; [cited 2021 Jun 7] <http://is.cuni.cz/webapps/archiv/public/book/bo/1751652802704438/466/?lang=en>. After working as an assistant physician in Professor Wölfler's private clinic in Prague, Sattler was appointed assistant physician of the provincial hospital in Sarajevo (Pilsener Tagblatt, 26. Sept. 1900, p. 5). He was employed in the Department for Venerology and Dermatology, which was headed by renowned Bosnian dermatologist Leopold Glück (1854–1907). According to Moritz Sattler's obituary, he was denied the chance to succeed Glück as he had intended (16); instead, he was appointed district physician ("Bezirksarzt") in the communities of (Bosansko) Grahovo at Bosnia's western border and Bosanski Petrovac in the northwest of the country. Upon his marriage in 1912, he returned to Sarajevo as "physician of the police department" ("Polizeiarzt") in 1912 or 1913. Sattler published materials on syphilis prevention during World War I. After the war, he did not request an extension of his civil service and retired as an official physician. In January 1920, Sattler and Sattler-Feuerstein's names were included on an official list of private doctors in BH (17). Sattler died on November 28, 1927 (18), while visiting a patient (16), and he was buried in the Old Jewish Cemetery in Sarajevo. Sattler's obituary, which was published in a newspaper for the Jewish community in Sarajevo, extols his human qualities and popularity in the local Ashkenazi community (16).

married on September 24, 1912, in Vienna.<sup>10</sup> Daily newspapers in Vienna and Prague noted the extraordinary marriage between “physician and woman physician”, which was considered “remarkable” (19) (Picture 7).



Picture 7. Newspaper notice on the “remarkable wedding” of Dr. Rosalie Feuerstein as a female physician and Dr. Moritz Sattler as physician. Source: Prager Tagblatt. 1912, September 22; p. 3.

After her marriage, Rosalie (Rosalia) Sattler-Feuerstein continued to work as an assistant physician at the Kaiser Franz Josef Hospital in Vienna,<sup>11</sup> and her parents moved to Vienna as well. Her father died in Vienna in 1916, after which her widowed mother moved to Sarajevo, where she lived with her daughter and son-in-law until<sup>12</sup> her death in 1930.<sup>13</sup> To enable her move to Sarajevo, Sattler-Feuerstein informally applied to the AH provincial public health department as an official female physician in 1914. Her application was approved, and she was appointed female health officer on August 31, 1914 (9). In her case, marriage was not considered an obstacle to employment, whereas Gisela Januszewska in Banja Luka and Rosa Einhorn in Travnik were both urged to resign from their office upon marriage (2, 3). However, Sattler-Feuerstein

never exercised her office, but she worked as an employee of the provincial public health department, probably with administrative duties.

After the collapse of the AHE, Sattler-Feuerstein continued her employment as an official physician of the Kingdom of Serbs, Croats, and Slovenes, and she swore her oath of office to King Petar in March 1919 (9). Barbara Martin determined that Sattler-Feuerstein resigned soon after and practiced as a private physician in Sarajevo beginning in 1920 (9). Her practice was listed in an address and telephone directory of the Drina Banovina in 1938 but was missing from a Sarajevo directory of 1940 (9). Martin concludes that Sattler-Feuerstein, who had been widowed in 1927 and lost her mother in 1930, left Sarajevo around 1938 for an unknown destination. From that point on, her person cannot be traced; it is unclear whether she moved to another location in Bosnia or Yugoslavia, emigrated elsewhere, or was deported and became a victim of the Holocaust.<sup>14</sup>

### Rosalie Sattler-Feuerstein’s Professional Activities

In mid-September 1914, a series of German-language newspaper articles in the AH Empire reported that “Mrs. Rosalia Sattler-Feuerstein, MD” had been appointed official female physician in Bosnia and assigned to the provincial government’s public health department in Sarajevo (20). This assign-

<sup>14</sup>Rosalie Sattler-Feuerstein was never pronounced dead. Barbara Martin’s inquiries whether she became a victim of the Nazi persecution of Jews in Yugoslavia in 1941 and 1942 were negative (9). An investigation into a possible emigration of Sattler-Feuerstein to the US or Israel turned also out to be negative. She may have headed for a politically insecure destination such as the Czech Republic or Rumania in 1938/1939 and eventually sought refuge in Britain or France, possibly illegally and under a false name. However, a possible flight cannot be traced, nor Rosalie Sattler-Feuerstein’s residence after 1945. The situation is made even more complicated by the fact that both “Rosalie Sattler” and “Rosalie Feuerstein” are not uncommon names; among other, she must not be confused with “Rozalija Satler”, born 1858, a native of Zagreb who was murdered in the Holocaust [cited 2021 Aug 9]. Available from: [https://yvng.yadvashem.org/index.html?language=de&s\\_id=&s\\_lastName=Sattler&s\\_firstName=Rosalie&s\\_place=&s\\_dateOfBirth=&cluster=true](https://yvng.yadvashem.org/index.html?language=de&s_id=&s_lastName=Sattler&s_firstName=Rosalie&s_place=&s_dateOfBirth=&cluster=true).

<sup>10</sup>Archiv der Israelitischen Kultusgemeinde Wien (IKG), Trauungsbuch Wien-Alsergrund 68, No. 9.

<sup>11</sup>She is registered in Lehmann’s directory for Vienna as “Dr. Rosalie Feuerstein, Doctor der gesamten Heilkunde, Kaiser Franz-Joseph-Spital” from 1910–1914; cf. Adolph Lehmann’s allgemeiner Wohnungs-Anzeiger; nebst Handels- u. Gewerbe-Adressbuch für d. k.k. Reichshaupt- u. Residenzstadt Wien u. Umgebung, Wien 1910; 1911; 1912; 1913; 1914, Available online, <https://www.digital.wienbibliothek.at/wbrobv/periodical/titleinfo/5311>.

<sup>12</sup>Sarajevo Historical Archives. Census of the Sarajevo, 1925. Census form of Anna Feuerstein née Zellermayer [in Bosnian].

<sup>13</sup>Book of the Dead of the Ashkenazi Rite 1931-1945;(2):1[in Bosnian]. Sarajevo: Jewish Communities of Sarajevo.

ment was unusual because female public health officers were generally assigned to the district in which they were expected to exercise their office. The responsibilities of a female health officer included operating outpatient wards that provided free care to women and children, educating local women about hygiene and disease control (including implementing vaccinations) and, after 1906, participating in systematic syphilis eradication campaigns (1). In Sarajevo and the Sarajevo district, these tasks were performed by official female physician Teodora Krajewska, who was appointed in 1899 (21). Although three districts (Travnik, Bihać, Mostar) had not had an official or semi-official female physician since 1912, Sattler-Feuerstein became an employee of the AH provincial public health department in Sarajevo (7-9). She is listed as a court-sworn expert for forensic medicine in an annually published AH address and telephone directory for BH (22). She also practiced as a private doctor at the address “Terezija ulica 87”, Sarajevo (23).

As an official physician, Sattler-Feuerstein presumably performed administrative tasks, and her provisory employment was made permanent on November 22, 1915 (9). It seems that she was selected to take over the office of the official female physician of Sarajevo when Teodora Krajewska (then 60 years old) retired. However, Krajewska did not retire before the end of the monarchy. After World War I, Rosalie Sattler-Feuerstein and Moritz Sattler both resigned from their offices to establish themselves as private general practitioners. Both are included in an official list of all physicians in BH published in January 1920 under the heading “Private Doctors” (17); however, little is known about their practice. Moritz Sattler’s obituary (17) and a public expression of gratitude to both his (24) and Rosalie Sattler-Feuerstein’s address (25) which were printed in local Jewish newspapers, suggest that the patients in their private practice were predominantly from the former AH Ashkenazi community in Sarajevo and elsewhere in Bosnia.

## Concluding Remarks

Rosalie Feuerstein, born in Chernistvi, Ukraine (then Czernowitz, Austria) in 1883, was among the first women to study medicine at Vienna University after the first admission of female students to medical studies in Austria in 1899. At 17 years old, she started studying for her qualification for university entrance exam as a private pupil of the (boys’) state gymnasium in Czernowitz, and she passed the exam in 1904. After moving to Vienna, Feuerstein completed her studies at Vienna University in December 1909, after which she worked as assistant physician in the Kaiser Franz Josef Hospital in Vienna. Presumably at the instigation of her future husband Moritz Sattler, a physician from Plzen in the Czech lands in AH service in Bosnia, Feuerstein successfully applied for an internship at the provincial hospital in Sarajevo in 1912. Two years after her marriage to Moritz Sattler in Vienna in September 1912, she was appointed as an AH official female physician in BH. She was recruited as an intended successor to the soon-to-be retired official female physician of Sarajevo, Teodora Krajewska, and the possibility of her employment in one of the three vacancies at the time seems not to have been considered. Sattler-Feuerstein never took up her office; instead, she worked as an employee at the AH provincial public health department, presumably performing administrative tasks. After the collapse of the AHE, she initially remained as an official physician in the service of the Kingdom of Serbs, Croats, and Slovenes, and she quit the service in 1919. In the interwar period, she practiced as a private physician in Sarajevo with her husband Moritz Sattler, who died in November 1927. Rosalie Sattler-Feuerstein’s person cannot be traced in Sarajevo after 1938. The circumstances, place, and time of her death are unknown.

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