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# Rosacea dermatology life quality index and coping strategy

Azrumelashvili S. Kituashvili T.

## Abstract

**Background:** Rosacea is a chronic cutaneous inflammatory disorder characterized by persisting erythema, telangiectasia, papules, pustules, edema, phymas and ocular involvement. Because of its centro facial location rosacea can affect patients' psychological well-being and can cause: depression, anxiety which itself decreases patients' quality of life.

**Aim:** The aim of this study is to review, and summaries published literature about the rosacea, quality of life and coping strategies in patients with rosacea.

**Methods:** We searched all available literature in English, published in the PubMed and Google Scholar database. We used the key words: Rosacea, Dermatology Life Quality Index (DLQI) questionnaire and Carver coping strategies- COPE questionnaire.

**Conclusion:** Based on the literature review we identified that rosacea causes a marked decrease in DLQI in most patients. Data revealed that patients with rosacea use mostly avoidance strategies focused on emotions.

(TCM-GMJ October 2018; 3 (2):P4-P7)

**Keywords:** Rosacea; Quality of life; Coping; DLQI; Stigmatization.

## Introduction

Rosacea “acne rosacea”, “couperose” and “facial erythrosis”(1), is a common chronic inflammatory skin disease caricaturized by flushing, persistent erythema, telangiectasias, pimples and pustules on the face (2,3).

Rosacea is more common in patients with the Celtic skin type and a fair complexion (Fitzpatrick types I–II) than in Mediterranean types with darker skin (IV and V) (1,4). The usual age of onset is between 30 and 50 years; however, in rare cases, rosacea can already occur in children (4,5).

According the data of US Census Bureau, population estimates prevalence of Rosacea is 13 million people in the United States, in Georgia - 223,340. The prevalence varies greatly between countries from 1% to 22% (4).

Rosacea occurs in both men and women, although it is more prevalent in women than in men, especially in earlier stages of the disease, 80% of rosacea women patients are 30 years or older, with the highest prevalence at age of 61 to 65 years, whereas men are more frequently affected from the age of 50 upward with a peak prevalence around 76 to 80 years. However, men with the condition are more likely to develop phymatous changes (3,6,7).

## Pathogenesis

At present, pathophysiology of rosacea is poorly understood. Various potential pathogenic factors plays role in development of rosacea, such as: genetic, dysregulation of the innate and adaptive immune system, neuroinflammatory mechanisms, environmental trigger factors include exposure to extremes of temperature (hot and cold air), temperature changes, ultraviolet exposure, caffeine, alcohol, hot and spicy foods, sunlight, exercise, acute psychological stresses, menstruation, demodex mites, Helicobacter pylori, and certain medications (3,4), local inflammatory responses to cutaneous microorganisms, as well as changes in the regulation of vascular and lymphoid vessels seem to play a role in pathogenesis of rosacea (1,8,9).

There is no confirmatory laboratory test for revealing the disease (4,10). Due to the multifactorial pathogenesis that cannot be easily addressed therapeutically, treatment strategy currently focuses on symptomatic suppression of inflammation and reduction of disfiguring features (4).

## Clinical Manifestations and Subtypes of Rosacea

Rosacea diagnostic criteria are clinical and have been defined by the National Rosacea Society Expert Committee (NRSEC), to comprise primary (flushing, non-transient erythema, papules and pustules and telangiectasia) and secondary features (burning or stinging, plaques, dry appearance, edema, ocular manifestations, peripheral location and phymatous changes) (11,12). Rosacea can be divided into four subtypes of erythematotelangiectatic (ETR), ETR flares are due to acute vasodilatation and innate inflammation. In subtype - II papulopustular (PPR), inflammatory papules and pustules are seen in the central region of the face. Subtype III - phymatous (PR) rosacea, disfiguring growth of hyperplastic sebaceous glands on the nose

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and other facial regions (4,11). Subtype IV - ocular rosacea that can include symptoms such as conjunctivitis, blepharitis, irritation, dryness or keratitis<sup>13,14</sup>. Patients can present with more than one subtype however ETR and PPR are mutually exclusive.

## Treatment

Rosacea is treatable but seldom curable. Treatment schedules are determined by the stage and severity of the disease, it is characterized by an unpredictable pattern of exacerbations and remissions on a background of highly sensitive skin (15-17). Since rosacea is a chronic inflammatory condition that waxes and wanes, with many triggers, the goal of treatment should be to subside acute flares with rapid-acting treatments and maintain the results with lifestyle modification and prolonged combination therapy (18).

## Discussion

A standard classification system for rosacea was published in the April 2002 issue of the Journal of the American Academy of Dermatology. Developed by the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea and reviewed by rosacea experts worldwide, it describes primary and secondary features of rosacea and recognizes 4 patterns of signs and symptoms, designated as subtypes (12).

To enhance the utility of the system for both clinicians and researchers, the committee has devised a standard method for assessing gradations of the severity of rosacea (15). For clinicians assessing patients, primary signs and symptoms may be graded as absent, mild, moderate, or severe (0-3), and most secondary features may be graded simply as absent or present (12).

This investigational instrument is intended to help to provide a foundation for better understanding of rosacea among practitioners and researchers by establishing a common language for communication and facilitating the development of a research-based approach to diagnosis and treatment (12).

Because the facial skin is the predominant site of involvement during rosacea, many patients sense that rosacea alters their social and professional interactions, leading to problems on the job, in their marriage, or in meeting new people (19). Previous studies show that those with chronic dermatoses including rosacea are often affected by emotional disturbance and social stigma. The common misconception that both the facial redness and the rhinophyma associated with rosacea are due to excessive alcohol consumption makes rosacea a socially stigmatizing condition for many patients, many research proves displayed a marked impact of rosacea on patient's emotional well-being and social activities associated with a decrease in patients' self-esteem. Patients more frequently report feelings of anxiety, guilt and shame, they are depressed and have feeling of embarrassment (12,20,21). Patients have the Social Phobia, that includes items such as 'I get nervous that people are staring at me as I walk down the street', 'I feel awkward and tense if I know people are watching me' and 'I would get tense if I had to sit facing people on a bus or a train (9,10, 22-26). Race involvements during rosacea causes more work-related stress and are more sensitive to unkind comments in the workplace (17). Such psychological factors perpetuating the distress.

Stigmatization is defined as a discrediting feature that sets a person apart from others and implies disapproval from others (24). Psychiatric morbidity in dermatology patients usually takes the form of mood and anxiety disorders. The prevalence of psychiatric disorders, most commonly depression and anxiety, ranges from 25% to 43% among dermatologic patients (15, 27). Within the co-

hort of rosacea patients studied here, more men reported feeling of stigmatization than women, in part due to a higher prevalence of the phymatous subtype (24).

According to the studies the frequency of perceived stigmatization was highest amongst those aged between 18 and 24 years old, which may be due to the greater importance of facial appearance and social pressure encountered by younger patients (24).

Stigmatization is important in the daily lives of those with rosacea and should be taken into consideration in the management of these patients. All these psychological symptoms can influence patient's quality of life.

During researches most, scientists use Dermatology Life Quality Index (DLQI) questionnaire and Carver coping strategies (28).

DLQI questionnaire was used to assess the quality of life in patients with rosacea. The questionnaire was designed in 1992 by Finalary and Khan to assess the quality of life in patients with skin diseases, it has been widely used in various communities and through various studies which its validity has been proved as 93% (15,16,28,29).

DLQI is a 10-item survey evaluating the quality of life in patients with a skin disease, covering six domains: symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment<sup>30</sup>. The questionnaire was structured with each question having four alternative responses: 'not at all', 'a little', 'a lot' or 'very much' with corresponding scores of 0, 1, 2 and 3, respectively (31).

Rosacea is a challenging disease to cope with (32-34). Coping is a very broad concept with a long and complex history (33,34). Many different scientific studies exist not only in dermatology but also in psychology, deal with individual differences in experiencing difficult events. Extremely important, both for theoretical and practical reasons, is explaining what constitutes coping with stress (35,36).

Coping is considered one of the core concepts in health psychology and in the context of quality of life, and coping strategies are strongly associated with the regulation of emotion, especially anxiety, throughout the disease period (37).

Perhaps the most widely cited definition of coping continues to be that of Lazarus and Folkman (1984), almost 30 years since it was first presented Lazarus & Folkman (1984) "Constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person": Lazarus (2004) "Efforts to manage adaptational demands and the emotions they generate"; Compas et al. (2001) "Conscious and volitional efforts to regulate emotion, cognition, behavior, physiology, and the environment in response to stressful events or circumstances" (13,34,38).

There is continued debate about the underlying structure of coping and the subtypes that best capture the varied nature of coping responses. For example, Skinner et al. (2003) identified over 400 subtypes of coping that have been studied, noting that progress in determining the structure of coping has been slow (34).

Coping strategies were classified commonly within two dimensions by Lazarus and Folkman (1984), but three dimensions by Compas et al. (2001). Lazarus and Folkman in their transactional model, conceptualized the coping process as an iterative cognitive-behavioral process exercised in a stressful situation, and emphasized the importance of the mutual interaction between cognitive appraisal on a stressor and coping. Findings suggest that the status of the coping process in stressful situations varies among individuals (39). They proposed (a) problem-focused (e.g., strategies directed toward managing the stressor) and (b) emotion-focused (e.g., strategies directed at managing emotional distress) coping dimensions. Alternatively, Compas and colleagues have classified coping strategies within (a) task-orientated, (b) distraction-

orientated, and (c) disengagement-orientated coping (36,40,41).

According to the transactional model of stress and coping, problem and emotion focused coping mediate the impact of appraisals on adjustment following stressful events (42); Problem-focused coping is directed to the stressor itself: taking steps to remove or to evade it, or to diminish its impact if it cannot be evaded (33). It involves employing active strategies to resolve the stressor, while emotion-focused coping involves processing and expressing feelings arising from the stressor (42).

Coping within the task-orientated coping dimension consists of strategies aimed directly at managing stress and includes logical analysis, effort expenditure, and thought control (41).

Task-oriented coping aims at dealing directly with the source of stress and the resulting thoughts and emotions; it is represented by strategies such as increased effort, planning, relaxation, and cognitive reappraisal. Disengagement-oriented coping encompasses strategies through which people disengage themselves from the process of striving to make progress on a personal goal; it includes strategies such as denial, behavioral disengagement, alcohol and drug consumption, and venting of unpleasant emotions (40).

Successful adaptation to stress includes the ways in which individuals manage their emotions, think constructively, regulate and direct their behavior, control their autonomic arousal, and act on the social and nonsocial environments to alter or decrease sources of stress (36).

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# Epidemiological characteristics of tinea pedis in the military

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## Abstract

**Background:** Tinea pedis is one of the widespread diseases of the world, which can infect people of all ages and sex. Approximately 70% of the world's population has suffered this pathology at least once in a life. The main causative pathogens of tinea pedis are: trichophyton rubrum, trichophyton mentagrophytes, epidermophyton floccosum.

**Aim:** The aim of this study is to represent epidemiological characteristics of Tinea pedis based on some researches conducted on military personnel of different countries.

**Methods:** The review of the literature has been carried out using the "ScienceDirect", "Scopus" and "PubMed" scientific bases in order to define relevant scientific works - published in English.

**Results and conclusions:** According to the research analysis, prevalence of tinea pedis in the militaries is remarkably higher than in the civilians, more common in men than in women. The research revealed correlation between military branches, military ranks and prevalence of Tinea pedis. Also researches claimed that fungal infections are highly prevalent in military personnel deployed on combat and peacekeeping operations. (TCM-GMJ October 2018; 3(2):P8-P11)

**Keywords:** Tinea pedis; Epidemiology; Military.

## Introduction

Tinea pedis got widespread in the second part of the 20<sup>th</sup> century. It was caused by the increase in urbanization, intensive development of sports and fitness facilities(1), but it is worth to note that prevalence of tinea pedis in the militaries is remarkably higher than in the civilians. According to the few available literary data dermatophytosis is one of the common disease in military personnel (2). Hermetic clothes, sweatiness, physical and emotional stress, contagiousness – (common shower room, barracks, water pools) are risk factors of skin diseases, for which military personnel is considered to be a risk causing population. As tinea pedis has contagious and recurrent nature, this pathology is the most common disease in dermatomycosis. For this reason it represents a medical and social problem, particularly in militaries. This pathology is skin fungal disease which mostly damages interdigital web spaces or the sides of the feet.(1) Regular usage of military boots makes favorable environment for the disease to spread, which makes militaries different from the civilians.

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## Aim

The aim of this study is to represent epidemiological characteristics of tinea pedis based on some researches conducted on military personnel of different countries.

## Materials and Method

We searched epidemiological research material in the databases of "ScienceDirect", "Scopus", "PubMed", "ResearchGate" and "Google Scholar" published in English. We used following search terms: "tinea pedis", "epidemiology", "fungal infection", "soldiers", "army forces", "military" and "prevalence".

## Results and Discussion

The literary sources obtained by us reveal that skin diseases, respiratory infections and disease of the musculoskeletal system are the most frequent reasons for military personnel to seek medical care. This testifies to the research analysis conducted in Oslo Military Hospital in Norway, according to which 1360 patients with upper respiratory disease was the primary reason for seeking medical attention in 26% of the patients, 21 % visited the

clinic because of disease or pain in the musculoskeletal system, and 16 % suffered from a skin disease (3). Regime of militaries includes physical activity, stress, sweating, confrontation, common showers and barracks, the use of closed cloths, wearing military boots for a long time which makes military personnel being included in the risk group. The research revealed correlation between military branches, military ranks and prevalence of tinea pedis. The intensity of prevalent of the disease was high among infantry men and militaries with low rank.

During the research conducted among militaries in Israel to investigate the prevalence and risk factors of tinea pedis. 223 soldiers filled the questionnaire according to which risk groups were disclosed and all of them underwent laboratory research. It was found out that the clinical prevalence of the disease was 60.1% and mycological point prevalence was – 27.3%. Univariate analyses demonstrated that the prevalence of tinea pedis varied with the setting of military training (basic training: 70.3%, armor commander training – 56.4% , advanced infantry training– 81.5% and armor officer training – 34.8%.) and was associated with male gender, frequency of sock changes and the length of military service. This research confirmed that tinea pedis is highly prevalent Israeli soldiers (4).

Similar study was conducted in Japanese Self-Defence Forces undergoing special training. 74 servicemen were divided according to the width of these spaces into: group I- wide; group II - fairly wide; and group III - closed. At the same time significant correlation was identified between the duration of military service and prevalence of the disease. Prevalence tinea pedis was higher in subjects who had served for 10 years or more, than in those with fewer than 10 years of service. Classified by the disposition of their toes, group I included 10 subjects, group II - 34 , and group III - 30 . The prevalence of tinea pedis was 90% (27/30) in group III was significantly higher than in the other groups. A significant correlation was seen between length of service and severity. Soldiers with both a long service record and closed interdigital spaces showed both a high prevalence and marked severity (6).

In one of the military units in Turkey, the researchers determined the prevalence of skin diseases among Turkish soldiers. The results obtained were compared with the spread of skin disease in the civil sector. The location of the military unit was distinguished with high temperatures and moisture. The research was conducted in summer and the criteria for participation was: age from 20 to 31 years, serving from 1 month to 2 year. The military completed the questionnaires as a result of which 188 soldiers had dermatological disease. A total of 97 soldiers suffered from superficial fungal infections, from these prevalent tinea pedis was 25.5% (48 patients) and onychomycosis - 5.8% (11 patients);. In the civil sector spread of tinea pedis was only 0.72%. The cases of dyshydrous eszema reached 18.6% in militaries and 0.6% in civil sector. The results obtained showed that contagiousness of skin diseases is significantly higher in militaries than in civilians (7).

The researchers have received similar results even when the prosecution took statistical data from the military hospital and compared them with the data of the civil sector. They determined and compared the prevalence of skin conditions between civilian and military populations. For this reason 3382 has been surveyed in the Turkish military hospital (including 1148 militaries and 2234 civilians). Among militaries the most frequent dermatological condition was tinea pedis (15.8%) , it was 4.4% - among civilians. The results obtained showed that it is necessary to take preventive measures in Army (8).

As it is known, militaries often take part in peacekeeping missions which additionally supports spreading tinea pedis. In order to disclose dermatological diseases, Chinese researchers surveyed militaries of United Nations participating in peacekeeping mission in Libya. The research was prospective covering 1658 militaries among which 62% was Asian. It was found out that dermatitis and eczema are the leading nosology (27%), as for tinea pedis, it was noted in 13%, particularly in tropical regions (9). According to the research analysis held in different hot points of the world, one of the mostly widespread skin diseases was warts – 10.7%, fungal infection – 10.4%, acne – 9.0%, nonspecific eczematous conditions – 7.1%. It is worth to note that hot and humid climate in Vietnam, East Timor, was connected to the bacterial and fungal infections, while in dry climate, Bosnia, Iraq where eczematous conditions made up a larger part of the dermatologic case-load (10).

Interesting research was held among policemen in the city Abidjan, Africa, during which the epidemiology of tinea pedis was determined. 303 policemen involved in the research, 233 of which (76.9%) had a positive diagnosis after mycological examination. Causing factors were *Trichophyton interdigitale* (in 40.3% of the total cases), *Microsporum langeronii* (in 30.0%) and *Microsporum rubrum* (in 15.5%). The duration at the police school and the practice of sports activities were statistically associated with the occurrence of the disease(11). Researches held in Singapore showed that 24.5 cases from every 100 servicemen were characterized with dermatological problems (6.7% of which were fungal infections) (12).

A research was conducted during the War in Croatia from 1991 to 1992 , where the frequency of the spread of foot skin diseases was determined. 1702 Croatian soldiers from 2002 participating in the research were exposed to direct war activities. The control group consisted of 300 new recruits not involved in war activities. Among the 1,702 examined active duty soldiers, dermatomycosis was confirmed in 832 (49%) cases, 170 soldiers reported dermatomycosis before they were stationed on the battlefield (10%), while 662 soldiers (39%) developed the condition during the time of war activities. Dermatomycosis was confirmed only in 30 soldiers (10%) of the control group including 300 recruits(13).

Prior to the military service in Denmark, 665 recruits were examined clinically and microbiologically for tinea pedis. 546 of them were reexamined at the end of

military service. Clinical signs of dermatophyte infection were 6.2% respectively, during the second investigation it reached 7.0%. The prevalent of tinea pedis was 4.2% during the 9 months of military service. Of those infected at the first visit 41% had persistent infection mainly pathogens was *Trichophyton rubrum*, where as new infections were largely caused by *Trichophyton mentagrophytes* (14). Another similar study was conducted during which 73 military personnel were examined for tinea pedis as well as onychomycoses before and after a duty period of 6 months. It was found that the prevalence of the fungal infections prior to the beginning of military service was 16.4% and 32.3% - after the service. During the first examination the dominant pathogens were *T.rubrum* and *T.mentagrophytes*, while during the second investigation predominant pathogen was *Candida albicans* (15). According to the study, significantly high prevalence of tinea pedis was revealed in Brazil and Korea. In Brazil, 44.8% of 221 soldiers had dermatophyte infection. *T.rubrum* was the most prevalent – 33.3%, *T.tonsurans* – 13.1%, *T.verrucosum* – 11.1%, *T.interdigitale* – 9.1% and *T.mentagrophytes* – 6.1% (16). The research held in Korea showed that contagiousness of skin diseases was extremely high, particularly, 798(60.4%) soldiers among 1321 ones had one or more skin diseases. Three most widespread diseases were acne (35.6%), tinea pedis (15.2%) and atopic dermatitis (5.1%) The diseases were closely related to the period of military service (17).

We found the lowest rate of tinea pedis only in two works of the surveys conducted among the military. 1024 Italian naval forces cadets of 18-30 years have been checked. 975 (95.21%) of them were men and 49 (4.79%) were women. Studies revealed only 33 (3,2%) cases of clinic-laboratory confirmed tinea pedis, while onychomycosis was confirmed in 2 (0.2%) cases(18). Almost similar results were received as a result of cross-sectional study conducted in Pakistan. A random sample of 350 individuals was selected out of individuals who were undergoing initial military training. Out of 350 subjects on clinical examination tinea pedis was suspected only in 34 (9.71%). and 10 (2.8%) of them cases were confirmed in laboratory (19).

As for the Georgian Armed Forces, in our country, no study has been conducted to research the development and spread of tinea pedis. Giorgi Abramishvili Military Hospital of Georgian Armed Forces has no epidemiological data on tinea pedis, because these diseases are not registered separately. In our work we used 5 old data of the hospital mentioned above. It does not allow any base to conduct any fundamental analysis to determine the reasons of development and spread of tinea pedis. See Table 1.

The table shows that Dermatophytosis consisted 61.53% of total number of mycosis in 2013, 49.32% - in 2014, 63.15% - in 2015, 64% - in 2016 and 64.60% - in 2017.

## Conclusion

Different literary sources confirm that during recent five decades, tinea pedis got worldwide epidemiological and economic problem. Chronic and contagious nature of this pathology makes the disease one of the 21st century medical and social problem.

According to the research analysis, prevalence of tinea pedis in the militaries is remarkably higher than in the civilians. Based on the analysis of the results obtained, military personnel is considered to be a risk causing population. Among this specific population, risk factors of skin diseases are sweatiness, trauma, contagiousness, violation of hygienic norms, common showers, barracks and especially, wearing military boots intensively and for a long time.

Even though tinea pedis is not a life-threatening pathology, but due to high frequency and contagiousness, it remains one of the most important problems in the world.

In our country, with the exception of the absence of a real epidemiological picture of mycosis, including tinea pedis, there is a need to regulate accounting and develop a large-scale strategy. This will allow us to evaluate the real epidemiological situation, determine the causes of development and spread of the disease and develop appropriate preventive measures.

**Table 1. Mycosis in Giorgi Abramishvili Military Hospital**

Id-	Diagnosis	2013	2014	2015	2016	2017
35	Dermatophytosis	194	147	144	80	157
36	Other surface mycosis	118	151	77	38	60
37	Candidose			7	5	26
38	Coccidiomycosis				1	
47	Mycetoma				1	

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# The Long QT Syndrome: problem identification, diagnostic challenges

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## Abstract

The Long QT syndrome (LQTS) is inherited or acquired channelopathy resulting ventricular tachyarrhythmia torsade de pointes (TdP) which causes syncope and sudden death. The acquired LQTS might be drug-induced that is significant public health issue. The estimated prevalence of inherited LQTS in the USA is estimated at about 1:7000 or 1: 5000 individuals according to different sources. The article covers the most important issues of the syndrome, clinical and diagnostic challenges when QT interval prolongation is seen on ECG in order to assist doctors deal with the problem.

LQTS is caused by mutations of genes which encode for cardiac ion channels. Five genes, (LQT1,2,3,5,6) with over 200 mutations have thus far been discovered. Clinically, LQTS is identified by abnormal QT interval prolongation on the ECG. Genotype-phenotype studies of LQTS have provided new insights into risk mechanisms, electrocardiographic features, and long-term clinical course associated with this inherited disorder. Individuals with LQTS are practically healthy people without structural problems of the heart. The first manifestation of the disorder may be a fainting episode or syncope and sudden cardiac death. These events are due to the ventricular tachyarrhythmia torsade de pointes (TdP). ECG is informative and practically the main tool for diagnosis. The characteristic signs are QT interval prolongation and T wave abnormalities. Usually, the rate adjusted QT interval is calculated (QTc) using the Bazett formula ( $QTc = QT/\sqrt{RR}$ ). In case of suspicion, the QTc ranges from about 410 to over 600 msec. the most difficult task is to assess the risk of further arrhythmic events. Several approaches are implemented in clinical practice with this purpose (Schwartz score, Priority criteria). Management of LQTS includes mainly beta-blockers, education of patients to avoid triggers, pacemakers in case of bradycardia or ICDs. (TCM-GMJ October 2018; 3(2):P12-P14)

**Keywords:** Long QT Syndrome; Torsades de pointes; New insights of LQTS

## Introduction

**L**ong QT syndrome (LQTS) is inherited or acquired channelopathy resulting ventricular tachyarrhythmia torsade de pointes (TdP) which causes syncope and sudden death. The acquired LQTS might be drug-induced that is significant public health issue. The estimated prevalence of inherited LQTS in the USA is estimated at about 1:7000 or 1: 5000 individuals according to different sources. However, because of diagnostic challenges and variable genetic mutations, the prevalence of patients with overt or subclinical

manifestations of the syndrome is likely to be considerably greater than estimated prevalence (1).

The definitive description of LQTS occurred in 1957. Anton Jervell and Fred Lange-Nielsen described a Norwegian family in which 4 of 10 children were deaf and had recurrent syncope during exercise or emotion (2). Three died suddenly, at ages 4, 5 and 9 years. QT prolongation on the ECG was dramatic. Inheritance appeared to be autosomal recessive. A similar clinical syndrome of sudden death during exercise and emotion, but with normal hearing and autosomal dominant inheritance, was described in 1963 by Romano, et al, and in 1964 by Ward (2,3).

These two forms of inherited LQTS have respectively known as the Jervell, Lange-Nielsen (J, L-N) and the Romano-Ward (R-W) syndromes.

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## Genetics and Molecular basis

LQTS is caused by mutations of genes which encode for cardiac ion channels. Five genes, (LQT1,2,3,5,6) with over 200 mutations have thus far been discovered (4). Using published genotype information, phenotype analysis by ECG findings, and event triggers of patients from centers around the world, it appears that about 95% of LQTS cases are caused by mutations of the potassium genes. The LQT1/LQT5 combination appears to account for about 60%, LQT2/LQT6 about 35%, with mutations of LQT5 and LQT6 alone contributing about 1% each to these numbers. The sodium channel gene LQT3 accounts for about 4-5% of the cases, and Jervell, Lange-Nielsen less than 1%. The LQT4 genotype is very rare and may be present in only the proband family, as no other families with genotype have been described. During the past few years, mutations in other genes have been identified in single individuals or a few families in what can be categorized as "LQTS related" disorders.

Clinically, LQTS is identified by abnormal QT interval prolongation on the ECG. Genotype-phenotype studies of LQTS have provided new insights into risk mechanisms, electrocardiographic features, and long-term clinical course associated with this inherited disorder. For example, each of the 3 major genotypes (LQT1 to LQT3) seems to have a distinctive T-wave repolarization pattern on the ECG (figure 1) (5,6).

## Clinical Manifestations

Individuals with LQTS are practically healthy people without structural problems of the heart. The first manifestation of the disorder may be a fainting episode or syncope and sudden cardiac death. These events are due to the ventricular tachyarrhythmia torsade de pointes (TdP), (Figure 2). Most often, the TdP is self-terminating producing a syncopal episode. In a small minority of events the TdP degenerates into ventricular fibrillation and death occurs.

Syncope might be the first presentation of the disease in LQTS patients. The precise analysis of the syncope history is usually the key to the correct diagnosis. Palpitations and presyncope are uncommon due to LQTS. In LQTS it is precipitous and without warning in the vast majority of cases. Syncope in patients with the long-QT syndrome is generally attributed to the form of polymorphic ventricular tachycardia called torsades de pointes (Tdp) the usual rate of TdP is about 300-350/min, and the arrhythmia starts suddenly. The LQT3 form of the syndrome can also be associated with bradycardia, and slow heart rates may cause syncope in some patients. Death is usually due to ventricular fibrillation. The reason is that. No cardiac mechanical function occurs at such fast rates, thus, there is nothing to cause palpitations. A history of palpitations and presyncope is very much more likely to be due to vasovagal physiology, a different cause and type of VT, or SVT. A very careful history usually clarifies the situation. LQTS will be precipitous, as above, no symptoms typical of vasovagal physiology will be present, the event will not be during positional change, often absence of respiration and cyanosis will be detected, and the duration of the syncope is longer than the vasovagal event that is very usually very brief.

At least one-third (7) and probably about one-half of gene carriers never have symptoms, and it is common for the family history to be negative at the time of diagnosis in a member. However, a history of unexplained sudden death or repetitive syncope in young members of a family is certainly suspicious for LQTS.

## Diagnosis

ECG is informative and practically the main tool for diagnosis. The characteristic signs are QT interval prolongation and T wave abnormalities. There is significant variability of the QT within members of any family, between families and to a much lesser extent, between genotypes.

ECG diagnosis is based on QT measurements in certain lead (II and V5 or V6 with the longest value used). Usually, the rate adjusted QT interval is calculated (QTc) using the Bazett formula ( $QTc = QT/\sqrt{RR}$ ). The range of values in a normal population is about 350 to 460 msec. In case of suspicion, the QTc ranges from about 410 to over 600 msec. Consequently, there is overlap of QTc values between LQTS and normal in the 410 to 460 msec range. Values in this range are non-diagnostic and further studies are required.

T wave is further component of ECG to be evaluated. Moss, et al first reported a T wave pattern characteristic for each genotype (8). Zhang, et al further described patterns characteristic for each genotype, reporting four for LQT1, four for LQT2 and two for LQT3 (9). These T patterns can be helpful for predicting the correct genotype in families, and can be of assistance in the diagnosis of LQTS in cases of borderline QT duration.

However, LQTS is not the only cause of the QT prolongation on ECG. There are a number of causes of QT prolongation other than inherited LQTS including electrolyte disturbance, use of QT prolonging medications, mitral valve prolapse, diabetic autonomic neuropathy and cardiomyopathies. These conditions must be excluded when evaluating a patient who has a prolonged QT interval before a confident diagnosis of the Long QT syndrome can be made. Current evidence suggests that in the absence of these confounding factors, a QTc of  $\geq 480$  msec in females and  $\geq 470$  msec in males allow the diagnosis of LQTS. QTcs of  $< 410$  msec make LQTS quite unlikely. Values between 410 and 460 msec are ambiguous and further testing must be performed to clarify the status of these patients. That further testing includes additional ECGs, ambulatory ECGs and exercise ECGs. Exercise ECGs seem to be the most definitive. Genetic testing is helpful when available.

The sensitivity/specificity of the screening strategy is not well defined. Commercial genetic testing for de novo mutations is restricted. Commercial genetic testing for members of families with a known mutation is available, with analysis limited to the exon involved. De novo mutation screening is available in some research laboratories.

Importantly, approximately 30% of phenotypically affected subjects have no mutation identified on genetic analysis. They may have mutations of genes not yet recognized. Alternatively, they may have mutations of non-coding regions of the known genes, or regulatory or modifier genes.

## Clinical course and Risk Stratification

Regardless the philed/filed material, the natural history of the syndrome remains incompletely characterized and approaches to risk stratification are not well defined.

In 1985, Schwartz et al published the criteria for diagnosing LQTS, which were modified in 1993 and contain important guidelines for the initial evaluation of potential cases. This system uses a score of 1 to 9 based on the family history, and the clinical and electrocardiographic findings. The probability of disease is low at a score of  $\geq 1$ , intermediate at 2-3, and high at  $\geq 4$  (Table 1).

One of the most current and definitive data regarding the risk of complications come from the International LQTS regis-

try. Zareba, et al (5) reported on LQTS patients of all three genotypes. The death rate over 40 years was about 4% for each genotype. This finding has tremendous importance for treatment and follow-up strategies in LQTS patients. The rather low incidence of sudden death indicates that we badly need to identify reliable risk markers, not accurately possible at present. With such data, the large majority, who are at low risk, might be stratified to no treatment, whereas those at higher risk could be appropriately managed with aggressive and target driven beta-blocker therapy, ICDs or other genetic based therapies as they become available. Also, the Registry study determined that the frequency of cardiac events (syncope, aborted cardiac arrest and sudden death) was highest in LQT1 (60% of patients), then LQT2 (40%) and lowest in LQT3 (18%). Since the rate of death was the same in each genotype, the percentage of events which were lethal was highest in the LQT3 patients.

According to S.G. Priori, M.D., Peter J. Schwartz, et al, the genetic locus and the QTc, but not sex, were independent predictors of risk after evaluation of 647 patients from 193 consecutively genotyped families with the long-QT syndrome. The QTc was an independent predictor of risk among patients with a mutation at the LQT1 locus and those with a mutation at the LQT2 locus but not among those with a mutation at the LQT3 locus, whereas sex was an independent predictor of events only among those with a mutation at the LQT3 locus. Finally, they suggested a risk-stratification model in order to quantify, for each genetic variant, the risk of symptoms before the age of 40 years and before therapy on the basis of two simple clinical characteristics: sex and QTc (Table 1).

**Therapy**

Management of LQTS includes mainly beta-blockers, education of patients to avoid triggers, pacemakers in case of bradycardia or ICDs. The last one gained more popularity to prevent episodes of syncope due to TdP or avoid sudden cardiac death (SCD). It is indicated to be implanted in patients with high risk or as a secondary prevention of SCD.

**Gap in knowledge of LQT Syndrome**

The natural history of the syndrome remains incompletely characterized; as well as approaches to risk stratification are not well defined.

These gaps in knowledge are largely due to the fact that the long-QT syndrome is uncommon, cardiac events may be separated by long periods without symptoms, and the initial manifestation may occur late in life.

The diagnosis is based on QT measurement or T wave abnormality that is not always diagnostic- QT might be normal during investigation and could mask real mutation carrier. We need more distinctive clinical or diagnostic characteristics not to



miss the real .

Figure 2: Ventricular tachycardia - Torsade de pointes

Table 1. Schwartz Score for the diagnosis of Long QT

Variable	Points
Electrocardiogram	
• QTc ms ≥480	3
• 460-470	2
• 450 (males)	1
• Torsades de pointes	2
• T wave alternance	1
• T wave notches in 3 leads	1
• bradycardia	0.5
Clinical history	
• syncope with stress	2
• without stress	1
• Congenital deafness	0.5
Family history	
• Family members with confirmed LQTS	
• Unexplained death in first-order family members < 30 years	

**Syndrome**

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Type	Current	Functional Effect	Frequency Among LQTS	ECG <sup>12,13</sup>	Triggers Lethal Cardiac Event <sup>10</sup>	Penetrance <sup>*</sup>
LQTS1	K	↓	30%-35%		Exercise (68%) Emotional Stress (14%) Sleep, Repose (9%) Others (19%)	62%
LQTS2	K	↓	25%-30%		Exercise (29%) Emotional Stress (49%) Sleep, Repose (22%)	75%
LQTS3	Na	↑	5%-10%		Exercise (4%) Emotional Stress (12%) Sleep, Repose (64%) Others (20%)	90%

Figure 1: Main types of LQTS

# Clinical Groups in Oncology as Part of Former Soviet Health Care System – Georgian Experience

Lekashvili T.<sup>1</sup> Rukhadze T.<sup>1</sup>

## Abstract

**Background:** Number of new events of oncology diseases in Georgia ranges from 7 000 to 8 000 annually and is the second reason for population mortality indicators. Social challenges existing in the country and healthcare system during the years, structural reforms, problems with respect to medical service accessibility have evidently hindered availability of oncology diseases detection on their early stage of development. Reforms conducted in healthcare system of the county, widening of screening programs availability, cancer diseases detection on the early stage and activation of population registry in the country have considerably contributed to proper evaluation of epidemiological indicators, diagnosis and treatment results significant improvement. Notwithstanding conducted reforms and achieved success, current regulatory documents fail to correspond to the international standards and acknowledged regulations. They need certain refining in accordance with international guidelines and clinical experience.

**Method:** For the literature review we have revised articles, methodological guides, orders and manuals published PubMed, MEDLINE, CINAHL, CANCERLIT, EMBASE, PsychINFO and Google Scholar medical database. Unfortunately, data bases not properly recognized the keyword – “clinical groups” in oncology despite the soviet period regulatory documents and literature, which are still available and actual in current regulatory documents and orders in Georgia.

**Conclusion:** The concept Clinical Group in the practice of clinical oncology represents the unit of dispenserisation remaining from the soviet healthcare system. Unfortunately, in Georgia it is to the date the indicator for assessment of incurable patient status. Notwithstanding the fact that throughout the world, there are several factors defining general criteria for assessment of incurable patient, such as general standing of the patient, incidence/outbreak of oncological disease, concomitant diseases, current complications and along with the all above-mentioned, life quality of the patient, the elements of the soviet healthcare system remaining in Georgia precondition receipt of such significant treatment/service for the oncological patients, as adequate administration of the chronic pain, and build a kind of bureaucratic barrier between the patients and the medical service. To the date, use of the clinical groups in the medical practice is conditional and its presence interferes with the complete/perfect service rendering to the patients, making it impossible for the patients to be prescribed with opioids for medical needs in case of severe pain while anti-cancer radical treatment. (TCM-GMJ October 2018; 3(2):P15-P18)

**Keywords:** Cancer; Clinical groups; Assessment; Incurable status; Opioids; Quality of life.

## Introduction

In accordance with the literature data of post soviet region, through the years, attempt of scientists of this field was directed towards statistical analysis of oncology diseases, features of disease communication, early methods of diagnostics and possibilities, therapy effectiveness and their short or long term results improvement. Attention of scientists and field specialists was drawn to improvement of patients' health examination, and definition of clinical groups existing in oncology practice till today is related to the latter, and definition of patients' incurability was based thereon as well (1,2,3,7, 11,12).

In accordance with literature data, manuals and number of regulatory documents, standardization of oncology patients existed in healthcare system of post soviet countries including Georgia. Patients were divided into four main groups, called clinical groups:

**Group (1a)** – Patients with possible malignancy. This group used to unite patients initial research of which lasted for not more than 10 -14 days and afterwards, in case of suspected oncology disease they needed more detailed researches and they were moved to the following subgroup or they were removed from the group as further diagnostics was not necessary.

**Group (1 b)** – Patients with pre-cancer and/or benign diseases. Patients in this group are subject to further medical research and health examination.

In the second clinical group were united patients with malignant diseases, whose diagnosis was oncology disease and were subject to specific therapy. Majority of initial patients were in that group. In accordance with literature

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data and regulatory documents of clinical groups, majority of this group is subject to radical methods of treatment including, in most cases surgical intervention and much more rarely – radiation and chemo therapy, that may be disputable nowadays (2,3,4,5,6,14). In addition, it should be noted, that as some scientist thought, large number of patients of the second group represented objective indicator of successful operation of medical and diagnostic institutions.

The third clinical group consisted of practically healthy patients, who had oncology disease diagnosis even once throughout the life, they went through the specific therapy and were cured. They were on respective health examination registry. Patients of this group were subject to regular patronage and constant evaluation of condition with the following regimen: during the first year of radical treatment – once in a quarter; during the second and the third years – once in 6 months and afterwards, at least once in a year. In case of the third clinical group, patients' health examination monitoring was recommended at least for 5 years and in case of certain localizations (disease) even during the whole life (2,3,4,5,6,14).

The fourth clinical group consisted of patients with late stages of malignancies, when radical therapy was impossible and patient needed palliative and supportive therapy. Management of incurable patients' severe, chronic pain management and medical application of strong opioids are related to the definition of the fourth clinical group and incurable status (2,3,4,5,6,14). Definition of limited ability of patients is connected to that status as well. Notwithstanding the abovementioned, in accordance with various literature data and standard regulation, any surgical intervention, radiation or chemo therapy was not limited for the patient included in the fourth clinical group for the purpose of life quality improvement. Patients of the fourth group were subject to the constant health examination in accordance with the literature data (9,10,11,12).

Nowadays, healthcare system of Georgia doesn't include above-mentioned scheme of health examination. Internationally acknowledged clinical guidelines and oncology diseases screening, early detection and follow-up monitoring programs are functioning in the country. However, definition of the second and the fourth clinical groups is widely used in regulatory documents as well as in clinical practice till today (9,10).

In accordance with the abovementioned clinical groups, in order to prescribe strong opioid for the treatment of strong, chronic pain, the patient should have documentarily established fourth clinical group along with the pain. That provision opposes the management of those patients' strong, chronic pain, who are still subject to the treatment and are included in the second clinical group. However, strong opioids application in the treatment of patients included in the second group may be medically necessary.

Regulations and experience of opioids application with medical purposes in oncology patients, differ for country to country, including Georgia. In accordance with the legislative and regulatory documents, oncologist, surgeon, general practitioner, physician and specialist owning the diploma of palliative medicine subspecialty has the right and competence to prescribe the opioid. In case of non-oncology patient (e.g. somatic patient), procedure foresees management of this process by the commission, that is significantly complicated. Due to the western experience, this is not limited for the other specialists (9,10,14).

Phasing is internationally acknowledged in contemporary clinical oncology for the evaluation of patient's condition and disease status; ECOG and ECOG/Karnovsky scales are applied by oncologists for evaluation of patient's general condition; evaluation of quality of life is recommended on radical as well as on palliative – supportive therapy phases of oncology treatment (34,35,36,37). Special questionnaires for evaluation of quality of life (QOL) is widely acknowledged, that thoroughly describes patient's condition and further needs. Concept of quality of life is subjective, however, nowadays, in different searching systems (MEDLINE, CINAHL, CANCERLIT, EMBASE, PsychINFO) there are various information about systemized review, studies and works about evaluation of quality of patients' life, results of which are available, including cases of different diseases (15,31,40,48). What concerns the incurability – majority of clinician scientists rely on oncologic patients' general condition evaluation scales, that currently is deemed to be satisfactory instrument for patient's general condition evaluation (ECOG, Karnovsky) (27,28,29). RECIST 1.1 evaluation system is used as the ideal instrument for the evaluation of specific treatment effectiveness, which provides detailed information on disease progression, stabilization or regress (25,26,32,37).

Thus, nowadays, in order to prescribe adequate treatment (strong opioid) for strong pain in Georgia, it is necessary to establish the compliance with the fourth clinical group and incurability status. However, there are different experiences of the other countries (18,23,24). In accordance with the experience of the western countries and respective regulatory documentations, opioids prescription and their medical application is defined due to strong, chronic pain described by the patient and respective medical necessity (including dispnea, etc), specific QOL questionnaires enabling detailed evaluation of quality of life (16,17,21,22,38,39); while effectiveness of specific treatment is evaluated under RECIST 1. Thus, division of patients into clinical groups is not accepted in western practice and above-mentioned systems give possibilities to define patient's incurability as well as to evaluate quality of their lives and general condition, which is impossible in case of clinical groups system. What concerns the management of strong, chronic pain, based on long-term studies and clinical experience it appeared that patient needs prop-

er pain relieving therapy on every stage of treatment notwithstanding the clinical group (33,37,38, 41, 54, 55, 56). In addition, clinical group doesn't provide information about quality of patients' life. Often, organizational barrier is created during the oncology diagnosis and treatment and therefore patient's medical needs are not completely and timely met (42,50, 52,53). Disease specific treatment toxicity, even reasons created during radical treatment shall not become bureaucratic barrier for the patient in obtaining qualitative medical service. The aim of medical action shall be maintaining of quality of patient's life on each stage of the treatment (43,44,45,46,47). In conditions of limited regulatory documents, quality of patient's life and care is left out of attention while there exists experience of many countries about medical service oriented on the patient, meaning and necessity of evaluation of quality of patient's life (19,20,30,49).

## Conclusions

Clinical group is the unit of health examination of oncology patients and that system doesn't function in Georgia for the recent decades;

Application of clinical groups in medical practice is provisional; it represents the part of post-soviet system and the unit of oncology patients' health examination. Clinical group creates a barrier in providing complete service to patients, makes it impossible to prescribe opioids to patients with medical means during anti-cancer radical treatment in case of strong pains;

Clinical group fails to provide complete information on general condition of patient, quality of life. It is not applied in accordance with international clinical guidelines and is maintained only in the countries of post-soviet region;

In order to obtain qualitative medical service it is internationally acknowledged: disease course and progression shall be evaluated in accordance with respective guideline; patient's condition shall be evaluated using respective evaluation scales (ECOG and Karnovsky), and quality of patient's life shall be evaluated in accordance with the special questionnaire for quality of life (QOL);

International recommendation shall be always be applied in case of strong pain: strong, chronic pain shall be managed due to medical necessity.

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# Regression of hepatocellular carcinoma and Increase overall survival in patients treated with ledipasvir/sofosbuvir for hepatitis C virus infection: real-life single-center experience

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## Abstract

**Background:** Chronic hepatitis C induced liver cirrhosis is a one of the main causes of the Hepatocellular carcinoma (HCC). There are controversial data about effects of the different anti-hepatitis C virus treatment regimens on the risk of development and prognosis of HCC. Furthermore, there is not any data about HCC prognosis in patients who undergoes viral eradication therapy. Recently, “Nationwide hepatitis C elimination program” was launched in Georgia. According the protocol, patients with HCC also are included in the program.

**Aim:** Goal of the study was to determine effect of the Ledipasvir/Sofosbuvir on HCC regression, disease free and Overall Survivals in Patients with Hepatitis C Virus

**Methods:** Patient were enrolled in period of January – December 2015 year (n=6). Inclusion criteria – diagnosis of HCC or HCC recurrence and HCV-related cirrhosis who had been selected for surgical resection at the beginning of Led/Sof therapy. Clinical monitoring and management of adverse events were performed at regular base.

**Results:** Our data shows that in treatment group early phase (12 month) intrahepatic recurrence rate is less than in control data, but without statistical significance (40% versus 50%, p=0.747). Improvement of late survival (maximum observation time 36 month) is more evident - (40% versus 50%, p=0.12), but still failed to reach statistical significance.

Overall survival was significantly higher. In the treatment group mean overall survival was 34.0±2.0 month in comparison with control group - 25.2±3.6, P<0.05. In one case regression of the size of recurred tumour were observed.

**Conclusions:** Antiviral treatment can be included in management of the HCV patients with HCC. It may have additional benefits, in terms of improving of overall and recurrence free survival in cancer patients. Antiviral treatment could be indicated in the subgroup of patients with HCV-pure infection in whom recurrences can be significantly reduced. Also considering that our investigation is based on small group of the patients, Further study on should be made in larger cohorts. Also, it will be valuable to explain mechanisms of the effect of the Ledipasvir/sofosbuvir on cancer regression. **TCM-GMJ October 2018; 3(2):P31-P34)**

**Keywords:** Hepatocellular carcinoma (HCC); Hepatitis C virus (HCV); Tumour regression; Survival.

## Introduction

**Ch**ronic hepatitis C induced liver cirrhosis is a one of the main causes of the Hepatocellular carcinoma (HCC). There are controversial data about effects of the different anti-hepatitis C virus treatment regimens on the risk of development of liver complications, especially HCC and its prognosis (1). Some author reports reduced risk of HCC during viral eradication therapy by interferon (IFN)-based regimens (2-5). Other researchers show increasing incidence of the HCC recurrence after interferon-free direct-acting anti-

ral (DAA) treatment (6-9).

These controversies mainly come from different antiviral treatment options, measured outcome parameters and observed groups.

However, there is not any data about HCC prognosis in patients who undergoes viral elimination therapy. This is mainly due to the fact that generally such patients are not candidate for antiviral treatment. Recently, “Nationwide hepatitis C elimination program” was launched in Georgia. According the protocol, patients with HCC also are included in the program (10, 11). This program gives a great opportunity to study the effect of the Ledipasvir/Sofosbuvir (Led/Sof) therapy on the risk of HCC development and recurrence and HCC prognosis.

Given these circumstances we assessed the effect of LED/SOF therapy on regression of HCC, disease free and overall survival in patients with chronic HCV infection.

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## Methods

### Patients

Patient were enrolled in period of January – December 2015 year (St. John The Merciful Private Clinic). Inclusion criterias were - histologically proven HCC or HCC recurrence, and HCV-related cirrhosis. Also they must be selected for surgical resection at the beginning of Led/Sof therapy. For control parameters data from patients without Led/Sof therapy were used (12). Patients demographics and disease history, enrolled in this study, were comparable to ours.

### Follow-up

Clinical monitoring and management of adverse events were performed at regular base. HCC recurrence detection was accomplished through regular oncologic visits and assessing alpha-fetoprotein (AFP).

### Statistical Analysis.

Overall and recurrence-free survival curves were calculated using the Kaplan-Meier method and were compared by means of the log-rank test (13). For Statistical analyses “IBM SPSS Statistics 23” software was used.

## Results

Six eligible persons were included in the study. Data from clinical, laboratory and molecular investigations are not discussed in present paper, due to the small number of the observed cases. Follow-up period were ranged from 9 to 48 months (See table1). We focused our study on overall and disease-free survivals. For control data we used variables from other studies (12).

We compare data using Kaplan–Meier estimator. Result plots are given in Fig.1 and Fig.2. Our data shows that in treatment group early phase intrahepatic recurrence (Disease-free survival - DfS) rate (12 month) is less than in control data, but without statistical significance (40% versus 50%,  $p=0.747$ ). Improvement of late survival (maximum observation time 36 month) is more evident - (40% versus 50%,  $p=0.12$ ), but still failed to reach statistical significance.

Overall survival showed more significant results. In the treatment group mean overall survival was  $34.0 \pm 2.0$  month in comparison with control group -  $25.2 \pm 3.6$ ,  $P < 0.05$ .

In one case (treatment group, patient with recurrence), regression of recurred tumour size was observed.

## Discussion

HCC has a poor prognosis with a fatal course of the diseases, even with complex therapy. Five-year survival rate is less than 12% (14, 15). Curative treatment can be obtain only at early stages (0 and A) of diseases by combination of the surgery and transplantation(16).

Unfortunately diagnosis of hepatocellular carcinoma (HCC) in about 60% of cases are made at advanced stage of disease, when treatment options cannot improve overall survival (OS)(16). OS at advanced stages treated with chemoembolization remains poor, about 8 months in comparison with patients at intermediate stages, who can achieve OS of 26 months (17-19).

Spontaneous regression or remission (SR) of different cancers has been first defined and studied by Everson and Cole in 1966 (20, 21). Many mechanisms are discussed to be involved in such cases, but extremely rarity of the SR makes difficult to clarify this issue.

Tumour regression, spontaneous or associated with antiviral treatment, was described in patient with HCC (22-27). Some authors showed that the incidence of partial spontaneous regression of HCC is 0.4% (28) and complete SR – 1 in 140,000 cases of HCC (20).

We found 3 recent reports of HCC regression during antiviral therapy. Two of them after combined therapy with Pegylated interferon-2 $\alpha$  and Ribavirin (22, 24) and one -with Sofosbuvir (23). Authors give some explanations of the possible mechanisms of such phenomenon, but their concepts need to be proved. Understanding of the mechanisms of effect of HCV antiviral agents on the prognosis of HCC could change current approach of the HCC treatment.

In the current pilot paper, we discussed six cases of the patients with HCC during HCV treatment by novel direct antiviral drugs (Ledipasvir/sofosbuvir). There was not only significant reduction of the tumour nodules size in one patient, but also improvement of the overall and disease-free survival. Based on literature data and modern understandings of the pathologic basis of HCC on the one side, and the molecular mechanisms of the antiviral drugs, particularly ledipasvir/sofosbuvir on the other side, we can summarise potential mechanisms of this effect.

Possible mechanisms involved in spontaneous remission includes tumour hypoxia, systemic inflammatory responses and lifestyle changes (29). In our cases, none of these were possible reasons. Also, the incidence of regression is significantly higher, than incidence rate of SR given in systematic review papers (20, 28, 29). Consequently, only factor involved in regression of the HCC in our patient, could be antiviral therapy. It can be act by two mechanism: direct action on the tumour cells (antimetabolic or inhibition of gene expression) and modulation of the anti-tumor immunologic response.

Same mechanisms can be a cause of the OS and DfS improvement during Led/Sof therapy.

Our data showed Improvement of late disease-free survival and significant overall survival.

## Conclusions

Therefore, antiviral treatment can be included in management of the HCV patients with HCC. It may have additional benefits, in terms of improving of overall and recurrence free survival in cancer patients. Antiviral treatment could be indicated in the subgroup of patients with

HCV-pure infection in whom recurrences can be significantly reduced. Latest study showed effectiveness and safety of such approach (30). Also considering that our investigation is based on small group of the patients, Further study on should be made in larger cohorts. Also, it will be valuable to explain mechanisms of the effect of the Ledipasvir/sofosbuvir on cancer regression.

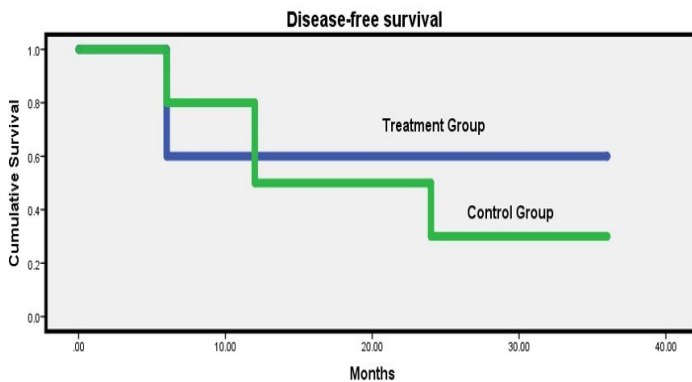
### Acknowledgements

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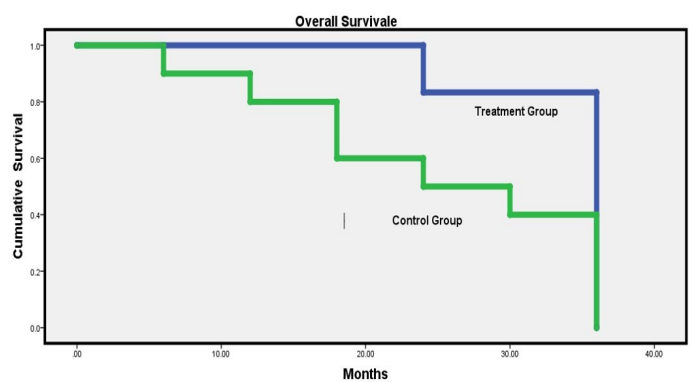
This study was supported by Shota Rustaveli National Science Foundation (SRNSF) [# PhD\_F\_17\_33 - Outcome, risk of development and new highly sensitive blood circulating tumour markers of a Hepatocellular Carcinoma in the course.

**Table 1.** Patient Data

Pat. N	Sex	Age	HCC Treatment option	HCV Treatment option	Cirrhosis	HCC (size in MM)	Recurrence (Month after surgery)	Time of follow up (Month)	Status
1	m	54	Liver bisegmentectomy	Led/Sof – for 24 week	F4	Uninodular - 60	6	48	Alive
2	m	56	Liver segmentectomy	Led/Sof – for 24 week	F4	Uninodular - 20	6	18	Alive
3	m	62	Liver segmentectomy	Led/Sof – for 24 week	F4	Uninodular - 30	-	18	Alive
4	m	57	Liver segmentectomy	Led/Sof – for 24 week	F4	Uninodular - 20	-	18	Alive
5	m	58	Liver segmentectomy	Led/Sof – for 24 week	F4	Uninodular - 30	-	9	Alive
6	m	55	No special treatment	Led/Sof – for 24 week	F4	Multinodular	No surgery (Regression of tumour size)	24	Dead



**Figure 1:** Kaplan–Meier estimator curve - Disease-Free Survival



**Figure 2:** Kaplan–Meier estimator curve - Overall Survival

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# Regression of hepatocellular carcinoma and Increase overall survival in patients treated with ledipasvir/sofosbuvir for hepatitis C virus infection: real-life single-center experience

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## Abstract

**Background:** Chronic hepatitis C induced liver cirrhosis is a one of the main causes of the Hepatocellular carcinoma (HCC). There are controversial data about effects of the different anti-hepatitis C virus treatment regimens on the risk of development and prognosis of HCC. Furthermore, there is not any data about HCC prognosis in patients who undergoes viral eradication therapy. Recently, “Nationwide hepatitis C elimination program” was launched in Georgia. According the protocol, patients with HCC also are included in the program.

**Aim:** Goal of the study was to determine effect of the Ledipasvir/Sofosbuvir on HCC regression, disease free and Overall Survivals in Patients with Hepatitis C Virus

**Methods:** Patient were enrolled in period of January – December 2015 year (n=6). Inclusion criteria – diagnosis of HCC or HCC recurrence and HCV-related cirrhosis who had been selected for surgical resection at the beginning of Led/Sof therapy. Clinical monitoring and management of adverse events were performed at regular base.

**Results:** Our data shows that in treatment group early phase (12 month) intrahepatic recurrence rate is less than in control data, but without statistical significance (40% versus 50%, p=0.747). Improvement of late survival (maximum observation time 36 month) is more evident - (40% versus 50%, p=0.12), but still failed to reach statistical significance.

Overall survival was significantly higher. In the treatment group mean overall survival was 34.0±2.0 month in comparison with control group - 25.2±3.6, P<0.05. In one case regression of the size of recurred tumour were observed.

**Conclusions:** Antiviral treatment can be included in management of the HCV patients with HCC. It may have additional benefits, in terms of improving of overall and recurrence free survival in cancer patients. Antiviral treatment could be indicated in the subgroup of patients with HCV-pure infection in whom recurrences can be significantly reduced. Also considering that our investigation is based on small group of the patients, Further study on should be made in larger cohorts. Also, it will be valuable to explain mechanisms of the effect of the Ledipasvir/sofosbuvir on cancer regression. **TCM-GMJ October 2018; 3(2):P31-P34)**

**Keywords:** Hepatocellular carcinoma (HCC); Hepatitis C virus (HCV); Tumour regression; Survival.

## Introduction

**Ch**ronic hepatitis C induced liver cirrhosis is a one of the main causes of the Hepatocellular carcinoma (HCC). There are controversial data about effects of the different anti-hepatitis C virus treatment regimens on the risk of development of liver complications, especially HCC and its prognosis (1). Some author reports reduced risk of HCC during viral eradication therapy by interferon (IFN)-based regimens (2-5). Other researchers show increasing incidence of the HCC recurrence after interferon-free direct-acting anti-

ral (DAA) treatment (6-9).

These controversies mainly come from different antiviral treatment options, measured outcome parameters and observed groups.

However, there is not any data about HCC prognosis in patients who undergoes viral elimination therapy. This is mainly due to the fact that generally such patients are not candidate for antiviral treatment. Recently, “Nationwide hepatitis C elimination program” was launched in Georgia. According the protocol, patients with HCC also are included in the program (10, 11). This program gives a great opportunity to study the effect of the Ledipasvir/Sofosbuvir (Led/Sof) therapy on the risk of HCC development and recurrence and HCC prognosis.

Given these circumstances we assessed the effect of LED/SOF therapy on regression of HCC, disease free and overall survival in patients with chronic HCV infection.

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## Methods

### Patients

Patient were enrolled in period of January – December 2015 year (St. John The Merciful Private Clinic). Inclusion criterias were - histologically proven HCC or HCC recurrence, and HCV-related cirrhosis. Also they must be selected for surgical resection at the beginning of Led/Sof therapy. For control parameters data from patients without Led/Sof therapy were used (12). Patients demographics and disease history, enrolled in this study, were comparable to ours.

### Follow-up

Clinical monitoring and management of adverse events were performed at regular base. HCC recurrence detection was accomplished through regular oncologic visits and assessing alpha-fetoprotein (AFP).

### Statistical Analysis.

Overall and recurrence-free survival curves were calculated using the Kaplan-Meier method and were compared by means of the log-rank test (13). For Statistical analyses “IBM SPSS Statistics 23” software was used.

## Results

Six eligible persons were included in the study. Data from clinical, laboratory and molecular investigations are not discussed in present paper, due to the small number of the observed cases. Follow-up period were ranged from 9 to 48 months (See table1). We focused our study on overall and disease-free survivals. For control data we used variables from other studies (12).

We compare data using Kaplan–Meier estimator. Result plots are given in Fig.1 and Fig.2. Our data shows that in treatment group early phase intrahepatic recurrence (Disease-free survival - DfS) rate (12 month) is less than in control data, but without statistical significance (40% versus 50%,  $p=0.747$ ). Improvement of late survival (maximum observation time 36 month) is more evident - (40% versus 50%,  $p=0.12$ ), but still failed to reach statistical significance.

Overall survival showed more significant results. In the treatment group mean overall survival was  $34.0 \pm 2.0$  month in comparison with control group -  $25.2 \pm 3.6$ ,  $P < 0.05$ .

In one case (treatment group, patient with recurrence), regression of recurred tumour size was observed.

## Discussion

HCC has a poor prognosis with a fatal course of the diseases, even with complex therapy. Five-year survival rate is less than 12% (14, 15). Curative treatment can be obtain only at early stages (0 and A) of diseases by combination of the surgery and transplantation(16).

Unfortunately diagnosis of hepatocellular carcinoma (HCC) in about 60% of cases are made at advanced stage of disease, when treatment options cannot improve overall survival (OS)(16). OS at advanced stages treated with chemoembolization remains poor, about 8 months in comparison with patients at intermediate stages, who can achieve OS of 26 months (17-19).

Spontaneous regression or remission (SR) of different cancers has been first defined and studied by Everson and Cole in 1966 (20, 21). Many mechanisms are discussed to be involved in such cases, but extremely rarity of the SR makes difficult to clarify this issue.

Tumour regression, spontaneous or associated with antiviral treatment, was described in patient with HCC (22 -27). Some authors showed that the incidence of partial spontaneous regression of HCC is 0.4% (28) and complete SR – 1 in 140,000 cases of HCC (20).

We found 3 recent reports of HCC regression during antiviral therapy. Two of them after combined therapy with Pegylated interferon-2 $\alpha$  and Ribavirin (22, 24) and one -with Sofosbuvir (23). Authors give some explanations of the possible mechanisms of such phenomenon, but their concepts need to be proved. Understanding of the mechanisms of effect of HCV antiviral agents on the prognosis of HCC could change current approach of the HCC treatment.

In the current pilot paper, we discussed six cases of the patients with HCC during HCV treatment by novel direct antiviral drugs (Ledipasvir/sofosbuvir). There was not only significant reduction of the tumour nodules size in one patient, but also improvement of the overall and disease-free survival. Based on literature data and modern understandings of the pathologic basis of HCC on the one side, and the molecular mechanisms of the antiviral drugs, particularly ledipasvir/sofosbuvir on the other side, we can summarise potential mechanisms of this effect.

Possible mechanisms involved in spontaneous remission includes tumour hypoxia, systemic inflammatory responses and lifestyle changes (29). In our cases, none of these were possible reasons. Also, the incidence of regression is significantly higher, than incidence rate of SR given in systematic review papers (20, 28, 29). Consequently, only factor involved in regression of the HCC in our patient, could be antiviral therapy. It can be act by two mechanism: direct action on the tumour cells (antimetabolic or inhibition of gene expression) and modulation of the anti-tumor immunologic response.

Same mechanisms can be a cause of the OS and DfS improvement during Led/Sof therapy.

Our data showed Improvement of late disease-free survival and significant overall survival.

## Conclusions

Therefore, antiviral treatment can be included in management of the HCV patients with HCC. It may have additional benefits, in terms of improving of overall and recurrence free survival in cancer patients. Antiviral treatment could be indicated in the subgroup of patients with

HCV-pure infection in whom recurrences can be significantly reduced. Latest study showed effectiveness and safety of such approach (30). Also considering that our investigation is based on small group of the patients, Further study on should be made in larger cohorts. Also, it will be valuable to explain mechanisms of the effect of the Ledipasvir/sofosbuvir on cancer regression.

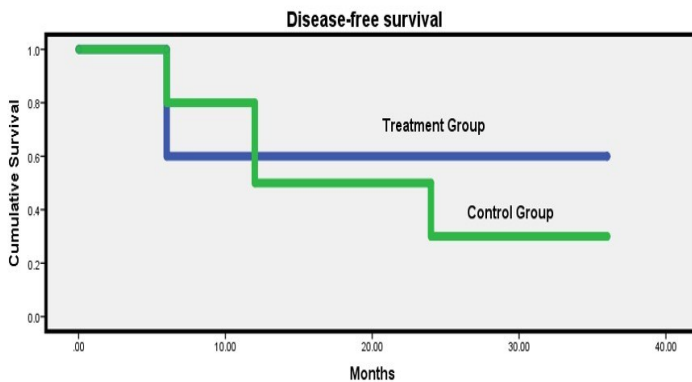
### Acknowledgements

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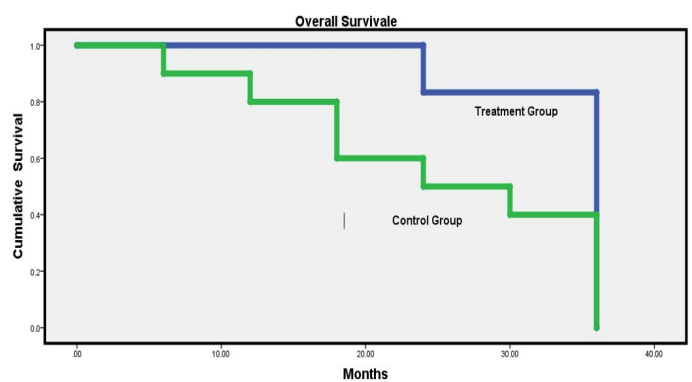
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**Table 1.** Patient Data

Pat. N	Sex	Age	HCC Treatment option	HCV Treatment option	Cirrhosis	HCC (size in MM)	Recurrence (Month after surgery)	Time of follow up (Month)	Status
1	m	54	Liver bisegmentectomy	Led/Sof – for 24 week	F4	Uninodular - 60	6	48	Alive
2	m	56	Liver segmentectomy	Led/Sof – for 24 week	F4	Uninodular - 20	6	18	Alive
3	m	62	Liver segmentectomy	Led/Sof – for 24 week	F4	Uninodular - 30	-	18	Alive
4	m	57	Liver segmentectomy	Led/Sof – for 24 week	F4	Uninodular - 20	-	18	Alive
5	m	58	Liver segmentectomy	Led/Sof – for 24 week	F4	Uninodular - 30	-	9	Alive
6	m	55	No special treatment	Led/Sof – for 24 week	F4	Multinodular	No surgery (Regression of tumour size)	24	Dead



**Figure 1:** Kaplan–Meier estimator curve - Disease-Free Survival



**Figure 2:** Kaplan–Meier estimator curve - Overall Survival

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