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SICKLE CELL THALASSEMIA IN AN ADULT FROM CENTRAL INDIA SHOWING MASSIVE SPLENIC INFARCTION AND GAMNA-GANDY BODIES IN SPLENIC PARENCHYMA WITH CONCOMITANT *PLASMODIUM FALCIPARUM* INFECTION (case report)

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Background. *Sickle cell thalassemia is a heterozygous state of HbS/β^+ or HbS/β^0 manifested clinically either as an asymptomatic carrier or have features akin to sickle cell anemia.*

Objective. *The aim of the study is to review the literature and discuss the varied clinical manifestations and diagnosis of a case report of haemoglobinopathy in an adult from Central India.*

Methods. *A case of haemoglobinopathy from central part of India is being investigated.*

Results. *A case of haemoglobinopathy in an adult presenting to a tertiary hospital with chronic back ache was reported. The patient was found to have massive splenomegaly with evidence of splenic infarction. Gross examination of spleen revealed multiple soft yellowish pasty areas, which on microscopic examination showed significant necrosis with presence of great amount pale amorphous yellow substance, Gamna-Gandy bodies (GGBs) and massive foreign body cell reaction in splenic parenchyma. Post-splenectomy peripheral blood smear (PBS) showed thrombocytosis and plasmodium falciparum gametocytes. The Hb electrophoresis revealed both elevation of Hb S (49.7%), Hb F (46.7%); Hb A2 (3.0%) and (Hb A 0.7%) consistent with as Sickle Cell Thalassemia Hb S/β^+ Thalassemia.*

Conclusion. *Sickle cell thalassemia with long standing huge splenomegaly, splenic infarction with GGBs deposition and concomitant falciparum malaria in clinically stable patient is rare indeed.*

KEYWORDS: **sickle-cell anemia; beta-thalassemia; malaria; plasmodium falciparum; Gamna-Gandy bodies.**

Introduction

Hemoglobinopathies are the most common inherited RBC disorders, thalassemia and sickle cell disease – the most frequent. Co-existent both sickle cell mutation and thalassemia mutation, commonly beta thalassemia, facilitating development to a compound heterozygous state known as sickle cell beta thalassemia, was first reported and described by Silvestroni and Bianco in 1944 [1]. The incidence of this condition is very common in Mediterranean region. Its prevalence in Indian subcontinent is underreported, perhaps due to underdiagnosis as most of these patients are normal and asymptomatic. Documented prevalence of sickle cell beta thalassemia in India is less than 1% in various studies [2].

Inherited as autosomal recessive disorder it occurs when one abnormal gene for production of hemoglobin S is inherited from one parent and one abnormal gene for production of beta thalassemia is inherited from the other parent. The genes for both hemoglobin and beta thalassemia are both located on chromosome 11.

Manifestation of the condition was studied in 1973 by Serjeant at el [3]. Clinical manifestations vary depending upon heterozygosity from being completely asymptomatic (Hb S/ β^+) to signs and symptoms very much akin to sickle cell anemia (Hb S/ β^0) [4].

Case Report

A 29-year-old serving soldier, the resident of central India, while being employed in high altitude area complained of chronic pain abdomen, which was found to be due to massive splenomegaly (23 cm in span) with sonographic evidence of splenic infarction. Approximately 7 years earlier, he had similar episode of abdomen pain for which he was worked up to rule

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any hematological disorder. He had microcytic hypochromic anemia with normal TLC and DLC. Thrombocytosis was noted. There was no documented evidence of any organomegaly in the past. Past Hb electrophoresis reports revealed HbS – 49.7%, Hb A – 0.7%, Hb A2 – 3.0% and Hb F – 46.7%; consistent with as Sickle Cell Thalassemia (Hb S/β^+ Thalassemia).

His general, systemic examinations were within norm during pre-anesthetic check-up. He was taken up for the splenectomy operation and specimen sent to Dept of Pathology for histopathological examination.

Lab received a grossly enlarged specimen of splenectomy weighing 1.2 kg and having apparently normal architecture externally. Serial cut section of the fresh specimen showed multiple soft yellowish areas of splenic infarction. Formalin-soaked cotton were placed in between these cut surfaces and whole specimen was put in 10 % formalin for 24 hours. Multiple sections from these necrosed soft areas were submitted along with normal appearing areas of spleen. H&E stains slides were studied by microscopy.

Histopathological examination revealed significant necrosis in infarcted area and there were multiple areas showing deposition of yellowish granular substances in splenic tissue which were Congo-red negative and birefringence negative under polarized light. Sickle cells in the sinusoids were also seen.

Post splenectomy period was uneventful with no fever, however, there was incidental findings of different forms of plasmodium falciparum including gametocytes in the peripheral blood. Thrombocytosis was also noted as expected.

Discussion

Sickle cell thalassemia, described originally as micro-drepanocytic disease by Silvertroni and Bianco [1], is a clinical condition where mutations in both HbS gene and Thalssemia gene (commonly beta gene) occur resulting in two heterozygous states of either Hb S/ β^+ or Hb S/ β^0. Heterogenicity in the beta thalassemia mutations leads to different beta globin synthesis and hence different amounts of HbA are synthesized which result in variable clinical manifestations ranging from nearly asymptomatic to a severe condition similar to sickle cell anemia (homozygous HbS) [4].

Laboratory investigations reveal microcytic hypochromic red cells with target cells and occasionally sickled forms. Hemoglobin electrophoresis may reveal 60-90% Hb S, 0-30% Hb A, 1–20% Hb F and an increased HbA2 level. In Hb S/β^+Thalassemia, as in our case, variable amounts of Hb A dilute Hb S and consequently inhibit polymerization-induced cellular damage. Increased levels of Hb A are usually associated with a milder phenotype [2, 5, 6, 7].

In our case, in the pre-splenectomy period, the patient was consistently having microcytic anemia as shown in Table 1 with leukopenia and increased LDH indirectly suggesting hemolysis. Platelet was adequate. No malarial parasite was seen in the peripheral smear. Post splenectomy, anemia improved but mild leukocytosis and thrombocytosis was evidenced as expected. LDH was found decreasing. Incidentally, peripheral smear showed numerous gametocytes of Plasmodium falciparum. Molecular tests for confirmation of sickle cell thalassemia were unavailable in the lab. Hence diagnosis was purely based on tests for sickling and Hb electrophoresis. Role of PBS examination and relevant histopathological sections could not be undermined.

Individually, both thalassemia and sickle cell trait offer protection from malarial infection, however when both occurs in the same individual protection offered by thalassemia can be reversed by another additional genetic polymorphism such as HbS mutation. The two mutations essentially cancel each other and the individual becomes susceptible to malaria [8]. Heterozygotes for the sickle gene (Hb genotype AS) are relatively protected against death due

Table 1. Relevant present investigations

Sr No.	Pre splenectomy	Post splenectomy
Hb (gm/dL)	6.6	10.1
MCV (fL)	68	69
TLC	2450	11220
DLC	P-69%, L-23%, M-07%, E-01%	P-82%, L-11%, M-04%, E-03%
Platelets (10^5/µL)	1.1	5.56
LDH (U/L)	>1000	634
PBS	No malarial parasites	Malarial parasites evidenced

Fig. 1. Gross specimen before and after fixation showing areas of infarction.

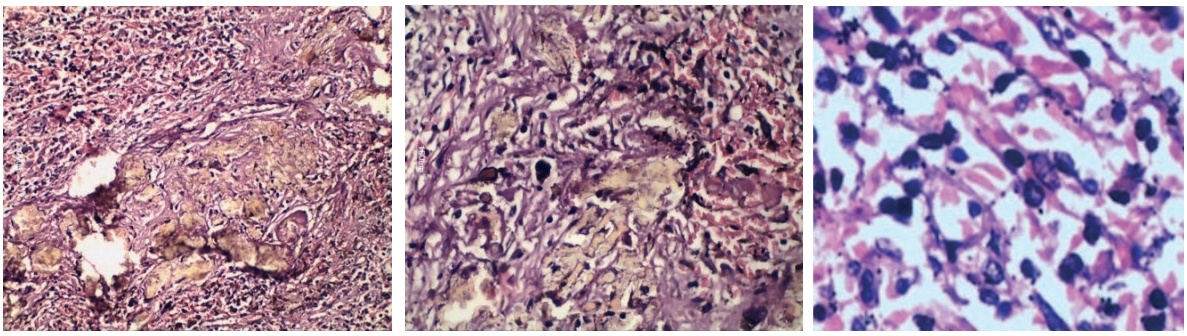

Fig. 2. Photomicrographs from H&E sections showing deposition of yellowish fine granular to amorphous (inset) substances in spleen (Gamna-Gandy bodies) and sickle cells.

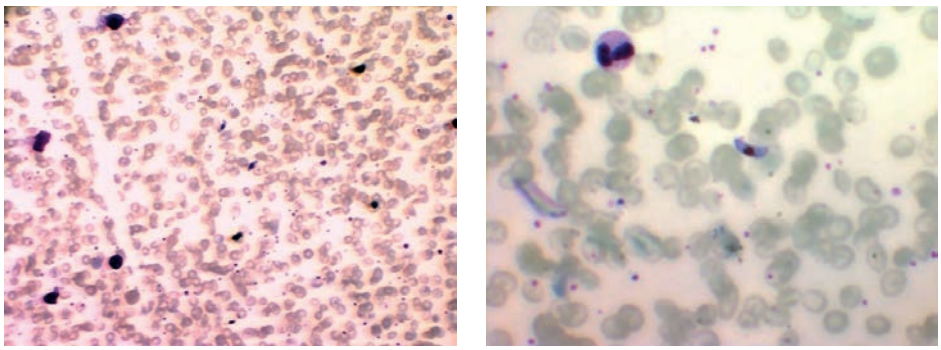

Fig. 3. Photomicrographs showing numerous gametocytes and trophozoites of Plasmodium falciparum and thrombocytosis.

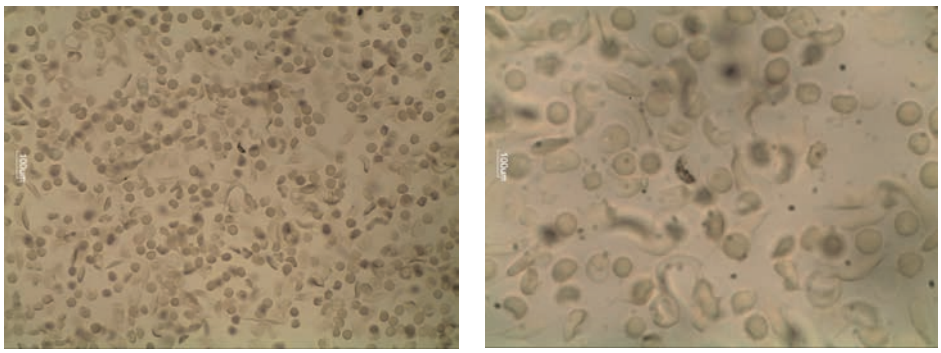

Fig. 4. Photomicrographs showing positive sickling with malarial gametocytes.

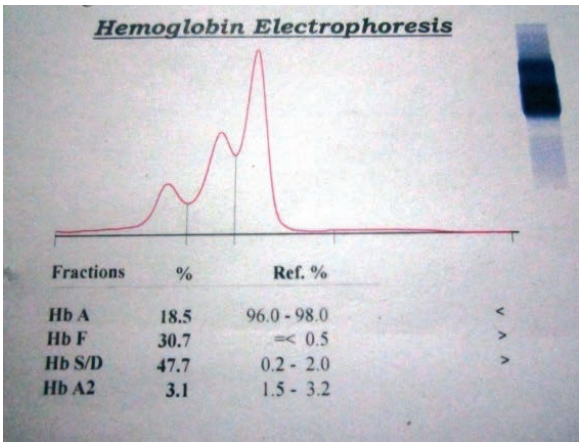

Fig. 5. Hb electrophoresis at alkaline pH showing a prominent band in SDG region, Hb F and faint band in HbA2 (Hb S – 47.7%, Hb F – 30.7%, Hb A – 18.5 % and Hb A2 – 3.1 %).

to malaria, probably through accelerated clearance by macrophages of Plasmodium falciparum-infected erythrocytes and by inhibiting growth of parasites in RBCs by increasing intracellular potassium, reduced PH and increasing endothelial adherence of infected cells [9]. On the other hand, homozygous (Hb SS) sickle cell anemia patients are not protected from malaria or any other infections [10,11] and, hence, there is increased chance of dying from malaria which is additionally aggravated by having dysfunctional spleen [12,13] or in the post-splenectomy period as removal of abnormal RBCs and other intracytoplasmic inclusion bodies is the primary function of spleen [14,15]. In our case, the pre-splenectomy period blood did not show any malarial parasites due to effective hyperactive enlarged spleen but once patient's spleen was removed, numerous forms of plasmodium falciparum were seen in the blood as the individual was devoid of major protection offered by spleen including removal of infected RBCs and other inclusion bodies.

People living in the malaria endemic areas have some degree of acquired immunity against malaria which may weaken over absence of recurrent exposures or when individuals moved to non-endemic areas [16]. This partial acquired immunity against malaria develops during the first 5 years of life and is dependent on the intensity of transmission, on exposure frequency and so it decreases with time if re-exposure does not occur [17]. In sickle cell disease, auto-splenectomy or functional asplenia occurs in early adulthood in homozygous state, however, in sickle beta-thalassemia the spleen may persist and remain enlarged even in adults. This splenomegaly may cause massive pooling of blood in the spleen (splenic sequestration), which leads to its enlargement and resulting in severe anemia and hence a more compelling indication for splenectomy in sickle beta-thalassemia. This reduces substantially the rate of blood transfusion [18].

Also, multiple areas in splenic parenchyma with deposition of yellow-brownish fine granular to amorphous substance with associated foreign-body giant cell reaction were found [19]. They were Gamna-Gandy bodies. Initially described by Marini as siderotic nodules in 1904, French physician Charles Gandy in 1907 found it in biliary cirrhosis patient. In 1921, the etiology was better described by an Italian pathologist Carlos Gamna, who observed deposits of amorphous material composed of iron and calcium sulfate in the spleen of a patient, who died of chronic hemolytic anemia; it was named Splenogranulomatosisiderotica. The name "Gamna-Gandy bodies" has been widely used ever since [20]. It is formed in sickle cell disease (SCD) due to chronic episodes of vaso-occlusion and hemolysis in the central arteriole of the white pulp with periarteriolar hemorrhages followed by mineral elements of the blood. It can be seen as either fine granular deposits in red pulp or as perivascular deposits or subcapsular deposits. GGBs can vary in size, ranging from 10 to 49 microns [21]. The GGDs is not pathognomonic of sickle cell disease as it can be found in many other diseases and in several other organs.

Conclusion

Splenomegaly in a case of sickle cell thalassemia is an established association, however to such extent that infarction with deposition of Gamna-Gandy bodies deposition is rare indeed. Loss of protective mechanism due splenectomy also predispose the individual to manifest subclinical malarial infection. Our case highlighted patient's high endurance and acquired immunity against all the conditions mentioned by virtue of his birth with inherited mutations in an endemic area of malaria. Diagnosis in the era of molecular tests still count on Hb electrophoresis, sickling test and peripheral blood smear.

Conflict of Interests

Authors declare no conflict of interest.

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Author's Contributions

Thongam Sachin Singh – conceptualization, methodology, formal analysis, writing – original draft, writing – reviewing and editing; *Raj Singh* – data curation, writing – reviewing and editing; *Rahul Pandey* – investigation, formal analysis.

СЕРПОВИДНО-КЛІТИННА ТАЛАСЕМІЯ З МАСИВНИМ ІНФАРКТОМ СЕЛЕЗІНКИ ТА ВУЗЛАМИ ГАМНА-ГАНДІ В ПАРЕНХІМІ СЕЛЕЗІНКИ З СУПУТНЬОЮ МАЛЯРІЙНОЮ ІНФЕКЦІЄЮ У ДОРОСЛОГО З ЦЕНТРАЛЬНОЇ ІНДІЇ (клінічний випадок)

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Вступ. *Серпоподібноклітинна анемія – це спадкова гемоглобінопатія, яка характеризується гетерозиготним станом Hb S/β⁺ або Hb S/β⁰ і клінічно може не проявлятися у гетерозиготних носіїв*

Мета. *Метою дослідження є огляд літератури та обговорення різноманітних клінічних проявів і діагностики клінічного випадку гемоглобінопатії у пацієнта із Центральної Індії.*

Методи. *Описано випадок гемоглобінопатії у пацієнта із Центральної Індії.*

Результати. *Ми повідомляємо про випадок гемоглобінопатії у дорослого, який звернувся до лікарні третього рівня з хронічним болем у спині. Було виявлено масивну спленомегалію з ознаками інфаркту селезінки. При загальному дослідженні селезінки виявлені множинні м'які жовтуваті тістоподібні ділянки, які при мікроскопічному дослідженні показали виражений некроз з наявністю великої кількості блідо-аморфної жовтої субстанції, тілець Гамна–Ганді (GGBs) і виражену реакцію гігантських клітин на чужорідне тіло в паренхімі селезінки. Мазок периферичної крові після спленектомії показав тромбоцитоз і гаметоцити Plasmodium falciparum. Електрофорез гемоглобіну виявив підвищення Hb S (49,7%), Hb F – 46,7%; Hb A2 – 3,0% & Hb A – 0,7%, що відповідає серповидноклітинній талассемії Hb S/β⁺ талассемії.*

Висновки. *Серповидноклітинна талассемія з тривалою спленомегалією, інфарктом селезінки з тільцями Гамна-Ганді і супутньою малярією у клінічно стабільних пацієнтів є справді рідкісним явищем.*

КЛЮЧОВІ СЛОВА: **серповидно-клітинна анемія; бета-талассемія; малярія; малярійний плазмодій; Тільця Гамна–Ганді.**

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IMPACT OF COVID-19 PANDEMIC ON THE RADIOTHERAPY AND CANCER PATIENTS IN A TERTIARY HEALTH CARE CENTER OF ASSAM, NORTHEAST INDIA: A RETROSPECTIVE SINGLE INSTITUTION STUDY

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Background. *The COVID-19 pandemic has affected every sector of health care system including the cancer care.*

Objective. *The purpose of the study is to analyse the impact of the current COVID-19 pandemic on routine radiotherapy practice at a tertiary hospital of Northeast India.*

Methods. *This is a retrospective study of all patients planned for radiotherapy at Assam Medical College, a tertiary care centre, in Assam, India from January 1, 2020 to May 31, 2020. The study samples are divided into two groups: group A – patients treated from January 1, 2020, to March 20, 2020 (pre-lockdown,) and group B – patients treated from March 21, 2020, to May 31, 2020 (lockdown). The department registration numbers of all the patients were collected from the entry register, and the respective paper files were then accessed to obtain the required data.*

Results. *A total of 153 patients were planned for radiotherapy during the study period, of these 113 patients receiving radiotherapy in the pre-lockdown period and 40 patients receiving it in the lockdown period. The number of female patients decreased from 66 (58.40%) in the pre-lockdown period to 20 (50%) during the lockdown. The number of male patients also decreased from 47 to 20 but the proportion increased from 41.5% to 50%. The proportion of patients who completed radiotherapy was 90.8% in group B compare to 88.3% in group A.*

Conclusion. *There was a decrease in number of cancer patients, especially female during the lockdown. The pandemic has severely disrupted every aspect of cancer care.*

KEYWORDS: **COVID-19; radiotherapy; pandemic; lockdown; oncology.**

Introduction

The Coronavirus outbreak caused by the severe acute respiratory syndrome started in Wuhan in December 2019. Since then it has spread across every corner of the world [1]. With the spread of COVID-19 disease in 2019, countries have instituted lockdowns for the benefit of public health at the expense of national economy. During the lockdown, in the fear of getting infected with the virus in the public health care, people avoid screening, diagnosis and treatment of other non-COVID diseases like cancer, which have impacted proper treatment of the cancer patients. The prognosis of cancer like complex set of diseases depends largely on the timing of diagnosis and immediate interventions [2].

The government of India witnessed a sudden and complete lockdown, in phased wise manner to combat the COVID-19 pandemic in late March 2020. This lockdown affected the entire country [3]. Due to the restrictions during the lockdown every sector of health care delivery system has been affected along with the cancer care system. Cancer patients remain very much susceptible to different kind of infections due their immunosuppressed status. They are also at risk of severe complications if they get infected with the coronavirus compare to the general populations [4].

Radiation therapy is one of the primary and useful modality of cancer treatment and it remained a valid treatment option during coronavirus pandemic as well. Radiation therapy in generally does not need any intensive care unit bed or respirators which are in demand resources during the pandemic. Moreover, majority of radiotherapy regimens are comparatively less immunosuppressive than to chemotherapy regimens. Lasting by following proper personal protection equipment and practicing social distancing proper cancer care and treatment can be given to the patients through radiation

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therapy according to the schedule of the respective patient [5].

Although, in the treatment of cancer patients, radiotherapy is one of the primary options but the high cost of machines and associated infrastructure along with the requirement of trained personnel have restricted its availability to only a few urban centres of India. Therefore, the travel restrictions imposed during the lockdown are likely to have affected the access to this treatment for patients coming from the distant places to radiotherapy centres [6].

Considering this, we have planned this study to assess the impact of the current COVID-19 pandemic on the patients receiving radiotherapy at a tertiary care hospital of upper Assam region of Northeast India.

Methods

This is a retrospective study completed in the Department of Radiation Oncology at Assam Medical College, a tertiary cancer centre in Assam, India, from January 1, 2020, to May 31, 2020. The inclusion criterion was all the patients who were planned for and who received radiotherapy at the centre during the study period, and the patients who have defaulted after planning radiotherapy were excluded from the study sample. In our analysis, the patients were divided into two groups: group A included the patients treated from January 1, 2020, to March 20, 2020, the period before the lockdown; and group B included all the patients treated from March 21, 2020, to May 31, 2020, the period of the lockdown. The study is planned with a primary objective to assess whether the impact of the COVID-19 pandemic varied in patients with cancer depending on their age, gender, site of disease, and intent of radiotherapy. The department registration numbers of all the patients receiving radiation therapy during the study period were collected from the entry register, and the respective paper files were then accessed to obtain the required data. The patients' characteristics and results between the two groups are compared by the Pearson Chi-Square test. Results are considered to be of significant difference if p-value is ≤0.05.

Screening for COVID-19 was done for every patient before starting the radiation therapy and thereafter weekly during radiation therapy. Patients who were asymptomatic were not tested prior to starting radiotherapy. There was no patient tested positive for COVID-19 while on radiotherapy during the study period in the hospital.

Results

In the study a total of 153 patients were planned for radiotherapy during the study period from January 1, 2020, to May 31, 2020. Out of these 153 patients, 113 patients are placed in group A (pre-lockdown period); and 40 patients – in Group B (lockdown period). None of patients has defaulted from treatment in both groups. There is decrease in number of new patients receiving radiotherapy during the lockdown compare to the pre-lockdown period but it is not statistically significant. Age distribution is almost similar in both groups; about 95% of the patients were aged between 30 and 70 years old in both groups. The gender-wise analysis showed that there were 66 (58.40%) female patients in the pre-lockdown period and the number decreased to 20 (50%) in the lockdown period. Likewise, the number of male patients decreased from 47 to 20 but the proportion increased from 41.5% to 50%. In our study in both groups, three the most common sites of occurrence of cancer were the head and neck cancers, gynaecological cancers and breast cancers. The number of patients with head and neck, gynaecological, and breast cancers were 43 (38.05%), 21 (18.58%), and 17 (15.04%), respectively, in the pre-lockdown period, and 17 (42.50%), 8 (20%), and 7 (17.5%), respectively, in the lockdown period. This indicates there was an increase in the proportion of patients with head and neck cancer and a decrease in the proportion of patients with gynaecological and breast cancers from the pre-lockdown to lockdown period.

Our study shows that 102 (90.3%) patients were treated with a radical intent in the group A, and 11 (9.7%) patients were treated with palliative intent. While in the group B 34 (85%) patients were treated with radical intent and 6 (15%) patients were treated with palliative intent. The patients treated with a palliative intent increased from 11 (9.7%) in the group A to 6 (15%) in the group B. There was no modification in the radiation fractionation used for the patients treated with a curative intent or palliative intent in both groups. The compliance to the planned treatment protocol was similar in both groups. The proportion of patients who completed radiotherapy was 90% in the group B as compared to 87.61% in the group A.

The changes in data reported, either increase or decrease in the lockdown period compared

to the pre-lockdown period, with respect to any variable is found to be statistically insignificant.

Discussion

Our study showed a decrease in the number of patients planned for radiotherapy and the number of new patients starting radiotherapy at their scheduled time during the lockdown period compared to the pre-lockdown period. However, once the treatment was started, almost the same number of patients completed the planned radiation therapy in the pre-lockdown and lockdown periods. The age distribution of patients was similar in both groups. There was a decrease of female patients coming for radiotherapy during the lockdown period. Both during the pre-lockdown and the lockdown periods three the most common sites for occurrence of cancer were head and neck followed by gynaecological and breast cancers. Curative intent radiotherapy was delivered to 90.3% of patients in the pre lockdown period as compared to only 85% during the lockdown period. The proportion of patients receiving palliative intent radiotherapy have increased during the lockdown.

Table 1. Distribution of patients in the lockdown and pre-lockdown periods

	Group A Pre-lockdown	Group B Lockdown
Time period	Jan 1, 2020 to Mar 22, 2020 (n=113)	Mar 23, 2020 to May 31, 2020: (n=40)
Number of patients defaulted	0	0
Number of patients, who completed radiotherapy as per schedule	113	40
Number of patients, who completed radiotherapy as per schedule	99 (87.61%)	36 (90%)
Total number of patients	113	40

Table 2. Distribution of gender, intent of treatment, age and radiotherapy completion in the cohort of patients receiving radiotherapy during the study period

	Group A Pre-lockdown period (n=113), n (%)	Group B Lockdown period (n=40), n (%)	Absolute difference (%)	P
Gender				
Male	47 (41.6%)	20 (50%)	8.4	0.459
Female	66 (58.4%)	20 (50%)	8.4	0.459
Intent of treatment				
Radical	102 (90.3%)	34 (85%)	5.3	0.386
Palliative	11 (9.7%)	6 (15%)	5.3	0.386
Age				
Below 30 years	1 (1%)	1 (2.5%)	1.5	1
30-70 year	108 (95.5%)	38 (95%)	0.5	1
Above 70 years	4 (3.5%)	1 (2.5%)	1	1
Concurrent chemotherapy	38 (33.62%)	13 (32.5%)	1.12	1

Table 3. Site-wise distribution of patients receiving radiotherapy during the study period

Site	Group A Pre-lockdown period (n=113), n (%)	Group B Lockdown period (n=40), n (%)	Absolute difference (%)	P
Head and neck	43 (38.05)	17 (42.5)	4.45	0.707
Gynaecological	21 (18.58)	8 (20)	1.42	1
Breast	17 (15.04)	7 (17.5)	2.46	0.801
Gastrointestinal	13 (11.50)	6 (15)	3.50	0.582
Others	19 (16.81)	2 (5)	11.81	0.105

There was no modification in the radiation fractionation or the use of concurrent chemotherapy in the patients treated with radical intent or palliative intent in either of the two groups. A study done by Chauhan et al. [6], in a charitable hospital of Eastern India have also reported decrease in number of patients during the lockdown period compared to the pre-lockdown period. They also showed a significant decrease in the number of female patients in the lockdown period.

The decrease in the number of cancer patients in the lockdown was more drastic during the first week of lockdown, then the numbers improved gradually but were still low compared to the pre-lockdown period. Restriction on public transport was the main reason for the increase of patients. The study was conducted at a government medical hospital of Northeast India. Here the most of the patients came from the distant rural areas for their treatment and most of them also belonged to the low socioeconomic stratum. They came from remote villages and were mainly depended on the public transport for their arrival to the hospital. Moreover, many patients as well as the attendants feared of getting infected with coronavirus on exposure to the health care setup. Therefore, many asymptomatic patients requiring post-operative adjuvant radiotherapy delayed their treatment.

The COVID-19 pandemic has affected every sector of health care system along with the cancer care. Due to the restrictions during the lockdown there is a halt in national cancer screening program [7]. In developing countries like India there is no easy access to affordable screening and diagnosing setup for cancer along with a lack of awareness among people about the suspected signs and symptoms of cancer that leads to delayed diagnosis of cancer.

The strict lockdown also leads to closing of hotels and guest houses nearby the hospital, local people also avoid renting theirs houses to any patients in fear of coronavirus pandemic; thus, there is hardly any place for accommodation near the cancer treatment centre for the patients. Another reason for the increase of patients during the lockdown is the continuously affected poor financial status of the patients and their family. As majority of the patients belong to lower socioeconomic status, many of them are daily wedge earner or run small business. Restrictions imposed on their workplaces due to the lockdown have affected their financial condition badly.

Our study also shows a decrease of female patients during the lockdown compared to the pre-lockdown period. A similar decrease in number of female patients in lockdown is also reported by Chauhan et al. [6]. Financial and social dependency on male is one of the reasons for this decrease of female patients in the lockdown. Moreover, the female patients might be reluctant to spend the limited resources of the family on themselves during the pandemic.

In our study we have reported that there is an increased number of patients coming for palliative intent radiotherapy during the lockdown period compared to the pre-lockdown period. The studies by Chauhan et al. [6] and Ghosh et al. [8] have also reported similar increase of number of patients coming for palliative intent radiotherapy in lockdown period. In most of the parts of India including the Northeast India there is a lack of social and personal awareness in between the people regarding the cancer related early sign and symptoms, lack of communication and knowledge regarding importance of screening for common cancers, eligible age groups for screening and different risk factors for different cancers. There is also a lack of affordable cancer care centres easily accessible for the public [9]. All of this leads to diagnosis of cancer in an advance stage in many people for whom palliative radiation therapy would be an effective option. These patients suffer unbearable pain and other symptoms which can be relieved by palliative therapy.

Our study shows that the majority of the patients in both the lockdown and pre-lockdown periods are in between 30-70 years of age. Similar findings were seen in the study by Chauhan et al [6]. Our study also shows that the most common type of cancer in both the lockdown and pre-lockdown periods is head and neck cancer followed by gynaecological cancer and breast cancer. The major cause of the head and neck cancers primarily of the gingivobuccal complex in the developing countries like India are smokeless tobacco by men [10]. Although smoking of bidis, chewing tobacco, betel nut quid and areca nut as well as alcohol consumption are main risk factors for head and neck squamous cell carcinoma; nevertheless a strong association of human papillomavirus (HPV) with head and neck squamous cell carcinoma in non-smoking cases is also reported [11].

Head and neck cancer are followed by cervical and other gynaecological cancer and

breast cancer. In Northeast India and many other rural areas of India the cases of cervical cancer are reported more than breast cancer although breast cancer is more common overall. This can be explained by the lack of knowledge and awareness regarding the screening age group, sign and symptoms of cervical cancer, in practicular no vaccination and risk factors like low socioeconomic status, early marriage, multiparty etc. [9,12].

Our study was performed in the Department of Radiation Oncology, Assam Medical College and Hospital, Dibrugarh. Assam Medical College and Hospital, Dibrugarh is a tertiary cancer care centre in the state of Assam of Northeast India. The Department of Radiation Oncology is equipped with one cobalt teletherapy machine. More than 30 patients are treated in the Department of Radiation Oncology daily. The Institute caters are mainly the patients from districts of upper Assam and Arunachal Pradesh. During the COVID-19 pandemic some changes were taken in treatment protocol following various guidelines published in high impact journals, government advisories, and hospital policies [13]. Regular OPD work was minimized to bare minimum and follow up and non-emergency visits are, avoided if possible, by giving telephone consultation during the pandemic for the safety of patients and health care workers [14].

This is the analysis of the few studies regarding the impact of COVID-19 pandemic in radiation therapy practice and cancer patients as a whole in upper Assam area of the north east India. As our study is a retrospective and observational in design, the study has many limitations. The generalised stage data of the cancer patients for the study during the study period could not be assessed. Another main limitation of our study is that no follow up is included in the study for analysis.

Conclusion

A decrease in number of cancer patients planned for radiation therapy during the lockdown compared to the pre-lockdown period has been established in our study. COVID-19 pandemic is one of the deadly natural disaster of modern era. The COVID-19 pandemic has disrupted every aspect of health care system, including screening, diagnosis and management of the cancer patients. Being a deadly immunosuppressive disease, cancer patients suffer a lot during the pandemic that affects them physically, financially as well as psychologically.

Conflict of Interests

Authors declare no conflict of interest.

Author's Contributions

Chiranjiv Baruah – conceptualization, methodology, formal analysis, writing – original draft, writing – reviewing and editing, *Kankan Jyoti Deka* – writing – reviewing and editing, *Trishan Paul* – writing – reviewing and editing, *Biswajit Sarmak* – writing – reviewing and editing, *Partha Pratim Patowary* – writing – reviewing and editing, *Sharath Sreeni* – writing – reviewing and editing, *Badurjya Mahanta* – formal analysis.

ВПЛИВ ПАНДЕМІЇ COVID-19 НА ДОСТУП ДО ПРОМЕНЕВОЇ ТЕРАПІЇ ТА ОНКОЛОГІЧНИХ ПАЦІЄНТІВ У ЦЕНТРІ ТРЕТИННОЇ МЕДИЧНОЇ ДОПОМОГИ В АССАМІ, ПІВНІЧНО-СХІДНА ІНДІЯ: РЕТРОСПЕКТИВНЕ ДОСЛІДЖЕННЯ

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Вступ. *Пандемія COVID-19 вплинула на всі сектори системи надання медичної допомоги, включаючи систему надання онкологічної допомоги.*

Мета. *Метою нашого дослідження був аналіз впливу поточної пандемії COVID-19 на рутинну практику променевої терапії у закладі третинної медичної допомоги на північному сході Індії.*

Методи. *Проводилося ретроспективне дослідження із залученням пацієнтів, яким запланована променева терапія, в медичному коледжі Ассама, центрі третинної медичної допомоги, в Ассамі, Індія, з 1 січня 2020 р. по 31 травня 2020 р. Вибірку дослідження поділено на дві групи, група А включає пацієнтів, які лікувалися з 1 січня 2020 р. по 20 березня 2020 р. (прелокдаун), а група Б включає пацієнтів, які проходили лікування з 21 березня 2020 р. по 31 травня 2020 р. (локдаун).*

Результати. *Загалом 153 пацієнтам було заплановано проведення променевої терапії протягом періоду дослідження, з них 113 пацієнтів отримували променеву терапію в період до локдауну, а 40 пацієнтів отримували її у період карантину. Кількість пацієнток різко зменшилася з 66 (58,40%) у прелокдауні до 20 (50%) під час локдауну. Пацієнтів чоловічої статі також зменшилося з 47 до 20, але частка зросла з 41,5% до 50%. Частка пацієнтів, які завершили променеву терапію, становила 90,8% у групі Б порівняно з 88,3% у групі А.*

Висновки. *Під час карантину кількість онкологічних пацієнтів, яким надавалася медична допомога, особливо жінок, зменшилася. Пандемія серйозно порушила всі аспекти системи надання медичної допомоги онкологічним захворюванням.*

КЛЮЧОВІ СЛОВА: **COVID-19; радіотерапія; пандемія; локдаун; онкологія**

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ANTHROPOMETRIC VARIABLES IN BREAST LESIONS OF WOMEN OF REPRODUCTIVE AGE IN UNIVERSITY OF PORT HARCOURT TEACHING HOSPITAL

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Background. Benign breast diseases are a potential health concern to a large number of women. The incidence of cancer is increasing worldwide. A steady increase in incidence has been observed in most developed and developing counties.

Objective. Thus, our study seeks to investigate the anthropometric variables implicated in breast lesions of women of reproductive age.

Methods. This is a descriptive and prospective study with a random sampling method; the data was obtained from the Department of Surgery, Radiotherapy and Oncology Unit of University of Port Harcourt Teaching Hospital. A total number of 146 subjects (18-49 years) were involved into this study. A number of 90 were breast lump patients and 56 were breast cancer patients.

Results. Data obtained was analysed with Microsoft Excel. Our results show no statistically significant difference (P> 0.05) in the body mass index (BMI) and waist-hip-ratio (WHR) of both the breast lump and breast cancer patients. This study supports the fact that high BMI is a predictive marker for breast lumps and cancer in women.

Conclusion. The study has also identified that high BMI favours the incidence of breast lumps and breast cancers in women of reproductive age.

KEYWORDS: **anthropometric variables; BMI; waist-hip-ratio; breast cancer; breast lump.**

Introduction

Benign breast diseases are common throughout a woman's lifetime, from early reproductive life to the postmenopausal part of life, making it a potential health concern to a large number of women. Malignant lesions on the other hand are cancerous in nature and are characterized by progressive and uncontrolled growth. Breast cancer is one of the most common types of malignant diseases, affecting millions of women around the world, with a high rate of morbidity and mortality. The prevalence rate of breast cancer, particularly in Nigeria, accounts for 20% to 25% of tumours in women with an annual incidence of about 800 to 1000 cases [1]. African breast cancer patients tend to present at a younger age, with a lesion characterized by large and palpable tumour, multiple nodal involvements, and have poorer clinical and pathological prognostic factors compared with Caucasian patients [2]. These documented characteristics are somewhat similar to that of African-Americans but are in contrast with those of non-Hispanic Whites in the USA, which therefore calls for the consideration of genetic factors in the aetiology of breast cancer in general, and in people of African origin in particular [3, 4].

In 2017, an estimated 252,710 new cases of invasive breast cancer were diagnosed among women and 2,470 cases were diagnosed in men and thus approximately 40,610 women and 460 men were expected to die from breast cancer in 2017 [5]. The incidence of cancer is increasing worldwide. A steady increase in incidence has been observed in most developed and developing counties. Apart from incidence, cancer related deaths are also increasing. There were over 230,000 new cases of breast cancer each year in the United States as at 2015. Some studies had affirmed that the risk of breast cancer increase with age, and in the United States approximately one out of eight women will get breast cancer at some point in their lives [6, 7, 8]. Thus with 1.7 million new cases diagnosed in 2012, constituting 12% of all new cancer cases and 25% of all cancers in women, breast cancer remains the commonest site-

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specific malignancy affecting women and the most common cause of cancer death in women.

In Nigeria, female breast cancer is recognized as major cause of morbidity and mortality with incidence rate ranging from 36.3 to 50.2/100,000 live birth [9]. More so, late presentation of patients at advanced stages when little or no benefit can be derived from any form of therapy is the hall mark of breast cancer. Reasons given include poverty, under-education, lack of knowledge and poor access to care [10]. Indeed, the ratio of mortality to incidence in Africa is 0.73, compared to below 0.23 in North America and 0.354 in Latin America and the Caribbean [11]. Risk factors associated with breast cancer development include non-modifiable ones such as female sex, increasing age, a history of breast cancer in close relatives especially in mothers and siblings. Non-modifiable ones include early menarche before the age of 14 years or menopause later than the age of 55 years. Other risks include overweight and obesity, prolonged use of hormone replacement therapy, oral contraceptives, tobacco use, alcohol intake, nulliparity or having first child after age 35. Thus, our study seeks to investigate the anthropometric variables implicated in breast lesions of women of reproductive age.

High body weight (measured in terms of body mass index, BMI) has been recognized as an important risk factor for breast cancer among postmenopausal women in many previous epidemiological studies [12, 13, 14, 15]. After menopause, epidemiological evidence found a substantial positive association between BMI and breast cancer risk [16]. A meta-analysis showed that the substantial positive association between post-menopausal BMI and breast cancer risk was confined to hormonal factors [17]. Some studies have shown a decreased risk for premenopausal women [18, 19], while others have shown no association [20, 16]. Breast cancer has been documented in other studies as the most frequently occurring cancer in women of reproductive age [21].

Methods

This is a descriptive and prospective study with a random sampling method; the data was obtained from the Department of Surgery, Radiotherapy and Oncology Unit University of Port Harcourt Teaching Hospital. Demographic information such as age, body weight, height, waist circumference, hip circumference was obtained from the patients. A consent form was given to the patients prior to data collection. The population of this study includes breast lumps and breast cancer patients, the age range of 18 - 49 years old, of University of Port Harcourt Teaching Hospital, Rivers State, Nigeria. The participants voluntarily consented to the study which was conducted in compliance with the ethical standards. A total number of 146 subjects were involved into the study; 90 of them were breast lump patients and 56 were breast cancer patients. Data obtained was analysed with Microsoft Excel.

The following anthropometric variables were measured.

I. Weight (kg): Weight is measured to the nearest 0.1 kg when the subject is standing and putting on light indoor clothes excluding shoes, belt and sweater using a weighing scale. Heavy jewellery if any present was removed and pockets emptied.

II. Height (cm): Standing height is the measurement of the maximum distance from the floor to the vertex, when the subject is facing forward.

III. The BMI: It was calculated as the ratio of weight in kilogram by square of height in meters (m^2). i.e.: BMI (kg/m^2) = weight (kg)/ height (m^2). It is a measure of body mass corrected for height which is used to assess the extent of weight deficit or excess. BMI also provides a practical indicator of adiposity and hence overweight or obesity.

IV. Waist circumference (cm): The tape is used to circle the waist (like a belt would circle the waist) at the natural waistline, which is midpoint between the lowest rib and the iliac crest. The subject is asked to stand erect while measurements are taken. The measurement is taken at the midpoint between the lowest rib and the iliac crest. The measuring tape is placed perpendicular to the long axis of the body and horizontal to the floor, with sufficient tension to avoid slipping off but without compressing the skin. The measurement is made at the end of a normal expiration to the nearest 0.1 cm

V. Hip circumference (cm): The subject stands erect, the weight is evenly distributed on both feet. The tape is placed at the maximum extension of the buttocks, horizontal to the floor, with sufficient tension to avoid slipping off. The tape is held a bit tighter but without compressing the buttocks. The zero end of the tape is held under the measurement value recorded to the nearest 0.1 cm.

VI. Waist hip-ratio (WHR): This is calculated by dividing the waist measurement by the hip measurement, since the hips are the widest part of the buttocks. The formula is: WHR = waist circumference/hip circumference.

Ethical approval

Ethical approval was obtained from the Research Ethics Committee of University of Port Harcourt Teaching Hospital with the number of UPTH/ADM/90/S.II//VOL.XI/1270.

Informed consent was obtained from all respondents prior to data collection.

Results

The data in Table 1 shows that the mean BMI for age group (18-25) is 23.71, which is normal according to World Health Organization (WHO) classification.

Table 2 shows the anthropometric data for women with breast cancer who had the mean BMI of 26.89, 27.92, 26.85, and 28.62 for the various age groups studied. They therefore just like their counterparts with breast lumps are within the overweight category.

A T value of -0.88 means that there is some similarity between the BMI of those with breast lump and those with breast cancer; however, the T value shows some difference does exist. The negative T value shows that BMI values affect both the occurrence of lumps and that of cancer. The data shows that both patients with breast lumps and those with breast cancers all have high BMI: overweight.

A P value of 0.38 (>0.05) shows that there is no statistical difference in the BMI of patients with breast lump and breast cancer. Thus, high BMI favours the occurrence of breast lumps and cancers in women of reproductive age (Table 3).

A P value of 0.44 (> 0.05) shows that there is no statistical difference in the WHR of the patients with breast lump and breast cancer. However, those with breast cancer have a higher mean BMI and a higher mean WHR. Thus, BMI and WHR affects the incidence of breast cancer (Table 4).

Discussion

The results of this study showed that many of the participants involved were overweight. Also, for age groups (26-33), (34-41) and (41-42), their mean BMI were 25.69, 27.54 and 29.93,

Table 1. Average anthropometric values of reproductive age women with breast lump

Age group (years)	N	Weight (kg)	Height (m)	BMI	X	WC (cm)	HC (cm)	WHR	X
18-25	15	63.93	1.64	23.71	Normal	69.09	84.16	0.80	Normal
26-33	26	67.42	1.62	25.69	Overweight	74.25	89.66	0.83	Normal
34-41	29	73.97	1.63	27.54	Overweight	79.18	97.91	0.81	Normal
42-49	20	78.85	1.63	29.93	Overweight	83.95	101.48	0.83	Normal

Notes. N – number of subjects, BMI – Body Mass Index, WC – waist circumference, HC – height circumference, WHR – waist-hip ratio. WHR (Women): <0.85 = Normal, >0.85 = Risk, X – classification.

Table 2. Average anthropometric values of reproductive age women with breast cancer

Age group (years)	N	Weight (kg)	Height (m)	BMI	X	WC (cm)	HC (cm)	WHR	X
18-25	2	68	1.59	26.89	Overweight	76.20	88.9	0.85	Risk
26-33	9	75.78	1.65	27.92	Overweight	83.82	101.04	0.84	Normal
34-41	25	72.24	1.64	26.85	Overweight	82.30	98.14	0.84	Normal
42-49	20	73.90	1.61	28.62	Overweight	84.20	105.54	0.80	Normal

Notes. N – number of subjects; BMI – body mass index; WC – waist circumference; HC – height circumference; WHR – waist-hip Ratio. WHR (Women): < 0.85 = normal, > 0.85 = risk, X – classification.

Table 3. Relationship between BMI of breast lump and breast cancer patients irrespective of age group

X	N	Percentage, %	Mean±SD	T value	P value	Inference
Breast lump	90	61.64	26.90±4.71	-0.88	0.38	Not significant
Breast cancer	56	38.35	37.66±5.28			

Notes. X – classification; BMI – body mass index; SD – standard deviation.

Table 4. Relationship between the waist-hip ratio of breast lump and breast cancer patients irrespective of age group

X	N	Percentage, %	Mean±SD	T value	P value	Inference
Breast lump	90	61.64	0.82±0.06	-0.77	0.44	Not significant
Breast cancer	56	38.35	0.83±0.07			

Notes. X – classification, WHR – waist-hip ratio, SD – standard deviation.

respectively, indicating that they were all in the overweight category. The mean waist hip ratio (WHR) was within the norm for all the women within this age group and classification. Our data shows the anthropometric data for women with breast cancer, who had the mean BMI of 26.89, 27.92, 26.85, and 28.62 for the various age groups studied. They therefore just like their counterparts with breast lumps are within the overweight category. Their WHR were also within norm except for women within the age group 18-25 (Table 2). Again, both Tables 3 and 4 shows that there is no statistically significant difference (P> 0.05) in the BMI and WHR of both the breast lump and breast cancer patients. Thus, the same variables implicated in the incidence of breast lumps also affected those of breast cancers. Our study therefore shows that the same anthropometric variables present in reproductive age women with breast lump were also found in those women with breast cancer. High BMI thus influences the incidence of breast lump and breast cancers proportionately, as more than seventy percent of the subjects are within the overweight category. The WHR in the study was not a major factor to have influenced the lumps and cancers. About 62% of the patients studied had breast lumps and about 38% had breast cancers.

The findings were consistent with several other authors who reported that high BMI favours the occurrence of breast cancer in women, especially postmenopausal women [16, 22], although our study covered women within the reproductive age. It is therefore apparent to affirm that high BMI favours the occurrence of both breast lumps and cancers in women. One most classical biological explanation is as a result of a female hormone-related mechanism. This is for the fact that adipose tissue may be a major source of oestrogens [14], which are critical mitogens for mammary epithelial cells [12, 15].

Despite the fact that our findings are associated high BMI with cancer among women of reproductive age, some other studies among premenopausal women are inconsistent and unclear [23]. Some studies have shown a decreased risk for breast cancer among premenopausal women [18, 19] while others have shown no association [16, 20]. Our study did not compare breast cancer risk between healthy women and cancer patients though, as we only focused on the prevalent anthropometric variables among women with breast lesions. Most probably this comparison would have shown the level of risk association between the two groups as argued by previous researchers. Nonetheless our study has identified the association of high BMI with breast lumps and cancers in women of reproductive age.

Conclusion

This study supports the fact that high BMI can be used as a tool to predict breast cancer as well as breast lumps for women. More so the study has also identified that high BMI favours the incidence of breast lumps and breast cancers in women of reproductive age. The findings did not show any statistically significant correlation between high WHR and breast lumps and/or breast cancers as most of the subjects in this category were within the norm despite being diagnosed of a lump and/or cancer.

Conflict of interest

Authors declare no conflict of interest.

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Author's contributions

Clinton David Orupabo – conceptualization, methodology, formal analysis, writing – reviewing and editing; *Chelsea Odoya George* – investigation, data curation, writing – original draft.

АНТРОПОМЕТРИЧНІ ПАРАМЕТРИ УРАЖЕНЬ МОЛОЧНОЇ ЗАЛОЗИ У ЖІНОК РЕПРОДУКТИВНОГО ВІКУ В УНІВЕРСИТЕТСЬКІЙ ЛІКАРНІ ПОРТ-ХАРКОРТ

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Вступ. *Зростання частоти та поширеності доброякісних захворювань молочної залози становить потенційну загрозу для значної кількості жінок. Ця тенденція спостерігається в більшості розвинутих країн і країнах, що розвиваються.*

Мета. *Наше дослідження було спрямоване на дослідження антропометричних змінних уражень молочних залоз у жінок репродуктивного віку.*

Методи. *Проведене описове проспективне дослідження методом випадкової вибірки, дані були отримані з відділення хірургії, променевої терапії та онкології університетської лікарні Порт-Харкорта. Усього в цьому дослідженні було залучено 146 пацієнток (18-49 років). З них 90 були пацієнтами з ущільненням грудей і 56 – з раком молочної залози.*

Результати. *Статистична обробка даних зроблена за допомогою Microsoft Excel. Аналіз даних не виявив статистично значущої різниці (P> 0,05) між індексом маси тіла (IMT) та показниками співвідношення талії і стегон (WHR) як у пацієнтів із доброякісними новоутворами молочної залози, так і у пацієнтів з раком молочної залози. Однак, отримані нами дані вказують на те, що високий IMT є прогностичним маркером утворення і розвитку доброякісних і злоякісних захворювань молочної залози.*

Висновки. *Високий індекс маси тіла є сприятливим фактором виникнення доброякісних та злоякісних захворювань молочної залози у жінок репродуктивного віку.*

КЛЮЧОВІ СЛОВА: **Антропометричні змінні; індекс маси тілі (IMT); Співвідношення талії та стегон; Рак молочної залози; Доброякісні захворювання молочної залози.**

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HYPOFRACTIONATED RADIOTHERAPY WITH CONCURRENT CHEMOTHERAPY WITH WEEKLY CISPLATIN IN LOCALLY ADVANCED RELATIVELY RADIORESISTENT SUBSITES OF HEAD AND NECK CANCERS

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Background. *Locoregionally advanced head and neck cancers are more aggressive and locoregional failure rate after conventional radiotherapy is high.*

Objective. *The aim of the study is to assess the tumor response and toxicities of hypofractionated radiation therapy with concurrent chemotherapy in treatment of four relatively radioresistent tumor sites of head and neck.*

Methods. *A prospective randomised control trial was conducted in 27 head and neck cancer patients. All patients were treated with hypofractionated radiotherapy at 250cGy/fraction once daily to a maximum of 62.5Gy in 25 fractions with concurrent cisplatin 30 mg/m^2. Data were evaluated with SPSS version 21.0 for Windows with p-value <0.05.*

Results. *Complete and partial responses were achieved in 15 (57.7%) and 8 (30.8%) patients respectively with an overall response rate of 88.5% and three patients having stable disease. Grade 3 and 4 acute mucositis was experienced by 17 patients (65.4%) and seven patients (27%), respectively. Grade 3 dysphagia was found in 21 patients (80.7%) and grade 3 and 4 skin reactions – in 11 and 2 patients, respectively. Most patients had manageable acute toxicities. Most of the late complications were of grade 2 and 3. The median time to locoregional recurrence was 12 months and one year progression-free survival attained by 61.5% patients.*

Conclusion. *Treatment with hypofractionated radiotherapy with concurrent cisplatin appears feasible and safe and is associated with a good response rate. Although grade 3 and 4 toxicities were comparatively high but it was manageable. Late toxicities were within tolerable levels.*

KEYWORDS: **head and neck cancer; hypofractionated; radioresistent; response; mucositis.**

Introduction

The term "Head and Neck Cancers" usually refers to the variety of neoplasms arising from upper aero-digestive tract with majority (approximately 80%) of head and neck malignancies of squamous cell carcinomas [1]. Oral cavity and laryngeal cancers are the most common head and neck cancers globally [2]. In India, age adjusted rate (AAR) of incidence for head and neck squamous cell carcinoma (HNSCC) is approximately 988.9 per 100000 populations with male to female ratio 3:1. In North-East of India, AAR incidence of HNSCC is 459.7 per 100000 populations, hypopharyngeal cancer being the commonest cancer [3]. HNSCC have been a disease of older males with heavy life-long tobacco use, high alcohol consumption, poorly preserved diet, and bad dentition usually presents with pain, dysphagia, neck mass etc. [4].

Locoregionally advanced (LA) HNSCC is treated by multimodality approaches combining surgery, radiotherapy and chemotherapy; radiotherapy being the main modality for unresctable tumors [5]. Nevertheless, the outcome of conventional radiation was disappointing, especially in advanced stage (i.e., stage III or IV) with a 5-year survival less than 60% only [6, 7]. One of the important causes of failure of conventional radiation is accelerated repopulation of tumor clones which usually starts around the 4th week of radiotherapy. To prevent this an altered fractionation scheme was introduced [8].

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Tumor hypoxia is a major concern in HNSCC causing treatment failures with radiation therapy. Whereas many sites of head and neck are radiosensitive like nasopharynx or larynx, few inherently radioresistant tumors of base of tongue, vallecula, pyriform sinus, retromolar trigone are associated with increased metastases and decreased sensitivity to ionizing radiation [9]. Hence, hypofractionated schedules by using a small number of fractions with a larger dose per fraction and shortening of the overall treatment duration have been tried to counter the tumor hypoxia and repopulation [10]. A meta-analysis of 16 randomized clinical trials demonstrate that optimized hypofractionation can markedly improve tumor control probability by 35% to 49% for late-stage head and neck cancer by overcoming tumor repopulation in fast-growing tumors [11]. Addition of concurrent chemotherapy to radiation would increase the efficacy of the treatment along with tumor control [12].

The aim of this study is to assess the tumor response and toxicities of hypofractionated radiation therapy with concurrent chemotherapy in treatment of four relatively radioresistent tumor sites of head and neck. After reviewing the literature and surveillance data, we have selected four subsites for this study retromolar trigone (RMT), base of tongue (BOT) and vallecula and pyriform sinus (PFS) because of their rarity and aggressive behaviour along with increased incidence of treatment failure and less long-term survival. Cancer in these sites is more hypoxic.

Methods

A prospective non-randomized experimental study was undertaken in the Department of Radiation Oncology, Regional Institute of Medical Sciences, Imphal, Manipur for two years starting from October 1, 2019 to September 30, 2021 among 27 patients. The permission of the Research Ethics Board (REB), RIMS, Imphal, Manipur was obtained (No. A/206/REB-Comm(SP)/RIMS/2015/597/75/2019) before initiating the study.

Inclusion criteria:

1. Patients aged between 30-75 years of age.
2. Patients with histopathologically confirmed squamous cell carcinoma of the selected head and neck subsites of base of tongue, vallecula, pyriform sinus, retromolar triangle (AJCC 8th edition stage III, IVA & IVB).
3. Patients who were not eligible for curative resection due to advanced stage.
4. Karnofsky performance status (KPS) ≥60%.
5. Normal complete blood count, liver and kidney function, blood glucose and normal audiometry.

Exclusion criteria:

1. Subsites other than those included in inclusion criteria.
2. Patient not willing to give consent.
3. Patient with second malignancy, previously treated with radiation therapy / chemotherapy and / or surgery.
4. Patients with uncontrolled co-morbid illness, psychotic disease, pregnant and lactating women.

All patients were treated with external beam radiotherapy by THERATRON 780-C, Telecobalt machine administered on a 5-week schedule by shrinking field technique and hypofractionated radiotherapy at 250 Gy/fraction once daily to a maximum of 62.5 Gy in 25 fractions (BED=78.12). Primary tumor and whole neck were irradiated up to a dose of 45Gy in 18 fractions. Doses equivalent to conventional fractionation were calculated for late reacting tissue and spinal cord shielding was performed after 40Gy in 16 fractions (BED=73.33), which was biologically equivalent with 46 Gy/23 fractions (BED=76.66) in conventional radiotherapy. Clinically uninvolved areas were excluded after 45 Gy. Primary tumor with metastatic nodal regions was irradiated up to 62.5 Gy. Concurrent cisplatin was administered at a dose of 30 mg/m^2 weekly for a total of 5 doses. The patients received standard hydration, mannitol infusion and prophylactic antiemetic medications for cisplatin therapy. Laboratory requirements before the dose of cisplatin were Granulocytes ≥1,500/μL, Platelets ≥100,000/μL and serum creatinine ≤1.5 mg/dL and normal audiometry.

During the whole period of treatment, the patients were reviewed every to note any adverse or untoward side effect, performance status, subjective response. Tumor response was assessed in 6 weeks after the completion of radiotherapy using RECIST Criteria (version 1.1) [13] with local examination and contrast enhance computed tomography (CECT) imaging. Acute radiation toxicities were assessed during each week of the radiation treatment and graded according to the RTOG acute radiation toxicity grading. Late radiation toxicities were assessed in 3 months after completion of treatment and thereafter every 3 months till 1 year (minimum 6 months) using the RTOG late radiation morbidity grading [14].

Statistical analysis: SPSS-version 21 for Windows (IBM Corp, Armonk, NY, USA) was used for statistical analysis. Variables like age, Karnofsky performance scores were presented as descriptive analysis using mean, median, mode and standard deviation. Categorical variables like gender, primary site, staging, histology, tumor response and toxicity profile were presented in terms of percentages and proportions as frequency tables or charts. Test of significance was done with Chi-square test using p-value 0.05 for assessing the association of multiple factors with treatment response and progression-free survival (PFS). PFS was analyzed using Kaplan-Meier survival curve and descriptive survival table.

Results

Total 27 cases of confirmed locoregionally advanced HNSCC were studied during the study period. One patient stopped treatment in between and lost follow up was excluded from the study. Hence data assessment was done for the 26 patients who completed their full coarse treatment.

Seventeen patients completed the treatment within the planned period of 35 days. The median time of delivery for these patients was 37 days (range, 33–65 days). Delay in the treatment contributed by environmental factor (Covid-19 Pandemic), social factors (lockdown), patient factors (noncompliance), treatment factors (side effects) and mechanical factors (machine break down).

Characteristic features of the patients and tumor are presented in Tables 1 and 2, respectively. 19 out of 26 patients had history of tobacco consumption whereas 16 patients had history of alcohol consumption and 9 patients had consumed both tobacco and alcohol. Median follow up period was 11 months with a range of 18 months (6-24 months). There were 16 patients of Pyriform sinus (5 stage III, 7 stage IVA and 4 stage IVB patients), 5 patients of Retromolar trigone (3 stage III and 2 stage IVA patients), 3 patients of vallecula (2 stage IVA and 1 stage IVB patients) and 2 patients of base of tongue (both stage IVA).

Table 3 shows the overall treatment response at the end of 6 weeks after completion

Table 1. Patients characteristics

Variables	Sub variables	Frequency (n=26)	Percentage (%)
Median Age in years		58.5	
Sex	Male	20	77
	Female	6	23
KPS	60	2	7.7
	70	9	34.6
	80	10	38.5
	90	5	19.2

Table 2. Tumor characteristics

Variables	Sub variables	Frequency (n=26)	Percentage (%)
T stage	T1	2	7.7
	T2	10	38.5
	T3	10	38.5
	T4	4	15.4
N stage	N0	3	11.5
	N1	4	15.4
	N2	13	50.0
	N3	6	23.1
Stage Grouping	III	8	30.8
	IV A	13	50.0
	IV B	5	19.2
Grade	Well differentiated	7	26.9
	Mod differentiated	12	46.2
	Poor differentiated	6	23.1
	Un differentiated	1	3.8

Table 3. Response rate in the patients according to Response Evaluation Criteria in Solid Tumor (RECIST) criteria after 6 weeks of completion of treatment

Tumor response	Frequency (n=26)	Percentage (%)
Complete response (CR)	15	57.7
Partial response (PR)	8	30.8
Stable disease (SD)	3	11.5
Overall response rate (ORR) [CR + PR]	23	88.5

of treatment in the study population. All the 26 patients were available for assessment at the end of the 1st month. The patients were evaluated with local examination and CECT imaging. CR was disappearance of all target lesions in primary site as well as secondary nodes whereas PR was defined as at least 30% decrease in size of target lesions. Complete and partial responses were achieved in 15 (57.7%) and 8 (30.8%) patients respectively with an overall response rate of 88.5% and 3 patients were having stable disease. One patient with T4 disease and two patients with N3 disease had radiological CR.

All patients were assessed weekly during treatment. Most of them had no hematological toxicity. Grade 2 anemia occurred in four patients, grade 2 neutropenia was in three patients for which they received blood transfusion and granulocyte colony stimulating factors. Grade 3 and 4 mucositis was experienced by 17 patients (65%) and seven patients (27%), respectively. Grade 3 dysphagia was evidenced in 21 patients (80.7%). The patients suffering from grade 2 and 3 skin reactions were 9 and 11, respectively. More than 88 % experienced grade 2 hoarseness, and grade 2 and 3 acute salivary gland reaction was found in 11 and 15 patients, respectively. Grade 3 and 4 toxicity developed after 3 weeks of radiation which corresponds with 3750 cGy in 15 fractions dose. Most patients had manageable acute toxicity.

Late complications were assessed at the 3rd, 6th and 9th month after completion of radiation. Grade 2 and 3 dysphagia was seen in 19 (73%) and 5 (19%) patients, respectively, and grade 2 mucositis was experienced by 38.5% of the study population. Grade 2 xerostomia was present in 20 patients at the 3rd months and reduced on further follow up. Grade 2 subcutaneous reaction was evidenced in 12 patients at the 3rd month. Almost all the toxicities were reduced on further follow up.

The median time to locoregional recurrence was 12 months (ranging 2-24 months). In Total 10 patients experienced recurrence. Three patients had recurrence at primary as well as nodal site and six patients – at nodal site only.

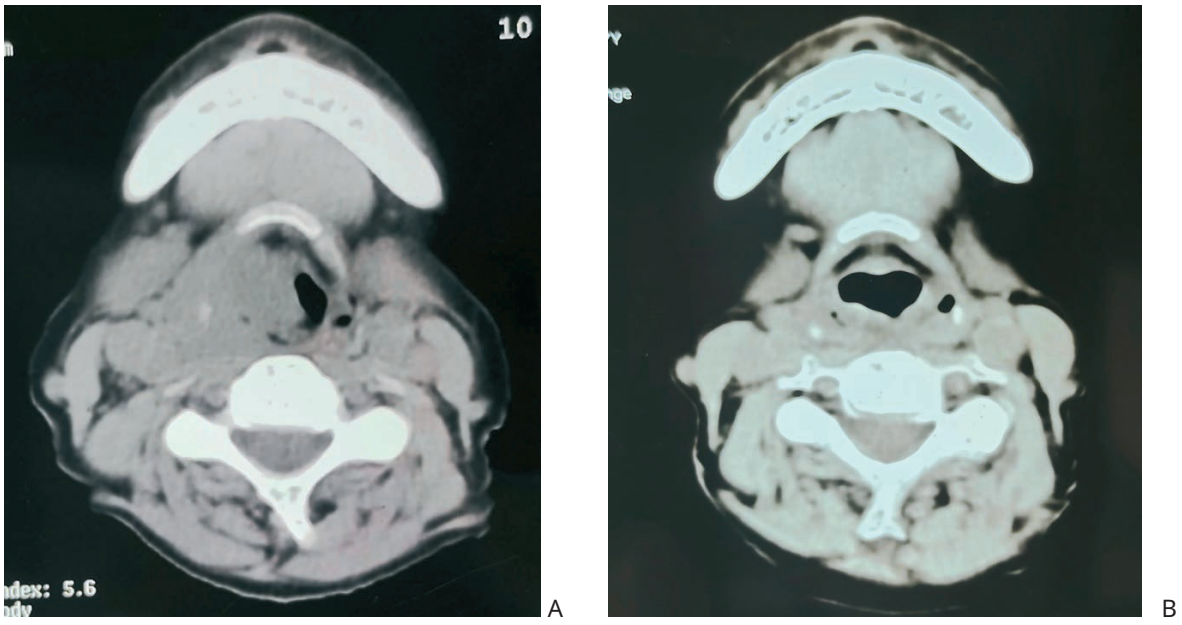

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Fig. 1. (A) Axial CT image of neck showing extensive pyriform fossa mass; (B) Response in the same patient in 6 weeks after completion of treatment.

Table 4. Acute radiation toxicity in study population according to the RTOG criteria, n=26 (%)

Toxicity	Grade	Week 2	Week 3	Week 4	Week 5
Anemia	Grade 2	0	2 (7.7)	3 (11.5)	2 (7.7)
	Grade 3	0	0	1 (3.8)	0
	Grade 4	0	0	0	0
Leucopenia	Grade 2	0	1 (3.8)	3 (11.5)	0
	Grade 3	0	0	1 (3.8)	1 (3.8)
	Grade 4	0	0	0	0
Mucositis	Grade 2	3 (11.5)	12(46.2)	8 (28.6)	7 (27.0)
	Grade 3	0	12 (46.2)	13 (50.0)	17 (65.4)
	Grade 4	0	0	7 (27.0)	2 (7.7)
Skin reaction	Grade 2	0	6 (23.1)	9 (34.5)	7 (27.0)
	Grade 3	0	0	6 (23.1)	11 (42.3)
	Grade 4	0	0	2 (7.7)	1 (3.8)
Dysphagia	Grade 2	3 (11.5)	13 (50.0)	4 (15.4)	7 (27.0)
	Grade 3	0	12 (46.2)	21 (80.7)	20 (76.9)
	Grade 4	0	0	0	0
Hoarseness	Grade 2	0	12 (46.2)	23 (88.5)	18 (69.2)
	Grade 3	0	0	1 (3.8)	4 (15.4)
	Grade 4	0	0	0	0
Salivary gland	Grade 2	0	17 (65.4)	11 (42.3)	11 (42.3)
	Grade 3	0	3 (11.5)	15 (57.7)	14 (53.8)
	Grade 4	0	0	0	0

Table 5. Late radiation toxicity in study population according to the RTOG criteria, n=26 (%)

Toxicities	Grade	3rd month	6th month	9th month
Skin reaction	Grade 1	17 (65.4)	19 (73.1)	11 (42.3)
	Grade 2	4 (15.4)	5 (19.2)	2 (7.7)
	Grade 3	0	0	0
Subcutaneous fibrosis	Grade1	13 (50.0)	9 (34.6)	4 (15.4)
	Grade 2	12 (46.2)	13 (50.0)	9 (34.6)
	Grade 3	0	0	0
Mucositis	Grade 1	13 (50.0)	12 (46.2)	4 (15.4)
	Grade 2	11 (42.3)	10 (38.5)	6 (23.1)
	Grade 3	0	0	0
Dysphagia	Grade 1	6 (23.1)	6 (23.1)	2 (7.7)
	Grade 2	19 (73.1)	13 (50.0)	8 (30.7)
	Grade 3	1 (3.8)	5 (19.2)	3 (11.5)
Hoarseness	Grade 1	13 (50.0)	16 (61.5)	10 (38.4)
	Grade 2	13 (50.0)	9 (34.6)	1 (3.8)
	Grade 3	0	0	0
Xerostomia	Grade 1	5 (19.2)	7 (27.0)	5 (19.2)
	Grade 2	20 (76.9)	16 (61.5)	7 (27.0)
	Grade 3	1 (3.8)	2 (7.7)	1 (3.8)

Recurrence with distant metastasis was evidenced in one patient. The patients with recurrent disease were planned for further salvage treatment.

When we have evaluated the dependence of progression free survival on the different factors related to patient and disease, tobacco consumption in any form along with the stage at presentation were found to be the two most important factors affecting the PFS with significant *P*-value (*P*=0.038 and 0.004 respectively).

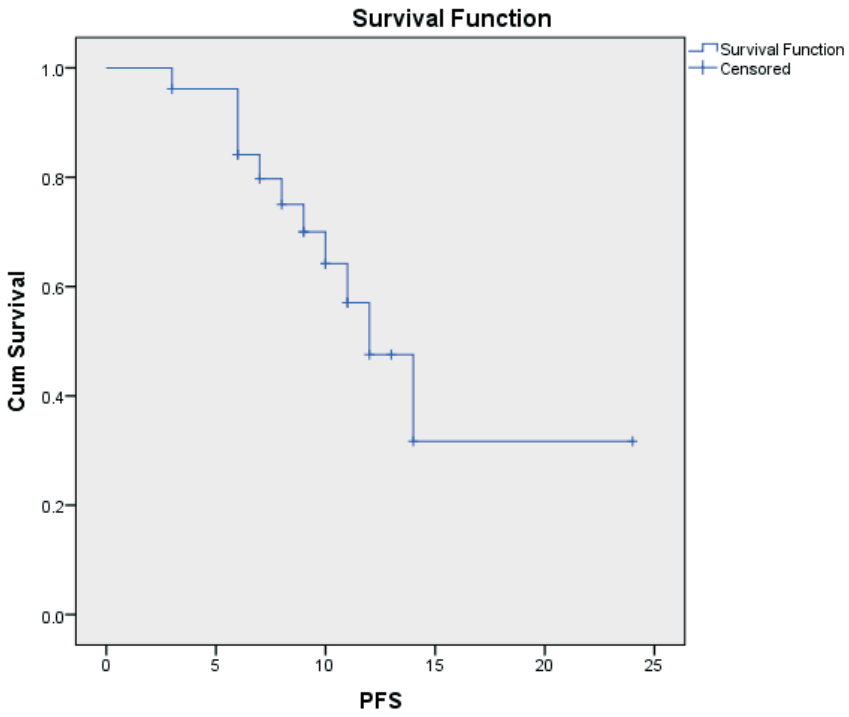

Fig. 2. Progression free survival (PFS) of the study population.

Discussion

National Comprehensive Cancer Network (NCCN) recommends for surgical resection of primary tumor in T3-T4a, N0 tumor along with neck dissection in N+ patients followed by RT, but for patients with stage T4b, N0-3, unresectable nodal status and unfit of surgery patients should be treated with concurrent chemoradiotherapy [15].

Prevalence of the head and neck malignancy in North Eastern part of India is high due to their continuous use of tobacco in various forms and their lifestyle. Most of them come with the advanced stage due to their negligence, unawareness, and poverty. Achieving long-term local control (LC) in locally advanced squamous cell carcinoma of the head and neck remains a challenge [16].

From radiobiological, economic and logistical points of view, a hypofractionated schedule would be the most suitable option. First, the treatment is completed before accelerated repopulation becomes a significant radiobiologic factor. Second, the reduction in the number of fractions also allows a more efficient use of resources, which can help avoid long waiting times for other patients; and lastly, considering that this group of patients are usually of elderly age and often have a poor performance status as well as significant co-morbidities, it is almost mandatory to keep the overall treatment time (OTT) as short as possible [17].

Moreover, during the recent first peak of the COVID-19 pandemic, many radiotherapy departments had reviewed their protocols for chemoradiation to make the OTT short by using hypofractionated schedules [18].

The patients characteristics were comparable with other studies [5, 19]. In this research by study design, PFS was the most common subsite followed by the RMT, Vallecula and BOT. Comparison between these subsites are not available in the literature for references. Other tumor characteristics were consistent with the previous studies [10, 20].

Response:

In this study, clinical complete response was observed in 15 (57.7%) patients and partial response in 8 (30.8%) patients with overall response rate of 88.5%. This report is consistent with the study by Proceddu et al. where 56% patients had complete response to the primary site and overall objective response rate was 80% [10]. Similarly, in the study by Teckie et al. 79% patients showed response to hypofractionated RT [21]. Our study has shown better result than the study by Nguyen NTA et al., where patients were treated with 8 Gy per fraction on the 0,7

and 21st day and documented complete response in only 30.9% patients with ORT of 81.8%, which means hypofractionated protocol of 62.5 Gy in 25 fractions is superior [20].

Koukourakis MI et al. studied Conformal hypofractionated RT with amifostine combined with cisplatin and cetuximab in patients with LAHNC, where the complete response rate was 68.57% [22]. The discrepancy is due to use of conformal hypofractionated RT, the use of amifostine, which reduced mucositis, that contributed to less interruption in treatment and some patients underwent nodal dissection.

The study by Valentina K et al. using conventional radiotherapy showed complete response in 72.3% patients which was superior than the present study findings. Use of 3DCRT with Linear accelerator in patients' treatment could be a factor for such result [23].

RT at either preoperative or post-operative stage in advanced HNSCC cases may influence the control rates, but many investigators in prospective studies have shown better response with concurrent chemoradiotherapy practice at any condition [24]. This suggests that patients undergoing accelerated RT with bulky lymph nodes sometimes may require neck dissection to gain benefit compare to conventional fractionation.

Toxicity:

Acute radiation reactions were high as expected, it contributed the major and minor deviation in the treatment plan for some patients and increase in overall treatment time.

In this study, grade 3 and 4 acute toxicities especially mucositis, skin reaction and dysphagia were high and developed after 3 weeks of radiation which is almost concordance with the previous studies [25, 26]. Study by Paul sanghera et al. [27] using hypofractionted RT with carboplatin showed Minimal Grade 3 mucositis was experienced by 60 patients (74%), with 5 (5%) patients with Grade 4 mucositis. Grade 3 dysphagia was evidenced in 44 patients (54%). The incidence of acute toxicity was very low in the patients treated with amifostine as observed by Koukourakis MI et al. [22].

The incidence of late side effects assessed at the 3rd, 6th and 9th months of treatment completion within a median of 11 months of follow-up was within acceptable levels, despite the use of hypofractionation. Longer follow-up is certainly needed to better estimate late adverse events. Reducing overall irradiation time by hypofractionation is an applicable alternative to conventional regimens with concerns that large fraction sizes may lead to greater toxicity in late-responding tissue supported by earlier studies. The reduction in number of fractions avoids long waiting times. There is no doubt that hypofractionation offers major potential advantages to patients and to the economy of health systems [19, 28, 29].

Progression free survival:

The median progression free survival in this study was 12 months. 38.5% patients had developed recurrence during the study period. PFS at the 6th and 12th month was 84.6% and 61.5%, respectively. This finding is almost similar with the study by Agarwal JP et al. [5] where 1-year PFS was 55%. Another study by Teckie et al. [21] demonstrated a locoregional PFS rate of 70% at the 6th month, 43% at the 12th month, and 29% at the 2nd year with median follow up of 11.9 months. Though overall response rate is good in this study, the sites chosen for the study are prognostically bad due to more hypoxia and less radiation responsiveness leading to poor progression free survival.

Of the various prognostic factors studied, tobacco consumption and higher stage had significantly affected the PFS. Other prognostic factors like age, sex, KPS, weight, site of tumor, T and N stage and the tumor grade did not show statistically significant difference on the PFS.

All the patients who had loco-regional failure presented with N3 node at initial presentation. This denotes that patients with a large nodal burden are probably less likely to be benefited by hypofractionation. This outcome is well-corroborated with MARCH collaborative group meta-analysis, which showed that the effect of altered fractionation was significantly more pronounced on the primary tumor than on the nodal disease [30].

Limitations of our study include a limited follow-up time, small sample size, treating with 2-D Cobalt-60 teletherapy machine. In view of the non-randomized single arm nature of the study, it would not be correct to draw any definite conclusions regarding local recurrence and survival patterns from this study. The use of neck dissection and the ability to complete treatment within the prescribed overall treatment time would have contributed better results.

Conclusion

Treatment of locoregionally advanced head and neck cancer (LAHNC) with hypofractionated RT with 62.5 Gy in 25 fractions concurrently with

cisplatin is feasible and safe and is associated with a good response rate. Although grade 3 and 4 toxicities were comparatively high but it was manageable. Late toxicities were within tolerable levels. These data highlight the potential usefulness of hypofractionation for LAHNC, especially for low to medium income countries, where access to advanced techniques of RT is poor. Long-term follow up with more sample size and comparative trials are needed for further recording of late response as well as toxicities to provide definitive conclusions about hypofractionated RT in the selected subsites LAHNC.

Conflict of Interests

Authors declare no conflict of interest.

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Author's Contributions

Kishalay Baidya, Yumkhaibam Sobita Devi, Yengkhom Indibor Singh – conceptualization, methodology, formal analysis, writing – original draft; *Kishalay Baidya, Akoijam Sunita Devi, Deepsikha Das* – data curation, writing – reviewing and editing; *Rahul Mahawar, Nongmaithem 0ima Devi* – investigation, formal analysis.

РОЛЬ ГІПОФРАКЦІОНОВАНОЇ ПРОМЕНЕВОЇ ТЕРАПІЇ З ОДНОЧАСНОЮ ХІМІОТЕРАПІЄЮ ЦИСПЛАТИНОМ ПРИ ЛОКАЛЬНО ПОШИРЕНОМУ ВІДНОСНО РАДІОРЕЗИСТЕНТНОМУ РАКУ ГОЛОВИ ТА ШИЇ

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Вступ. *Місцево-поширений рак голови та шиї є більш агресивним, і частота невдач терапії після звичайної променевої терапії є високою.*

Мета. *Оцінити реакцію пухлини та токсичність гіпофракціонованої променевої терапії з одночасною хіміотерапією при лікуванні чотирьох відносно радіорезистентних пухлин голови та шиї.*

Методи. *Проспективне рандомізоване контрольне дослідження було проведено за участю 27 пацієнтів з раком голови та шиї. Усі пацієнти отримували гіпофракціоновану променеву терапію в дозі 250 сГр/фракція один раз на день до максимуму 62,5 Гр у 25 фракціях з одночасним цисплатином 30 мг/м^2. Дані були оцінені за допомогою SPSS версії 21.0 для Windows із значенням p<0,05.*

Результати. *Повна та часткова відповіді були досягнуті у 15 (57,7%) та 8 (30,8%) пацієнтів відповідно із загальною частотою відповіді 88,5%, а у трьох пацієнтів захворювання було стабільним. Гострий мукозит 3 і 4 ступеня мали 17 пацієнтів (65,4%) і 7 пацієнтів (27%) відповідно. Дисфагію 3 ступеня спостерігали у 21 пацієнта (80,7%), а шкірні реакції 3 і 4 ступеня — у 11 і 2 пацієнтів відповідно. Більшість пацієнтів мали керовану гостру токсичність. Більшість пізніх ускладнень були 2-го та 3-го ступенів. Середній час до локального рецидиву склав 12 місяців і однорічну виживаність без прогресування захворювання досягли 61,5% пацієнтів.*

Висновки. *Лікування гіпофракціонованою променевою терапією з одночасним прийомом цисплатину видається можливим і безпечним і пов'язане з хорошим рівнем відповіді. Хоча 3 і 4 ступені токсичності були порівняно високими, але це можна було контролювати. Пізня токсичність була в межах допустимого рівня.*

КЛЮЧОВІ СЛОВА: **рак голови та шиї; гіпофракціонована; радіостійкий; відповідь; мукозит.**

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A RARE TUMOR – ADRENAL ANGIOSARCOMA (case report)

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Background. *Primary adrenal angiosarcoma is an exceptionally rare tumor with an incidence of <1% of soft tissue sarcomas. Less than 50 cases being described in literature; most of them were nonfunctional presenting with symptoms of abdominal lump, weight loss, fatigue or weakness. The treatment remains multi-modal with involvement of surgeon as well as medical oncologist.*

Objective. *The aim of this case report is to describe an entity which is rare in terms of incidence. It was functional as well as metastatic and managed with multimodality therapy.*

Methods. *The case is a 47-year-old man diagnosed with metastatic adrenal angiosarcoma. The patient was managed with chemotherapy followed by surgery.*

Results. *The final histopathological examination of the specimen and immunohistochemistry revealed angiosarcoma. At present the patient is under follow-up.*

Conclusion. *Even though surgery forms the main stay of management, the role of multi-modality therapy forms the cornerstone for adrenal angiosarcomas.*

KEYWORDS: **adrenal angiosarcoma; suprarenal; adrenalectomy; vasoformative tumor.**

Introduction

A tumor with an incidence of <1% of soft tissue sarcomas, angiosarcoma is a rare lesion arising out of vascular endothelium [1, 2]. Primary angiosarcomas of visceral organs and bones are exceedingly rare, though they account for metastatic sites. Most of the primary lesions are either from the skin or subcutaneous tissue [3,4]. Out of this meagre incidence of primary visceral angiosarcomas, adrenal angiosarcomas constitute an exceptionally uncommon variety with less than 50 cases reported in literature [5]. Hence this case report becomes important and unique due to the rarity of the tumor. This case depicts the management of a 47-year-old man with meta_ static left adrenal angiosarcoma.

Case report

A 47-year-old man with no previous comorbidities initially presented with blurring of vision of one-month duration. His initial clinical examination revealed a blood pressure of 225/150 mm of Hg for which he was diagnosed as hypertensive emergency with retinopathy and treated with antihypertensives. Assessment of his hematological and biochemical parameters revealed an abnormal serum urea 26.9 mg/dL, creatinine 2.14 mg/dL and uric acid 9.5 mg/dL. He was further evaluated for cause of the same and was found to have a left suprarenal mass measuring 15×18×22 cm extending on to the peripancreatic region on abdominal sonography. Further imaging with MRI of the abdomen revealed a large suprarenal mass lesion measuring 13×17×18 cm with fat, soft tissue areas and calcification with inferior displacement of kidney and loss of fat planes with left dome of diaphragm, anterior and posterior renal fascia. In addition, multiple soft tissue deposits were found along anterior abdominal wall, largest measuring 4.5 cm along left hypochondrium. Multiple retroperitoneal lymph nodes were also enlarged.

Whole body PET CT revealed diffuse FDG uptake in left suprarenal lesion of similar size along with multiple nodules in both lungs with FDG uptake in paratracheal lymph nodes. FDG uptake was also noted along the anterior abdominal wall in the left hypochondrium. Ultrasound guided fine needle aspiration cytology from left adrenal mass lesion as well as anterior abdominal wall deposits revealed a malignant vasoformative tumor with cells having large hyperchromatic nuclei and abundant vesicular cytoplasm. These cells stained positive for ERG, CD34 and CD31 on IHC. Patient was diagnosed as a case of metastatic adrenal angiosarcoma based on the imaging as well as tissue biopsy findings.

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Patient was started on chemotherapy based on Paclitaxel and administered six cycles. Follow up PET CT after 6 months of initial presentation revealed a relatively stable disease with no newer lesions. However, there was no regression in size of the lesions. In view of the same, patient was referred for left adrenalectomy. He underwent left open adrenalectomy along with splenectomy. Intra-operatively 15×15 cm highly vascular tumor was found with dense adhesions between spleen, greater curvature of stomach and tail and body of pancreas with involvement of splenic artery by the tumor necessitating a splenectomy. Left kidney was free of tumor. Patient had an eventful post-operative course with surgical site infection requiring frequent dressings for a period of two weeks and secondary closure. He was administered requisite vaccines against OPSI in the post-operative period.

Histopathological examination revealed tumor composed of sheets of highly bizarre plump endothelial cells forming anastomosing vascular channels with a high N:C ratio, marked nuclear pleomorphism, vesicular nuclei and prominent nucleoli. Brisk mitosis and numerous multinucleated giant cells were also found along with areas of extensive necrosis and blood lakes. Spleen was free of any atypia or malignancy. CD31 & CD34 were positive in neoplastic cells on IHC. The findings were suggestive of angiosarcoma. The patient is presently on follow-up and his antihypertensive medications have been stopped in view of normalization of blood pressure post-surgery. He is being planned for further follow-up imaging to assess the status of metastatic lesions.

Discussion

Adrenal angiosarcoma, first case described in 1988 in a 54-year-old male by Kareti et al., is a highly aggressive and rare malignancy [6]. The median age of presentation ranges from 34 to 85 years with a gender predilection for

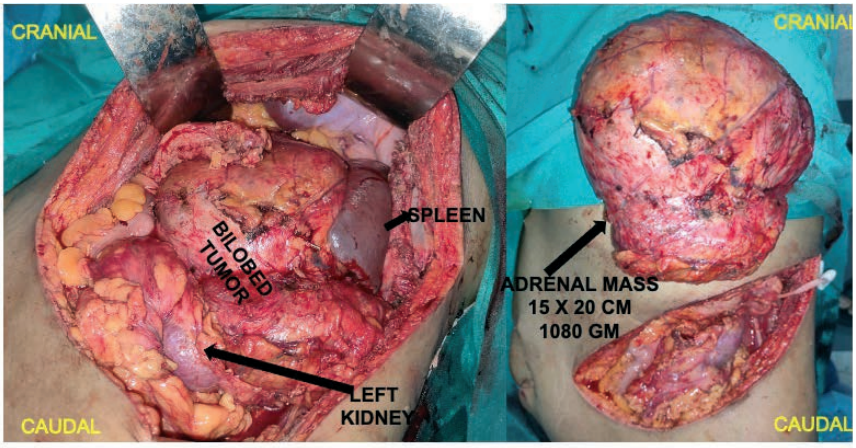

Fig. 1. Intraoperative findings of a bilobed left adrenal tumor adherent to pancreas and spleen.

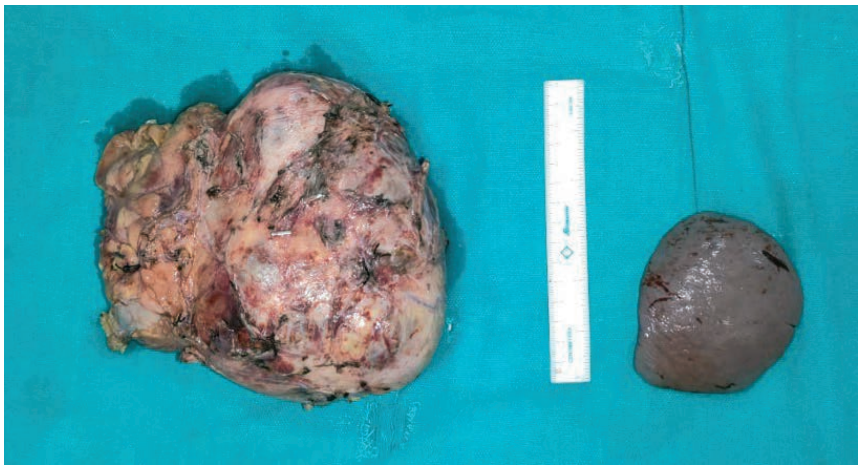

Fig. 2. Specimen of adrenal tumor along spleen.

males as reported by the countable number of cases reported in literature [7]. The symptomatology varies from typical abdominal or flank pain, palpable mass, weight loss, fatigue or weakness to being an incidental finding on imaging. Patients with systemic symptoms tend to have a poor prognosis [5,7]. The etiology of adrenal angiosarcoma is usually unknown, with few cases showing association with arsenic and vinyl chloride [3]. Hyperfunctioning tumors are yet to be reported in literature [8]. Detection of adrenal masses are on a rise due to the advances in imaging, most of them being nonfunctional and benign in contrast to this case [9]. This adrenal lesion was an incidental finding, but functional as well as malignant.

Though rare, these tumors have a high malignant potential with local infiltration as well as distant metastasis being commonly found at diagnosis [10]. This usually warrants removal of adjacent organs during surgical resection of adrenals as was with the splenectomy in our case. Being a tumor with very low incidence, there is no standardized treatment protocol described for these lesions [5]. Surgical resection usually results in a good outcome [11]. Adjuvant therapies are described for these lesions due to their aggressive nature [12].

The pathologists also have a dilemma in diagnosing primary adrenal angiosarcomas due to the non-specific histopathological characteristics with necrosis, hemorrhage and cystic components. Most adrenal angiosarcomas have a solid epithelioid pattern in contrast to other angiosarcomas with a vasoformative pattern [10, 13]. A definitive pathological diagnosis requires a wider immunohistochemistry staining in the form of CD31, CD34, FLI1 and factor VIII in addition to cytokeratins for epithelial components [14]. The tumor in our case stained positive for CD31 and CD34, thereby confirming the diagnosis.

Conclusion

This case of a rare tumor showcased the importance of multi-modality approach with Medical Oncology, Surgery, Radiology and Pathology for the challenging diagnosis as well as treatment. A standard treatment protocol needs to be developed even though the incidence of this lesion is very low. Surgical excision remains the mainstay of treatment along with adjuvant therapeutic options.

Conflict of Interests

Authors declare no conflict of interest.

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Author's Contributions

Arun Kumar M. – conceptualization, methodology, formal analysis, writing – original draft; *Nilanjan Roy* – conceptualization, methodology, formal analysis, writing – reviewing and editing, data curation, investigation; *Haris Jafri* – investigation, formal analysis, writing – reviewing and editing, data curation; *Vitesh Popli* – conceptualization, methodology, investigation, writing – reviewing and editing; *Thinley Phuntsho Roy* – methodology, data curation, investigation; *V. S. Karthik* – writing – reviewing and editing, data curation.

РІДКІСНА ПУХЛИНА - АНГІОСАРКОМА НАДНИРНИКІВ (клінічний випадок)

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Вступ. *Первинна ангіосаркома надниркових залоз є виключно рідкісною пухлиною з частотою <1% сарком м'яких тканин. У літературі описано менше 50 випадків, більшість з них були нефункціональними і супроводжувалися симптомами припухлості в животі, втрати ваги, втоми або слабкості. Лікування залишається мультимодальним із залученням хірургів та онкологів.*

Мета. *Метою був опис цього рідкісного захворювання, яке було функціональним, метастатичним і лікувалося за допомогою мультимодальної терапії.*

Методи. *Описаний випадок 47-річного чоловіка, у якого діагностували метастатичну ангіосаркому надниркових залоз, після чого було проведено хіміотерапію та згодом операцію.*

Результати. *Остаточне патогістологічне дослідження препарату та імуногістохімія виявили ангіосаркому. На даний момент пацієнт перебуває під наглядом.*

Висновки. *Незважаючи на те, що хірургічне втручання є основним напрямком лікування, роль мультимодальної терапії є наріжним каменем для лікування ангіосаркоми надниркових залоз.*

КЛЮЧОВІ СЛОВА: **ангіосаркома надниркових залоз; супраренальний; адреналектомія; судинна пухлина.**

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INTRAOPERATIVE STATE OF THE HEMOCOAGULATION SYSTEM IN PATIENTS WITH OPEN AND ENDOVASCULAR REVASCULARIZATION OF INFRAINGUAL ARTERIAL SEGMENT IN THE PRESENCE OF STENOTIC-OCCLUSIVE PROCESS OF TIBIAL ARTERIES

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Background. *Among all postoperative complications associated with revascularization of atherosclerotic steno-occlusive process of the femoral-distal artery, thrombosis of the reconstruction segment is 6-32%.*

Objective. *Prevention of thrombotic complications through vascular revascularization of the lower extremity by using a pathogenetically reasonable system of postoperative thromboprophylaxis.*

Methods. *The study involved 97 patients with atherosclerotic stenotic-occlusive process of the infrainguinal artery in cases of stenotic-occlusive lesions of the tibial arteries. In order to study the state of the hemocoagulation system on patients, the methods for studying the indicators of coagulation, fibrinolytic and aggregation systems were used.*

Results. *Development of hypercoagulable disorders in the patients who underwent endovascular revascularization of the arterial segment is more intense than in those who underwent open vascular revascularization methods. Hypercoagulation of blood at the intraoperative stage of revascularization takes place primarily due to the activity of factor IIa of the hemocoagulation cascade. Taking into account these circumstances, already at the surgery stage for thromboprophylaxis non-fractionated heparin (NFH) should be prescribed. At the same time for prevention of thromboembolic complications double anti-thrombocyte therapy: clopidogrel, acetylsalicylic acid should be prescribed.*

Conclusion. *Hypercoagulant ability of the blood system, which develops after arterial reconstructive interventions, takes place against the background of low activity of the fibrinolytic blood system, nevertheless a gradual increase in the activity of the aggregation capacity of the blood. Development of hypercoagulable disorders at the intraoperative stage of surgery in the patients with endovascular methods of arterial reconstructions is more intense than in those treated with open methods of arterial revascularization. Taking into account these circumstances, already at the surgery stage for thromboprophylaxis an anticoagulant should be prescribed that has a targeted effect on factor IIa of the hemocoagulant cascade with simultaneous prevention of thromboembolic complications – double anti-thrombocyte therapy.*

KEYWORDS: **blood coagulation system; aggregative assay; revascularization; thrombosis.**

Introduction

Treatment of patients with multilevel atherosclerotic lesions of the arterial bed of the lower extremities is still challenging and, in many cases, unresolved problem. This is especially true of the choice of surgical tactics for atherosclerotic lesions of several anatomical zones of the main arteries [1]. Open reconstructive interventions are leading in the revascularization of multilevel atherosclerotic lesions of the arterial bed of the lower extremity. This is important in revascularization of the arterial bed below the knee in cases of chronic critical ischemia [3].

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One of the ways to solve the problems of surgical treatment of multilevel lesions of the arterial bed of the lower extremities is use of hybrid revascularization technology such as endovascular angioplasty of one arterial segment in combination with bypass surgery of another [2]. According to some researchers, endovascular angioplasty of the femoral-distal artery and especially the tibial arteries in chronic critical ischemia is the only chance to delay or avoid amputation of the lower limb [4]. At the same time, the use of the suggested methods of revascularization (open, hybrid, endovascular) of atherosclerotic stenotic-occlusive process of the femoral-distal artery causes development of a number of complications of

6-32% of cases diagnosed with thrombosis of the reconstruction segment [6, 8].

Thus, the main goal of the study was to find a way for prevention of development of thrombotic complications of revascularization of the arterial bed of the lower extremity by using a pathogenetically reasonable system of postoperative thromboprophylaxis.

Methods

The study involved 97 patients with atherosclerotic stenotic-occlusive lesions of the infrainguinal arterial bed in cases of stenotic-occlusive lesions of the tibial arteries. According to the classification of Fontaine (1954) the following degrees of chronic arterial insufficiency were established: 2B degree in 47 patients, 3 degree in 21 patients and 4 degree in 29 patients. 53 (54.2%) patients were treated with open methods of revascularization, 44 (45.7%) – endovascular methods of revascularization of the arterial bed of the lower extremity.

The level of indicators of coagulative, fibrinolytic and aggregate systems was carried out as follows: fibrinogen (FG) – gravimetric method according to Rutberg R.A. (1964); fibrinostabilizing factor activity (FSF) – with the "kit for determining factor XIII" by research and production company SIMKO Ltd (Lviv); thromboplastic activity of blood (TPA) – by the method of Kudryashov B.A. and Ulitina P.D.; plasma recalcification time (PRT) – according to the method of Bergerhof and Roca; plasmin (PL), plasminogen (PG), total fibrinolytic activity (TFA) – by the method of Monastyrsky V.A. et al. (1988); euglobulin clots lysis time (ECLT) – using the "kit for determining the fibrinolytic activity (FLA) of blood plasma" by research and production company SIMKO Ltd (Lviv); antithrombin III (AT III) activity was determined by the method of Morbet and Wiltertein in the modification of Katsadze Y.L., Kotovshchikova M.A. (1982); platelet aggregation properties were studied using ADP at a concentration of 2.5 μmol/L with recording aggregatogramms on the analyzer AR 2110 Solar; D-dimer was studied by immunoanalytical method using a coagulometer; determination of soluble fibrin monomer complexes (SFMCs) was performed by the tablet method; von Willebrand factor (VWF) was studied by the method of Barkagan Z.S. (1988).

Statistical analysis was performed using the statistical software package STATISTICA 6.0 for Windows (StatSoft, Inc. Tulsa OK, USA) and Microsoft Excel (Microsoft office 2013, USA) with data in the form of mean and standard deviation (M±SD). Comparisons between several groups were performed by one-way analysis of variance (ANOVA) and Tukey's post-hoc analysis to analyse mean differences. A statistical p value of <0.05 was considered statistically significant.

Results

At the preoperative stage, an increased level of blood coagulation was observed in the patients of both study groups. Thus, when analysing the indicators of the coagulation system of patients' blood it was found that the level of the blood fibrinogen was significantly higher than the same indicator in the control group. The same was observed regarding the content of SFMCs, TFA, fibrin degradation products (FDP), fibrinopeptide A (FPA): these indicators significantly exceeded the level of similar indicators in the control group. Along with the results of the study, the level of AT III and PRT in the patients at the preoperative stage was within the control level, 88.56±7.49% and 91.17±5.23 sec. respectively, which differed from that of patients of the control group (Table 1).

Revascularization of the femoral / popliteal arterial bed of the lower extremity stimulated development of changes in the hemocoagulative system – contributed to maintenance of increasing hypercoagulant properties of blood during surgery. Similar changes in the hemocoagulable blood system occured with varying degrees of activity in both groups of patients and depended on the method of revascularization of the infrainguinal arterial arterial bed of the lower extremity. Thus, with the preoperative FG blood level of 5.56±0.48 g/L, in the period of 1.5-2.0 hours and 3.0-4.0 hours of the surgery with the use of the open revascularization methods it reached the level of 5.61±0.49 g/L and 5.76±0.53 g/L, respectively. The endovascular method of revascularization led to FG level of 5.98±0.53 g/L and 6.39±0.52 g/L at the same time points (Table 2).

More noticeable changes in the patients of both study groups were observed for the SFMCs, FPA and FDP levels. The level of these indicators at 3.0-4.0 hours of the surgery with the open method of revascularization was higher than in the preoperative period in 1.2, 1.9 ($p<0.05$) and 1.7 ($p<0.05$) times respectively, and with the use of the endovascular revascularization method – in 1.8 (<0.05), 2.1 ($p<0.05$) and 2.1 ($p<0.05$), respectively. At the same time,

Table 1. Preoperative state of hemocoagulation in patients with stenotic-occlusive atherosclerotic process of infrainguinal arterial bed in cases of stenotic-occlusive process of tibial arteries

Indicators	Control	Preoperative period
FG, g/L	3.68±0.41	5.56±0.48*
SFMCs, Ext. Units	0.48±0.06	0.71±0.15*
FPA, ng/mL	1.97±0.38	2.69±0.35*
FDP, μmol/mL	4.78±1.45	7.75±1.67*
FLA, %	53.18±4.52	56.23±4.57
AT III, %	81.41±6.71	88.56±7.49
PRT, sec.	103.61±4.97	91.17±5.23

*Note. * p<0.05 compare to the control group indicators.*

there was a significant difference between the indicators of the above components of the hemocoagulation in the patients treated with different methods of revascularization. Thus, the SFMCs, FPA and FDP levels in the patients treated with endovascular method were significantly higher than those treated with open methods, in 1.5 (p<0.05), 1.3 (p<0.05) and 1.3 (p<0.05) times, respectively (Table 2).

Along with the above, FLA and AT III content in the blood of patients during the surgery decreased gradually. The decrease in the FLA and AT III blood level in the patients with endovascular revascularization was more significant than in those treated with open revascularization methods. CRP with a significant difference between its indicators in the patients of both study groups was not evidenced (Table 2). All these changes in the coagulation system occurred in the background of a gradual shortening of the PRT. However, no significant difference between its levels in the patients of both study groups was observed (Table 2).

Lower extremity arterial bed revascularization, regardless of the method of restoring blood flow, contributed to activation of the anticoagulant system. Thus, in the 3.0-4.0 h of the surgery, PL serum level increased in 1.4 times (p<0.05), and ECLT was prolonged in 1.3 times (p<0.05) compared with the preoperative period. This took place due to a 1.2 time (p<0.05) reduction of the PG serum level, which contributed to a 1.2-time reduction in the TFA of the serum. It should be noted that the results of the anticoagulant blood system study indicated its inability to resist the increase in hemocoagulable capacity of the blood at the final stage of revascularization.

The results of the blood aggregation study at the preoperative stage did not reveal any visible difference between the indicators in the patients and the control group individuals. Revascularization of the femoral-distal arterial bed helped to activate the blood aggregation system. Thus, at 1.5-2 h of the surgery thrombocyte aggregation velocity (TAV) increased in

Table 2. Intraoperative state of the hemocoagulative system in the conditions of open and endovascular revascularization of the infrainguinal arterial bed

Indicator	Before surgery	Intraoperative period of revascularization					
		1.5-2.0 h of the surgery		3.0-4.0 h of the surgery		3.0 h after the surgery	
		open	endovasc.	open	endovasc.	open	endovasc.
FG, g/L	5.56±0.48	5.61±0.49	5.98±0.51	5.76±0.53	6.39±0.52	5.87±0.51	6.89±0.54
SFMCs, Ext.Units	0.71±0.15	0.74±0.12	0.89±0.12	0.87±0.15	1.27±0.17*	0.94±0.16	1.33±0.19*
FPA, ng/mL	2,69±0.35	3.68±0.31	4.47±0.31*	5.13±0.31	5.71±0.32*	5.45±0.31	6.67±0.35*
FDP, μmol/mL	7.75±1.67	9.56±2.31	12.74±2.41*	13.14±2.37	16.61±2.46*	14.28±3.21	17.69±3.27*
FLA. %	56.23±4.57	52.19±4.37	49.58±4.41	50.47±4.21	46.53±4.37	47.15±4.34	43.57±4.52
AT III. %	88.56±7.49	85.14±7.39	84.17±6.28	83.78±6.31	82.13±6.35	84.34±6.41	83.47±6.45
PRT. sec.	91.17±5.23	85.15±5.39	82.25±5.38	82.37±5.26	79.14±5.19	80.24±5.03	78.21±5.53

*Note. * p<0.05 – significant difference between the indicators in patients treated with open revascularization and those who underwent endovascular revascularization.*

1.3 times (p<0.05) and thrombocyte aggregation rate (TAR) slightly increased with a simultaneous acceleration of thrombocyte aggregation time (TAT) by 12.42%. During the surgery blood platelets level increased. Thus, in 3.0-4.0h of the surgery its level increased almost in 1.3 times compared to the preoperative period. As for the TAT, it was further reduced, reaching the level of 7.68±0.75 min, which was in 1.3 times (p<0.05) less than the preoperative TAT level.

When analysing the results of the blood aggregation system state it was found that there was a difference in its performance at the different stages of surgical treatment by different methods of revascularization. Thus, the patients treated with endovascular methods had a significantly higher TAV and TAR with a significant reduction in TAT than the patients treated with open revascularization (Table 3).

Discussion

The study has shown that revascularization of the femoral / popliteal arterial bed at the intraoperative stage of surgery is accompanied by an increase in the hypercoagulant ability of the blood system. It takes place in the background of low blood fibrinolytic system activity, nevertheless a gradual increase in the blood aggregation activity.

Revascularization of the infrainguinal arterial bed of the lower extremity contributes to increase of hypercoagulable properties of blood during surgery. Similar changes in the hemocoagulable blood system occur with varying degrees of activity in both groups of patients and depend on the method of revascularization of the infrainguinal arterial artery of the lower extremity. Thus, the FG blood content in the period of 1.5-2.0 h and 3.0-4.0 h of the surgery with open revascularization method reached the level of 5.61±0.49 g/L and 5.76±0.53 g/L, respectively, and with the endovascular method of revascularization, - 5.98±0.53 g/L and 6.39±0.52 g/L, respectively. The level of SFMCs, FPA, FDP at 3.0-4.0 h of the surgery using the open method of revascularization was in 1.2, 1.9 (p<0.05) and 1.7 (p<0.05) times higher, respectively, and with the endovascular revascularization method – in 1.8 (p<0.05), 2.1 (p<0.05) and 2.1 (p<0.05) times higher, respectively, than in the preoperative period. At the same time, a significant difference was found between the blood levels of SFMCs, FPA, FDP in the patients who underwent surgeries by different methods of revascularization. Thus, in those operated by the endovascular method, the levels of SFMCs, FPA, FDP in the blood were significantly higher, in 1.5 (p<0.05), 1.3 (p<0.05) and 1.3 (p<0.05) times, respectively, than in those treated with open methods of revascularization.

The differences in the results of the coagulation system study in the patients of both groups can be explained by trauma to the inner surface of the arterial bed during endovascular manipulations and, accordingly, the activation of blood coagulation ability [1].

Development of hypercoagulable disorders (syndrome) at the intraoperative stage of revascularization: increased FG content, increased SFMCs levels, increased thrombin levels, high FPA content and increased FDP, indicate the activity of factor IIa hemocoagulant cascade. Taking into account these circumstances, already at the surgery stage an anticoagulant that would have a targeted effect on factor IIa of the hemocoagulant cascade should be prescribed. Unfractionated heparin (UFH) has

Table 3. State of the blood aggregation system at the intraoperative stage of the infrainguinal arterial bed revascularization

Indicator	Platelet number, $\times 10^9$/L		TAV, min.		TAR, %		TAT, min.	
	open	endo-vasc.	open	endo-vasc.	open	endo-vasc.	open	endo-vasc.
Before surgery	301.56±14.06		14.17±1.58		74.46±0.62		10.15±0.68	
1.5-2.0 h of the surgery	321.26± 13.68	352.68± 15.42	13.26± 1.21	11.34± 1.17*	77.16± 0.87	82.37± 0.89*	9.52±0.81	8.33±0.77
3.0-4.0 h of the surgery	329.46± 12.78	383.45± 14.31	12.19± 1.13	9.68± 1.19*	89.41± 1.05	93.45± 1.01*	8.41±0.81	7.75±0.85
3.0 h after surgery	331.19± 13.83	378.75± 15.24	11.71± 1.11	9.57± 1.18*	85.82± 1.11	90.26± 1.07*	8.02±0.83	7.56±0.86

*Note. * p<0.05 – significant difference between the indicators rates in patients treated with open revascularization and those who underwent endovascular revascularization.*

a targeted effect on factor IIa, which activates markers of hypercoagulation at the intraoperative stage of surgery [8].

Thus, according to the study results, the thromboprophylaxis method for reconstructive interventions on the main arteries of the lower extremity should be as follows: immediately after the surgery, the first dose of UFG should be prescribed with its continuation to the next 7-9 days (APTT control) of the early postoperative period. Another scheme of thromboprophylaxis is as follows: UFG administration immediately after surgery with the continuation of its use until 12-24 hours of the early postoperative period. Also, after 12-24 hours, the thromboprophylaxis with low-molecular-weight heparin (LMWH) continues [9].

At the same time, for prevention of thromboembolic complications due to activation of the aggregate blood system at the intraoperative stage, following the recommendations of the European Society of Vascular Surgeons (ESVS), 2017, and the European Society of Vascular Medicine (ESVM), 2019, dual antiplatelet therapy should be prescribed: clopidogrel, acetylsalicylic acid for a month or longer.

Conclusion

Revascularization of the arterial bed of the lower extremity is accompanied by development of hypercoagulable syndrome at the intraoperative stage of surgery. Development of hypercoagulable syndrome at the intraoperative stage of surgery in the patients who underwent endovascular revascularization is more intense than in those treated with open methods of revascularization of the arterial bed.

Conflict of Interests.

Authors declare no conflict of interest.

Authors Contributions

I. K. Venger, S. Ya. Kostiv – conceptualization, methodology, formal analysis, writing – original draft, writing – reviewing and editing; *S. Ya. Kostiv, B. P. Selskyy* – data curation, writing – reviewing and editing; *M. P. Orlov, N. I. Tsiupryk* – investigation, formal analysis.

ІНТРАОПЕРАЦІЙНИЙ СТАН СИСТЕМИ ГЕМОКОАГУЛЯЦІЇ У ХВОРИХ З ВІДКРИТОЮ ТА ЕНДОВАСКУЛЯРНОЮ РЕВАСКУЛЯРИЗАЦІЄЮ ІНФРАІНГВАЛЬНОГО АРТЕРІАЛЬНОГО СЕГМЕНТУ ЗА НАЯВНОСТІ СТЕНОТИКО-ОКЛЮЗІЙНОГО ПРОЦЕСУ АРТЕРІЙ ГОМІЛКИ

І. К. Венгер, С. Я. Костів, Б. П. Сельський, М. П. Орлов, Н. І. Цюприк

ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І.ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ

Вступ. *Серед усіх післяопераційних ускладнень, пов'язаних з реваскуляризацією атеросклеротичного стено-оклюзійного процесу стегново-дистальної артерії, тромбоз реконструкційного сегмента становить 6-32%.*

Мета. *Профілактика тромботичних ускладнень шляхом реваскуляризації судин нижньої кінцівки з використанням патогенетично обґрунтованої системи післяопераційної тромбопрофілактики.*

Методи. *У дослідження включено 97 пацієнтів з атеросклеротичним стенозо-оклюзійним процесом підпахвинної артерії на тлі стенозо-оклюзійного ураження великогомілкових артерій. Для вивчення стану системи гемокоагуляції у хворих застосовували методи дослідження показників коагуляційної, фібринолітичної та агрегаційної систем.*

Результати. *Формування гіперкоагуляційних розладів у пацієнтів, які застосовували ендоваскулярні методи реваскуляризації артеріального сегмента, відбувається більш інтенсивно, ніж у пацієнтів, яким проводили відкриті методи реваскуляризації судин. Гіперкоагуляція крові на інтраопераційному етапі реваскуляризації відбувається в першу чергу за рахунок активності фактора IIa каскаду гемокоагуляції. Враховуючи вищезазначені обставини, вже на етапі завершення оперативного втручання з метою тромбопрофілактики слід призначити – нефракціонований гепарин (НФГ). Одночасно для профілактики тромбоемболічних ускладнень слід призначати подвійну антитромбоцитарну терапію: клопідогрель, ацетилсаліцилову кислоту.*

Висновки. *Гіперкоагулянтна здатність системи крові, яка виникає після реконструктивних артеріальних втручань, виникає на тлі низької активності фібринолітичної системи крові, але з поступовим підвищенням активності агрегаційної здатності крові. Формування гіперкоагуляційних розладів на інтраопераційному етапі хірургічного втручання у пацієнтів з ендоваскулярними методами артеріальних реконструкцій відбувається більш інтенсивно, ніж у пацієнтів з відкритими методами*

артеріальної реваскуляризації. Враховуючи ці обставини, вже на етапі завершення оперативного втручання з метою тромбопрофілактики слід призначити антикоагулянт, що має цілеспрямовану дію на фактор IIa гемокоагулянтного каскаду з одночасною профілактикою тромбоемболічних ускладнень – подвійну антитромбоцитарну терапію.

КЛЮЧОВІ СЛОВА: **система згортання крові; сукупний аналіз; реваскуляризація; тромбоз.**

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PROSPECTIVE DESCRIPTIVE STUDY OF NON-THYROIDAL NECK SWELLINGS IN WESTERN INDIAN POPULATION

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Background. *Nonthyroidal neck swellings are common and cause diagnostic challenges. This study highlights various diagnosis associated with non-thyroidal neck swellings and their management challenges.*

Objective. *This pilot study highlights the various diagnosis associated with nonthyroidal neck swellings and their management challenges. The clinical spectrum of two most common aetiology of nonthyroidal neck swelling: tubercular cervical lymphadenopathy and lymphomas, are also compared.*

Methods. *This prospective study was conducted in a tertiary care teaching hospital from 01 Jun 2018 to 31 Dec 2019. The first 100 nonthyroidal neck swellings presented to the surgical outpatient department were included and assessed clinically, radiologically and histopathologically. Comparison was carried out between the first two common diagnosis of tubercular cervical lymphadenitis and lymphoma. Continuous variables were analysed using Student's t-test and categorical data were analysed using the Chi square test. A statistical p value <0.05 was taken as significant.*

Results. *There were 73 lymph node swellings and 27 non-lymph node swellings in the study. The most common diagnosis was tubercular cervical lymphadenitis (n=38) and lymphoma (n=17). The mean volume of lymph nodes in the lymphoma group (38.72±22.12 cm^3) was significantly bigger than in the tuberculosis group (9.44±5.99 cm^3) P=0.00001. The mean age (33.81±11.8 years) of tubercular patients was significantly less than the lymphoma (52.38±25.3 years) with P=0.000167. The clinical diagnosis was nearly accurate in 85% of cases. However, in 15 cases clinical diagnosis was changed after fine needle aspiration cytology.*

Conclusions. *Ultrasonography and fine needle aspiration cytology are very useful adjunct in arriving at a definite diagnosis of a lymph node swelling in neck. Tubercular cervical lymphadenopathy and lymphoma were two major diagnosis. Tubercular cervical lymphadenopathy is significantly different from lymphomas in terms of early age of presentation and smaller size at the time of presentation.*

KEYWORDS: **neck mass; cervical; lymphadenopathy; tubercular; lymphoma.**

Introduction

Neck swellings are commonly seen in the general surgery outpatient departments. Cervical lymphadenopathy constitutes around half of these swellings. Thyroid swellings are the next common neck swelling which account for 32% of all neck mass [1]. Non thyroidal neck swellings are varied and sometimes cause diagnostic dilemma. There are many more diagnostic variants, emerging diseases and diagnostic surprises when managing nonthyroidal neck mass. This pilot study highlights various diagnosis associated with nonthyroidal neck swellings and their management challenges. This study also compares the clinical spectrum of two most common aetiology of nonthyroidal neck swelling: tubercular cervical lymphadenopathy and lymphomas.

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Methods

This prospective study was conducted in a tertiary care teaching hospital in Western India from 01 Jun 2018 to 31 Dec 2019. The first 100 nonthyroidal neck swellings presented to the surgical outpatient department were included in the study. The exclusion criteria were symptom that lasted less than one week, thyroid swelling, known primary with lymph node metastasis and recurrent swelling of neck. All patients were scrutinised with detailed history and clinical examination in a well-lit room. All swellings were classified into a lymphnodal swelling and non-lymphnodal swelling. After

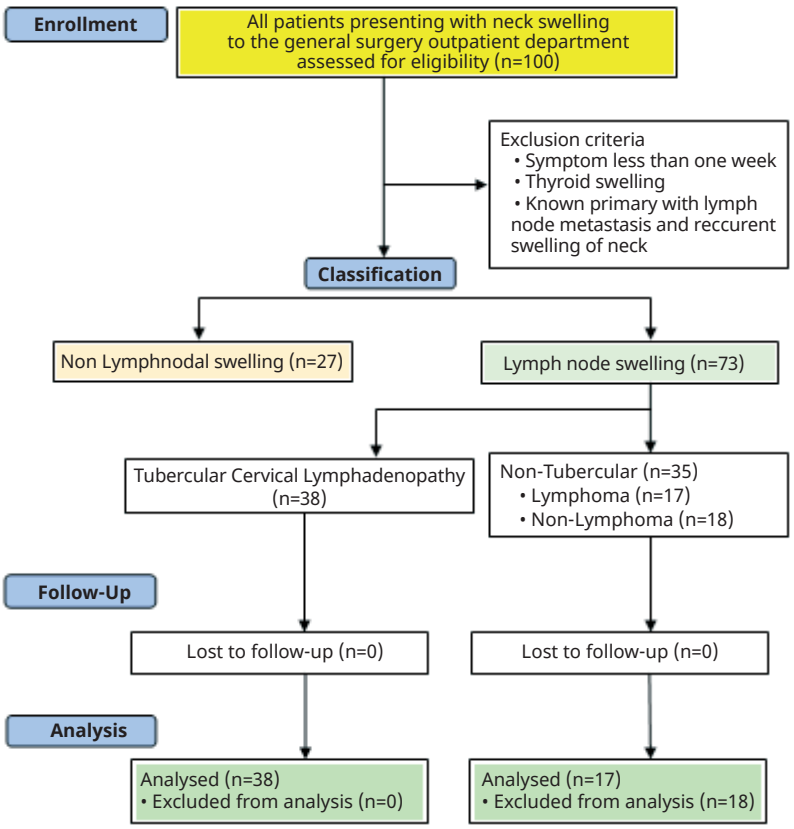
clinical examination all patients with lymph node swelling underwent haematological examination for complete hemogram and base line biochemistry tests. Three sputum samples, two early morning and one routine was sent for Acid Fast Bacilli as per recommendations. Further tests and management were based on the hospital protocol as summarised in the consort diagram.

Radiological examination included ultrasonography for neck and chest radiogram posteroanterior view. All ultrasonography was performed in the dept of radiology by consultant radiologists in a Siemens 4D Ultrasound machine using multi frequency linear array probe. Chest X-ray was performed according to the standard protocol for posteroanterior view. All chest X-rays were studied for presence of tuberculosis and malignancies. All patients underwent fine needle aspiration cytology (FNAC) either free hand or USG guided for histopathological diagnosis. FNAC was performed under aseptic condition using a 23-gauge needle fitted to 10 ml disposable syringe attached to a plunger. If the FNAC findings were inconclusive, an excision biopsy was contemplated. All non-lymph node swellings also underwent surgical excision and specimen were sent for histopathology. A final diagnosis was made with histopathological examination of the excision biopsy or of the specimen in all 100 cases. No immunohistochemical studies were carried out. Comparison was also carried out between the clinical and final histopathological diagnosis. Computed tomography and magnetic resonance imaging were done in selected cases, in our study only for 16 cases, where the ultrasound and FNAC were inconclusive or additional information was required.

Benign cases were managed medically or surgically depending upon aetiology but for malignant lesions, if primary – detected definitive treatment was carried out with radical excision and appropriate neck dissection. However, in cases of unknown primary, options of chemotherapy/radiotherapy/surgery were explored based on a case to case basis and existing protocols of the hospital.

Statistical analysis was completed using IBM SPSS Version 26. For data with normal distribution the Levene's test of equity of variance was performed. Means of continuous variables were analysed using the Student's t-test for statistical significance. Categorical data were analysed using the Chi square test. A statistical p value < 0.05 was taken as significant.

CONSORT Diagram



Results

A total of first 100 cases of nonthyroidal neck swellings were included in this study. There were 61 men (61%) and 39 women (39%). The mean age was 39.14±16.9 (range 1-76 years). The majority of the patients were in the third and fourth decade of life (47%). Duration of the swelling was variable with 68% cases having a short duration of one to six weeks and 32% cases with swelling more than 6 weeks. Most of the patients (42%) presented in first two weeks of swelling onset and had reactive lymphadenopathy managed with antibiotics.

The commonest associated symptom was fever of low grade (42%), non-productive cough (18%) and weight loss (14%). A typical evening rise of temperature was evidenced in 26% of cases. Brief spell of fever at the onset was reported in 14% cases. Only five cases presented with specific complaint of loss of appetite, in rest of the cases it was either associated with fatigue, night sweats or dysphagia. The rest 46% of patients had no associated symptoms. The majority of swellings were unilateral 56%, and 44% were bilateral. Only 22% cases presented with a solitary swelling, and 78% cases – with multiple swellings. The majority of swellings (47%) were in range of 1-3 cm (60%). There were 24 cases of swelling size of 3-5 cm and 29 cases with swelling of more than 5 cm.

In our study, 73% were lymph node swelling and 27% were non-lymph node swelling. The majority of the lymphnodal swelling were clinically and histopathologically diagnosed to be benign. There were more cases of cervical tubercular lymphadenitis (n=38) compared to non-tubercular cervical lymphadenitis (n=35). It is pertinent to mention that the incidence of tuberculosis infection in this part of the country is 210 per one lakh population. The commonest non-tubercular cervical lymphadenitis were lymphoma (n=17) followed by reactive lymphadenopathy (n=8), carcinoma of unknown primary (n=4), HIV associated lymphadenopathy (n=4) and one patient each of Kikuchi Fujimoto disease and cat scratch disease (Fig. 1-3). The incidence of lymphoma in this part of the country is 2.5 per 100000 population.

The mean volume of lymph nodes in the lymphoma group (38.72±22.12cm^3) was significantly bigger in the tuberculosis group (9.44±5.99cm^3) with *P*=0.00001. It was also seen that the mean age (33.81±11.8years) of tubercular patients was significantly lower than the lymphoma (52.38±25.3years) with *P*=0.000167. There was no statistical significance in any other parameter among these groups (Table 1).

The clinical diagnosis was nearly accurate in 85% of cases. However, in 15 cases the clinical diagnosis was changed after FNAC and a new pathology was discovered that changed the complete line of management. They were six cases of tubercular lymphadenitis, three cases of metastatic lymphadenopathy, and one case each of lymphangioma, neurofibroma, carotid body tumour, adenoid cystic carcinoma and inflamed branchial cyst.

There were 27 non-lymph node swellings and they were lipoma (n=6), sebaceous cyst (n=6), salivary gland tumour (n=6), branchial

Fig. 1. A – cervical tubercular lymphadenopathy Level 5; B – cystic hygroma; C – metastatic carcinoma mass in neck; D – dermoid neck; E – cold abscess; F – Kikuchi Fujimoto disease.

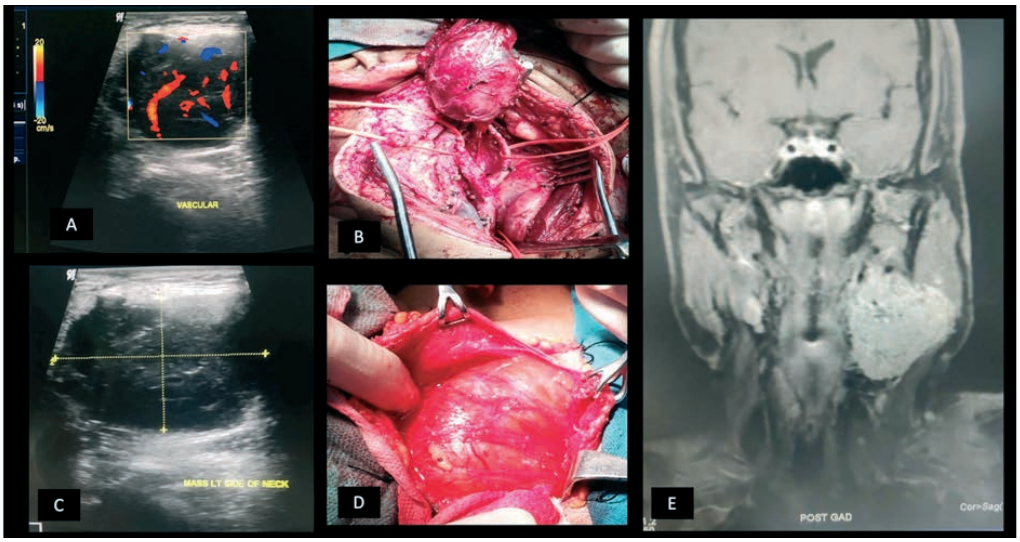


Fig. 2. Investigation and operative pictures: A – vascular doppler neck mass – carotid body tumour; B – intra-operative image of carotid body tumour; C – ultrasonography neck showing cystic hygroma; D – intra-operative image of neck nymphangioma; E – MRI right sided carotid body tumour.

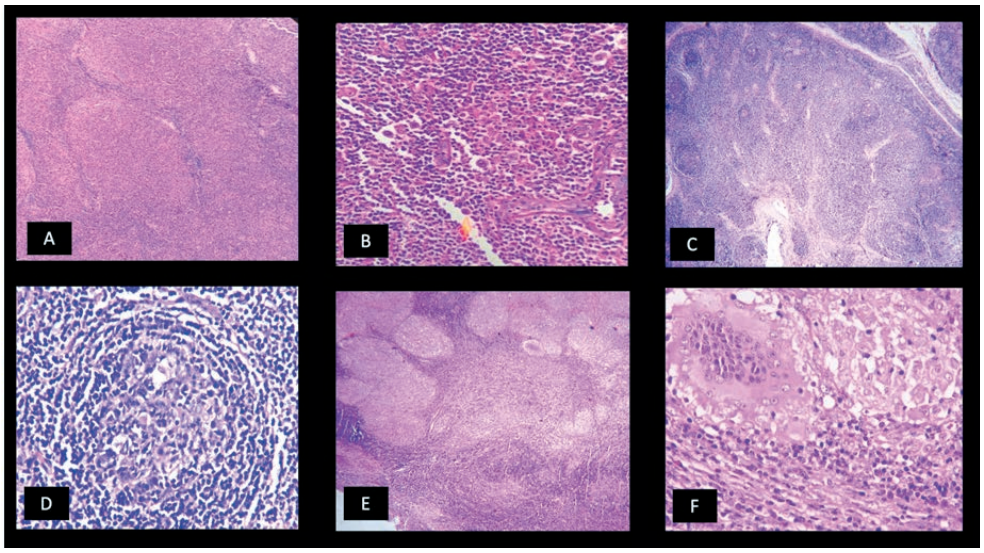


Fig. 3. Histopathological findings: A – follicular lymphoma (40×); B – Hodgkin's lymphoma (400×); C – reactive lymphadenitis (40×); D – reactive lymphadenitis (400×); E – necrotising granuloma (40×); F – necrotising granuloma (400×).

Table 1. Comparison of tubercular cervical lymphadenopathy and lymphoma presenting as a neck mass

Variable		Tubercular lymphadenitis (n=38)	Lymphoma (n=17)	P-value
Sex	Male	22	12	
	Female	16	5	
Age (Years)	Mean (SD)	33.81 (11.18)	52.38 (25.28)	0.000167
Duration of symptoms (weeks)	Mean (SD)	4.28 (3.69)	3.83 (2.45)	0.318085
Mean Size (cm^3)	Mean	9.44 (5.99)	38.72 (22.12)	<0.00001
Associated symptoms	Fever	19	9	0.9654
	Weight Loss	11	5	0.972046

cyst (n=2), cystic hygroma (n=3), carotid body tumour (n=1), parathyroid adenoma (n=1), adenocystic carcinoma (n=1), lymphangioma (n=1).

Discussion

Thyromegaly is a major diagnosis in neck swelling and accounts for only 20-30 % of all neck swellings. The other neck masses are non-thyroidal in origin. More than 50% of the neck swellings revealed in the general population originate from the cervical lymph nodes. Commonly tuberculosis and malignancies present as cervical lymphadenopathy. Other considerations are infections, lymphoma, leukaemia, and metastatic swellings. Neck swelling in younger age group tend to be more benign and are congenital, infectious or benign neoplasms. However, the chances of malignant swelling in neck increases to a greater extent after 40 years of age [2]. This correlates with our findings.

Von Haller in 1743 was the first to describe a non-thyroidal swelling of the neck which later was known as carotid body tumour [3]. Von Mikulicz-Radecki, in 1888, reported a patient who experienced bilateral, painless, symmetrical swelling involving lacrimal, submandibular and parotid gland. This disease was later termed as Mikulicz disease [4]. Martin in 1957 published his classic work "Surgery of Head and Neck Tumors" which first gave a varied and detailed description of neck masses [5]. There are other rare cases of non-thyroidal neck swellings described in medical literature. Recently Kikuchi Fujimoto disease is an emerging cause of necrotizing cervical lymph node mass revealed particularly in the Asians. The disease is very much amenable to management with steroids [6]. Kawasaki disease is another uncommon cause of cervical lymphadenopathy but can deteriorate to multiorgan failure in a short span of time [7]. In 2021, Kesavan et al. described two unusual cases of neck swelling. First was a case of achalasia cardia reported as neck swelling in a 75-year-old man [8]. Abuzayad et al. described a swelling in the region of carotid in a 15-year-old girl, which was later diagnosed as Castleman disease [9].

Sometimes the neck masses may not be of any pathological significance. These lesions called pseudo lesions may be due to normal variant anatomy, atypical location of organ of other location and foreign bodies due to iatrogenic causes or self-introduction [10]. Cervical ectopic thymus is one of the common such pseudo lesion and is widely reported [11]. Many studies were conducted in regards to evaluation of neck swellings but the diagnostic accuracy of clinical examination was purely discussed. In our study we were accurate by 85% in correctly diagnosing the cause for nonthyroidal neck swellings. However, the physical examination frequently requires to be supplemented by proper investigation to improve the diagnostic accuracy. The two important investigations that help to diagnose neck swellings are ultrasound and FNAC.

Ultrasound has been found to be a reliable and sensitive diagnostic tool in diagnosis of soft tissue cysts, vascular neoplasms, deep neck abscesses, palatal tumours, salivary gland diseases, fractures of facial bone, solid and cystic lesions of the jaws, temporomandibular joint pathology, head and neck cancer and nodal metastases. The recent Indian study conducted in 2011 by Chandak et al. pointed out that the diagnostic accuracy of clinical examination of 85.7% in diagnosis of neck swellings, while ultrasonography of neck had a sensitivity and accuracy of 98.5% [12]. In another study regarding the ultrasonographic evaluation of cervical lymphadenopathy, the most significant distinguishing feature is strong internal echoes seen in 84% of tubercular lymph nodes. This finding is found in only 11% of metastatic nodes and absent in lymphomatous nodes [13]. The other findings such as irregular margins, hypoechoic centre, fusion tendency, peripheral halo and absent hilus are helpful in differentiating reactive from diseased nodes but show considerable overlap in the 3 groups of tubercular, metastatic and lymphoma lymph nodes. However, ultrasound for neck masses is a valuable diagnostic tool, its accuracy depends on the characteristics of the ultrasound probe and the experience of the radiologist [14].

This vulnerability was overcome by higher modes of radiological diagnostic procedures. The capabilities of CT scan to distinguish between soft tissue structures coupled with the added advantage of utilizing intravascular contrast, particularly suits the examination of neck disorders. With improved equipment permitting thinner sections and shorter exposure times, applications in head and neck diagnosis are increased. CT is used in the evaluation of salivary gland enlargements, staging of known tumours and evaluation of a variety of neck swellings. In some cases, CT alone may be the only imaging procedure necessary, while in other situations, CT may comprise an important portion of comprehensive imaging evalua-

tion [15]. Important anatomic variants are pointed out so the surgeon can avoid potential intraoperative complications. Secondly, nodal staging can be assessed in an effort to increase the number of abnormal nodes detected by physical examination and more importantly to precisely define their location by a standard classification system that can be understood and consistently applied by the radiologist, surgeon, radiation oncologist and pathologist. Although secondary to the previously described tasks, CT scan imaging frequently enables saving the patient unnecessary risk and shortening the time to diagnosis and ultimate treatment [16].

Fine needle aspiration cytology (FNAC) is the most important step in the management of neck lumps. It is easy to perform and also relatively cheap. FNAC has high sensitivity (94.6%), specificity (97.9%), accuracy (96.7%), and both positive predictive (95.9%) and negative predictive (97.2%) value in the diagnosis of neck masses [17]. FNAC also serves as an excellent preliminary screening procedure. FNAC can be performed free-hand or ultrasound-guided to increase confidence of diagnosis if the lesion is impalpable. FNAC has excellent patient compliance, is simple and quick to perform in the outpatient department and can be readily repeated. Studies reveal the burden of tubercular lymphadenitis to be significant in most developing countries [18]. FNAC is deemed as frontline investigation with further investigations based on FNAC result. However, histopathological examination is still the most dependable diagnostic tool. Surgical intervention is definitely required in many cases, though most of the cases are medically curable [19]. Out of 100 cases 36 (36%) had tubercular lymphadenitis. The high percentage of tubercular lymphadenopathy in the Indian subcontinent setting is mirrored by similar findings by Fatima et al in Pakistan where the incidence of tubercular lymphadenopathy of 52.7% [20]. FNAC was a prime diagnostic tool in establishing the diagnosis in this study. A total of 95 patients were subjected to FNAC excluding cases of cystic hygroma, lymphangioma and carotid body tumour. Of the 95 neck swellings, FNAC was accurate in 81 cases, inconclusive in 11 cases and disparate with the final diagnosis in 3 cases. Thus, in 85.26% the FNAC diagnosis correlated with the final histopathological diagnosis. This is similar to the findings by Pandey et al., who reviewed the role of FNAC in 395 patients [21]. In our study FNAC has been accurate in 94% for diagnosis of tuberculosis. Das et al. has shown in their series of 180 cases an accuracy of 84.4% for detection of tuberculosis [22]. In our study, a total of 72% of neck swellings were found to be of lymph nodal in origin. This is similar to the findings by Jasani et al., which found the prevalence of lymph nodal swellings to be 69% in a series of 450 patients, who underwent FNAC [23].

In our study, 4 patients were finally diagnosed with metastatic lymphadenopathy labelled as carcinoma of unknown primary source (CUPS). The success rate of diagnosis of metastatic carcinoma by FNAC was 100 percent in this study. These findings are similar to the study published by Narang et al., where the success rate of diagnosing metastatic carcinoma by FNAC was 100% [24]. There were total of 17 cases of lymphoma in this series, comprising of 14 non-Hodgkin's (14%) and 3 Hodgkin's lymphoma (3%). This is similar to the findings in the British study by Smith et al., where 11 cases of lymphoma were reported in a series of 100 cases [25]. There were 10 cases of non-specific adenitis in our series, constituting 19.6% of lymph node swellings that was similar to the 2007 study by Song et al., showing the prevalence of non-specific adenitis to be 22.4% in 147 patients with lymph node swellings [26].

In our series 8% of the neck swellings were diagnosed to be lipomas. Similar incidence was seen in a series of 109 patients where four fifth of lipomas are 1.0-5.0 cm in maximum dimension [27]. In our series 4 lipomas were approximately 3 cm in size and 2 were 4-5 cm in size. There were two cases of cystic hygroma in our study, constituting 1.8% of benign tumour of the neck. Both were located in the posterior triangle. This is similar to the finding in the older study which showed one case of cystic hygroma in 100 consecutive cases. There were two cases of branchial cyst in the same study. Both swellings were in right lateral position. This conforms to previous published series by Liston et al., where it is mainly either on right or on left side. It rarely occupies the midline position [28]. Our study reported a total of 6 cases of salivary gland tumour. In our study there was one case of chronic sialadenitis of sub mandibular gland. This is consistent with the findings of Hag et al., where less than 5% cases of sialadenitis were detected in 225 neck swellings [29].

Conclusion

Non thyroidal neck swellings are commoner diagnosis than goitre. Most of the time diagno-

sis can be correctly established after a thorough history and clinical examination. The ultrasonographic and fine needle aspiration cytology are very useful adjunct in arriving at a definite diagnosis. Tubercular cervical lymphadenopathy and lymphoma were two major diagnosis constituting more than 50% of nonthyroidal neck swellings. Tubercular cervical lymphadenopathy was found to be significantly different from lymphomas in terms of mean age and the mean size of swelling.

Limitations

The limitations of this study were: a) single centre observation b) small duration of study c) hospital-based study. The advantages of this study were the prospective data collection and adequate sample size. As this is a pilot study a multicentre prospective study with more participants is recommended based on this study design.

Conflict of Interests

Authors declare no conflict of interest.

Author's Contributions

Jafar Husain, S. Rajagopalan, Vipin Venugopal Nair, R. Nagamahendran, Pawan Sharma, Pankaj P. Rao – conceptualization, methodology; *Jafar Husain, S. Rajagopalan, Vipin Venugopal Nair, R. Nagamahendran, Pawan Sharma, Nilanjan Roy* – investigation, data curation, formal analysis; *Jafar Husain, Vipin Venugopal Pawan Sharma, Pankaj P. Rao* – writing – original draft; *Rajagopalan, Vipin Venugopal Nair, R. Nagamahendran, Pawan Sharma, Nilanjan Roy, Pankaj P. Rao* – writing – reviewing and editing.

ПРОСПЕКТИВНЕ ОПИСОВЕ ДОСЛІДЖЕННЯ НЕТИРЕОЇДНИХ НАБРЯКІВ ШИЇ У НАСЕЛЕННЯ ЗАХІДНОЇ ІНДІЇ

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Вступ. *Нетиреоїдні набряки шиї є поширеним явищем і викликають труднощі у діагностиці. У цьому дослідженні висвітлюються різні діагнози, пов'язані з нетиреоїдними набряками шиї, і проблеми з їх лікуванням.*

Мета. *Це пілотне дослідження висвітлює різні діагнози, пов'язані з нетиреоїдними набряками шиї, і проблеми з їх лікуванням. У цьому дослідженні також порівнюється клінічний спектр двох найпоширеніших етіологій нетиреоїдного набряку шиї – туберкульозної шийної лімфаденопатії та лімфом.*

Методи. *Дане проспективне дослідження проводилося у навчальній лікарні третинного рівня з 01 червня 2018 р. по 31 грудня 2019 р. Перші 100 нетиреоїдних набряків шиї, представлених до хірургічного амбулаторного відділення, були оцінені клінічно, радіологічно та гістопатологічно. Проведено порівняння перших двох поширених діагнозів туберкульозного шийного лімфаденіту та лімфоми. Безперервні змінні аналізувалися за допомогою t-критерію Стьюдента, а категоричні дані аналізувалися за допомогою критерію хі-квадрат. Статистичне значення $p < 0,05$ вважалося значущим.*

Результати. *У дослідженні було виявлено 73 випадків збільшень лімфатичних вузлів і 27 набряків не пов'язаних із лімфатичними вузлами. Найбільш частим діагнозом був туберкульозний шийний лімфаденіт (n=38) та лімфома (n=17). Середній об'єм лімфатичних вузлів у групі лімфоми (38,72±22,12 см^3) був статистично більшим у порівнянні з об'ємом лімфовузлів у групі туберкульозу (9,44±5,99 см^3) P=0,00001. Середній вік хворих на туберкульоз був 33,81±11,8 років, порівняно з віком пацієнтів з лімфомою 52,38±25,3 років (P=0,000167). Клінічний діагноз був точним у 85% випадків. Однак у 15 випадках клінічний діагноз був змінений після тонкоголкової аспіраційної цитології.*

Висновки. *Ультразвукове дослідження та тонкоголкова аспіраційна цитологія є дуже корисним допоміжним засобом для встановлення точного діагнозу збільшень лімфовузлів на шиї. Туберкульозна шийна лімфаденопатія та лімфома були двома основними діагнозами. Туберкульозна шийна лімфаденопатія суттєво відрізняється від лімфом раннім віком появи та меншими розмірами на момент появи.*

КЛЮЧОВІ СЛОВА: **пухлини шиї; шийний; лімфаденопатія; туберкульозний; лімфома.**

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FETAL BILATERAL ADRENAL HEMORRHAGE (case report)

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Background. *Fetal supra renal mass revealed incidentally by routine antenatal ultrasound is a great challenge for diagnosis and management by a surgeon. This is a matter of parental anxiety and diagnostic dilemma to a physician. Indeed, such masses turn out to be complicated by an intra-tumor hemorrhage in neuroblastoma or antenatally diagnosed adrenal hemorrhage. The first one needs intensive management and the latter needs watchful observation.*

Objective. *A case of bilateral fetal adrenal mass revealed by routine fetal ultrasound examination at 28th week of gestation which turned out to be adrenal hemorrhage is presented. This is aimed to make awareness to ensure that clinicians always keep benign etiologies first and thoroughly investigate in case of incidentally detected fetal adrenal mass.*

Methods. *The study is a single case report of incidentally revealed supra renal mass. This case report encompasses differentiating features between the two and investigations that aid the surgeon to avoid unnecessary intervention in a benign hemorrhage.*

Results. *The baby was kept on follow up with serial ultrasound scans in the postnatal period and by the second scan in a month, the hemorrhage had resolved completely.*

Conclusion. *In cases of benign looking masses like adrenal hemorrhage or spontaneously resolving neuroblastoma, appropriate antenatal assessment and close monitoring with serial ultrasound scans can avoid surgery.*

KEYWORDS: **bilateral fetal adrenal hemorrhage; neuroblastoma; adrenal mass.**

Introduction

The supra renal glands were discovered in 1522 by Eustachius and described by him in 1563. The adrenal glands are responsible for essential physiologic functions including stress response, electrolyte balance, metabolism, immune function, blood pressure regulation and sexual development. Supra renal masses have been a longstanding source of fascination for both physicians and surgeons especially in neonatal period. Adrenal glands are relatively larger in size with high vascularity during fetal and neonatal period. This predisposes to its hemorrhage in early life. Neonatal adrenal hemorrhage is rare and is seen in 0.2-0.5% of cases [1]. With the recent advancement in imaging modalities, diagnosis and management of supra renal masses has become more efficient. Assessment of hemodynamic stability, adrenal insufficiency and exclusion of a hormonal active adrenal tumor proves to be a topical issue in management of such suprarenal masses [2]. Association of adrenal hemorrhage with thrombosis of major blood vessels is also reported in the literature [3]. Thus, a rare case of antenatally diagnosed bilateral adrenal mass which turned out to be benign adrenal hemorrhage is presented. This case report envisages the need for watchful observation and importance of short interval follow up imaging in management of benign disorders of adrenal gland before any surgical intervention.

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Case report

Rare presentation of neonatal adrenal masses is a diagnostic dilemma in differentiating benign adrenal fetal hemorrhage from neuroblastoma. This case report encompasses differentiating features between the two and investigations that aid the surgeon to avoid unnecessary intervention in a benign hemorrhage. Following is the case report of a 27 years old Gravida 3, Para 2, Live 2 woman, who was referred to our pediatric surgery center at 28 week of gestation for evaluation of bilateral supra renal cystic mass. Her previous medical history was unremarkable. On evaluation with sonography, bilateral cystic mass was located

superior to both kidneys measuring 15×10 mm on the right side and 14×9 mm on the left side.

Fetus was evaluated further by Doppler examination of umbilical cord, biophysical profile and fetal biometry and were in norm. Evaluation with antenatal MRI scan on 28 weeks of gestation was suggestive of bilateral fetal adrenal hemorrhage. The antenatal mother was kept on serial ultrasound follow up, scans at 32 weeks and 35 weeks revealed multicystic lesions of both adrenals. The right adrenal measured 21×12 mm and the left one – 20×13 mm without any abnormal vascularity. Mother underwent elective lower segment caesarean section at 38 weeks of gestation. The surgery and postoperative period was uneventful. A 2.815 kg, healthy female child was delivered with normal peripartum period.

Discussion

Ultrasonography of Abdomen on the 2nd day of life revealed mild resolution of bilateral suprarenal areas to 15×15 mm in the right and 13×14 mm in the left with hypo echoic foci within. Further biochemical evaluation of serum aldosterone, renin, cortisol and plasma ACTH levels were in norm. The baby was kept on follow up with serial ultrasound scans and by the second scan in a month, the hemorrhage had resolved completely.

Spencer, in 1892 first described adrenal hemorrhage in stillborn infants. Based on extensive autopsy reports, the incidence of adrenal hemorrhage is estimated to be about 1.7 per thousand births and the incidence of antenatal detection is not established due to its rarity [2]. Bilateral adrenal hemorrhage is found in 5-15% of cases with right side preponderance with right and left side ratio of 3:1 [4].

The increased use of perinatal ultrasound has led to early detection of an increasing number of neonatal suprarenal masses [5]. In ultrasound, the adrenal glands typical looks like wishbone appearance in the form of cap or an inverted V over the kidneys [6]. Adrenal hemorrhage is rarely associated with adrenal insufficiency. Even in cases with severe bilateral adrenal hemorrhage, it is hardly ever encountered as less than 10% availability of functional glandular component that is enough to prevent adrenal insufficiency [7].

Adding to the existing knowledge of management of supra renal masses, which are detected antenatally, it is prudent from our study that serial radiological monitoring is crucial. Masses with radiological reduction in size should be given full consideration for conservative management [8]. Rare occurrence of fetal adrenal hemorrhage should be kept in mind in those cases where surgery can be avoided.

Conclusion

Differentiation between fetal adrenal hemorrhage and congenital neuroblastoma is difficult and urgent. In cases of radiologically benign looking supra renal masses, appropriate antenatal assessment and close monitoring with serial ultrasound scans can avoid unnecessary surgical intervention as they resolve spontaneously.

Limitations

Single case report in a tertiary care center.

Conflict of Interests

Authors declare no conflict of interest.

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Author's Contributions

Dr. Jaskiran Singh Randhawa – conceptualization, methodology, formal analysis, writing – reviewing and editing; *Dr. R. Nagamahendran* – investigation, writing – original draft, writing – reviewing and editing; *Dr. R. Shankaran* – investigation, formal analysis, data curation.

ДВОСТОРОННЯ КРОВОТЕЧА З НАДНИРКОВИХ ЗАЛОЗ У ПЛОДА (клінічний випадок)

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Вступ. *Утворення в наднирниках плода, випадково виявлені під час звичайного допологового ультразвукового дослідження, викликають занепокоєння батьків і створюють діагностичну проблему для лікуючого лікаря. Такі утворення можуть виявитися ускладненим внутрішньопухлинним крово-*

виливом у нейробластому або антенатально діагностованим крововиливом у надниркові залози. Перший потребує інтенсивного лікування, а другий – уважного спостереження.

Мета. *Представлено випадок двостороннього утворення в надниркових залозах плода, виявленого під час планового ультразвукового дослідження плода на 28-му тижні вагітності, які виявилися крововиливом у надниркові залози. Випадок представлено з метою загострення уваги та настороженості клініцистів щодо доброякісної патології та проведення ретельного обстеження у випадку випадкового виявлення новоутворень надниркових залоз плода.*

Методи. *Представлено випадок випадково виявлених утворень надниркових залоз. Описано відмінності між ними та дослідження, які допомагають хірургу уникнути непотрібного втручання при доброякісному крововиливі.*

Результати. *У післяпологовому періоді дитину спостерігали за допомогою серійних ультразвукових досліджень. До другого УЗД через місяць крововилив повністю розсмоктався.*

Висновки. *У випадках доброякісних новоутворень, таких як крововилив у надниркові залози або нейробластома, що спонтанно розсмоктується, відповідна антенатальна оцінка та ретельний моніторинг за допомогою серійних ультразвукових досліджень можуть допомогти уникнути операції.*

КЛЮЧОВІ СЛОВА: **двостороння фетальна надниркова кровотеча; нейробластома; утворення в наднирниках.**

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COMPARATIVE CHARACTERISTICS OF SYMPTOMS IN NEUROTIC AND AFFECTIVE PATIENTS AFTER COVID-19

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Background. *COVID-19 pandemic has negatively affected people's mental health and created new barriers for those who have already suffered from mental illnesses.*

Objective. *The aim of the study was to compare the symptoms of mental disorders in neurotic and affective patients, who recovered from COVID-19.*

Methods. *The features of disorders during the pandemic in 35 neurotic and 31 affective patients were analysed. The Hamilton anxiety and depression scales (HAM-A, HAM-D), Insomnia Severity Index (ISI), Schulte tables, Jacobson short-term memory study were used.*

Results. *Moderate and severe anxiety was more likely to develop in neurotic patients (34.29% and 37.14%, respectively), mild and moderate – in affective ones (38.71% and 32.26%). Neurotic patients had a higher level of depression (moderate – by 31.42%, severe – by 48.57%) than affective patients (mild – by 32.26%, severe – by 35.48%). The degree of memory loss was higher in affective patients (51.62% – low, 35.48% – very low) than in neurotic ones (41.94% – low, 20.00% – very low). Most of patients had reduced attention. Insomnia severity was higher in patients with neurotic disorders (25.72% – subthreshold, 45.71% – moderate) than in affective patients (38.71% – subthreshold, 22.58% – moderate). A higher level of anxiety and depression severity was observed in patients who had COVID-19 in 2021 than in those who had it in 2020, while the severity of insomnia and memory impairment – vice versa.*

Conclusion. *Anxiety, depression, insomnia, memory and attention loss were detected. Anxiety and depression were more severe in neurotic patients but the degree of memory loss was higher in affective patients.*

KEYWORDS: **pandemic; mental health; depression; anxiety; insomnia.**

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), first detected in Wuhan, China, in December 2019, rapidly spread around the world in 2020. The outbreak of coronavirus disease (COVID-19) is still having a global impact on people today. The association between SARS-CoV-2 infection and mental illness is a topical issue, as the COVID-19 pandemic has negatively affected mental health of many people and created new challenges for those already suffering from a mental illness [1].

With an increase in the number of infected people, there is a simultaneous increase in the number of recovered patients with preserved clinical manifestations of coronavirus infection after complete elimination of the virus from the organism, which indicates the post-COVID syndrome. A lot of people report persistent fatigue, joint and bone pain, rapid heartbeat, headache, dizziness, insomnia, anxiety, and depression [2, 3]. Residual phenomena of the disease are manifested by damage to many internal organs, including the nervous system, causing neuropsychiatric syndromes that affect cognitive, behavioural, affective and perceptual disorders [4].

The aetiology of psychiatric consequences of coronavirus infection is multifactorial and may include direct effect of the virus, cerebrovascular diseases, hypoxia, immune response, social isolation, psychological impact of a new potentially fatal disease, anxiety about infecting others and stigma or discrimination [4]. SARS-CoV-2 is a neurotropic virus that can enter the brain in various ways, including the olfactory neural pathway, and trigger inflammatory response affecting both the peripheral and central nervous systems (CNS) [3].

At least seven mechanisms of development of affective and neurotic disorders and cognitive dysfunction are established, i.e.: viral replication in innate immune cells, dysregulation of the

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immune response, cytokine storm, antibody-mediated response, hypoxemia, ischemia due to hypercoagulation, neuronal damage [1, 2].

Lung damage and consequently hypoxemia caused by COVID-19 is likely to contribute to neuronal damage and further cognitive decline. SARS-CoV-2 affects the vascular endothelium causing endothelial dysfunction followed by coagulopathy and thrombotic complications. The virus also causes systemic vasculitis and cytokine storm, which can damage brain structures. The hypercoagulatory and hyper-inflammatory states evidenced in COVID-19 may contribute to delusions and future cognitive decline. In addition, peripheral pro-inflammatory cytokines such as tumour necrosis factor alpha (TNF-α), interleukin-1 (IL-1), IL-6 effect the permeability of the blood-brain barrier through cyclooxygenase-2 (COX-2), upregulation and activation of matrix metalloprotease and enter the CNS, causing microglial activation and oxidative stress which induce apoptosis and eventually alterations in neurotransmitter signalling leading to synergistic cognitive impairment, psychiatric disorder development and progression. Induced neuroinflammation can contribute to short-term delusions and severe long-term cognitive deficits [1, 2].

The aim of our study is to compare the symptoms of mental disorders in patients with neurotic and affective mental disorders, who have recovered from COVID-19.

Methods

In compliance with the principles of biomedical ethics, on the basis of informed consents, 61 respondents (15 men and 46 women) with no previous psychiatric history were interviewed; 30 respondents among them were not previously infected with COVID-19 and 31 respondents who had suffered from this disease before; and 66 recovered patients (26 men and 40 women) who got previously sick with coronavirus infection and at the time of the study were undergoing inpatient treatment in the Psychiatric Departments of the Ternopil Regional Clinical Psychoneurological Hospital (the psychiatric illness of the cohort was diagnosed before coronavirus disease). The average age of respondents of the control group was (39±7) years, ranging from 19 to 47 years old. The average age of patients was (50±13) years, ranging from 20 to 63 years old. Among respondents who were infected with COVID-19, 24 respondents had a mild course (77.42%), 7 respondents – moderate severity (22.58%). Among the patients, 35 respondents had a mild course (53.03%), 21 – moderate course (31.82%) and 10 – severe course (15.15%).

The study was conducted from December 2021 to January 2022 at I. Horbachevsky Ternopil National Medical University and the Ternopil Regional Clinical Psychoneurological Hospital. The printed questionnaires were distributed among the volunteer respondents who agreed to participate after being invited on private social media pages.

To collect data and optimize the obtained results the following tools were used:

1. General questionnaire with sociodemographic data (age, sex), type of activity, hobbies and support of relatives, previous history of mental disorders.
2. Information about the date of COVID-19 onset and the course of the disease.
3. Hamilton Anxiety Rating Scale (HAM-A).
4. Hamilton Depression Rating Scale (HAM-A).
5. Insomnia Severity Index (ISI).
6. Schulte Table test.
7. Short-term memory study.

Results

The respondents were divided into four groups: two control groups (respondents who were not previously infected with COVID-19 and recovered respondents with no mental disorder), neurotic patients (35 patients: 10 patients with F40, 16 patients with F41, 9 patients with F43), affective patients (31 patients: 9 patients with F31, 12 patients with F32, 10 patients with F33), and six subgroups according to the date of COVID-19 onset:

1. Group 1 – 30 respondents who were not previously infected with COVID-19.
2. Group 2 – 31 respondents who had COVID-19:
   - Subgroup 2.1 – 15 people who were ill in 2020 (48.39%);
   - Subgroup 2.2 – 16 people who were ill in 2021 (51.61%).
3. Group 3 – 35 neurotic patients who recovered from COVID-19:
   - Subgroup 3.1 – 13 people who were ill in 2020 (37.14%);
   - Subgroup 3.2 – 22 people who were ill in 2021 (62.86%).
4. Group 4 – 31 affective patients who recovered from COVID-19:
   - Subgroup 4.1 – 13 people who were ill in 2020 (41.94%);

- Subgroup 4.2 – 18 people who were ill in 2021 (58.06%).

Based on the questionnaire which included the Hamilton Anxiety Rating Scale (HAM-A), the level of anxiety was assessed in the respondents, who were not previously infected with COVID-19, and the recovered respondents with no mental disorder, neurotic patients and affective patients, who recovered from COVID-19.

During our study it was established that among the respondents-volunteers, who were not previously infected with COVID-19 (group 1), 30.00% did not experience anxiety, 70.00% had mild anxiety. Among the respondents with COVID-19 (group 2), only 6.45% had no anxiety, mild anxiety was evidenced in 54.84% of people, moderate and severe anxiety were found in 25.81% and 12.90%, respectively. Among the patients with neurotic disorders (group 3), all of them suffered from anxiety, 28.57% of patients had mild anxiety. In this group moderate and severe anxiety were more common in 34.29% and 37.14% of patients, respectively.

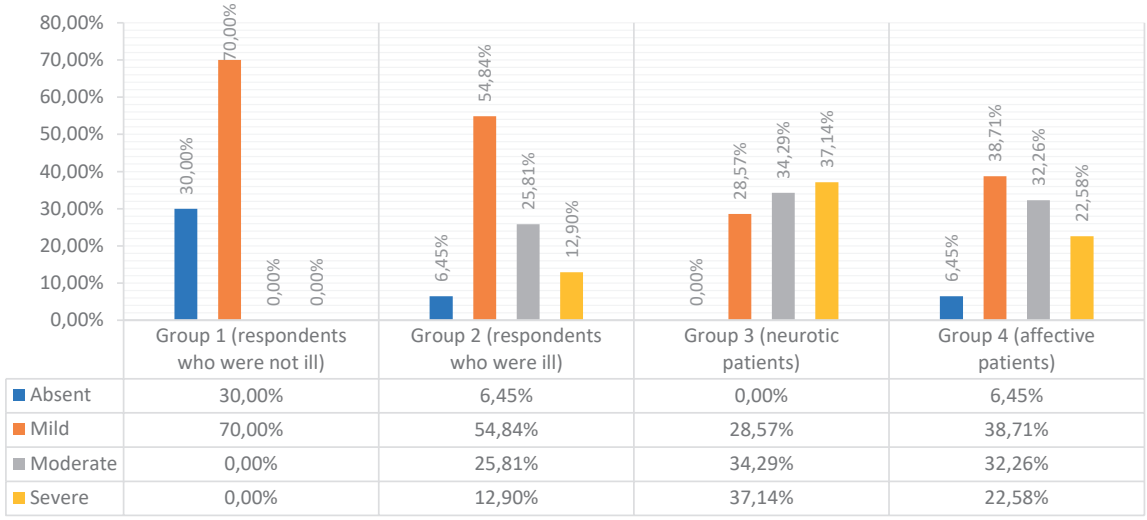
Among the patients with affective disorders (group 4,) 6.45% had no anxiety, mild and moderate anxiety prevailed in 38.71% and 32.26% of them, respectively, and the other 22.58% of patients had severe anxiety (Fig. 1).

Therefore, an increase in the frequency and severity of anxiety in the recovered respondents and patients was evidenced compared to the respondents who were not previously infected with COVID-19. The patients in groups 3 and 4 were more likely to experience moderate and severe anxiety, while the respondents in group 2 were more likely to have mild anxiety. Comparing the anxiety severity in the respondents of groups 3 and 4, moderate and severe anxiety was more common among the neurotic patients while mild and moderate anxiety – among the affective patients.

Assessing the anxiety severity in the patients by the date of COVID onset, mild anxiety was evidenced more in those patients, who were ill in 2020 (53.85% of neurotic and 53.85% of affective patients), and the patients, who were ill in 2021, had moderate anxiety (50.00% of neurotic and 50.00% of affective patients) (Table 1).

Based on the survey, which involved the Hamilton Depression Rating Scale (HAM-D), the level of depression was assessed in the respondents-volunteers, who were not previously infected with COVID-19, and the recovered ones, neurotic and affective patients, who recovered from COVID-19.

During our study it was established that among the respondents of group 1, 80.00% had no depression, 16.67% had mild depression, and only 3.33% of people had moderate depression. Among the respondents, who recovered (group 2), only 25.81% of them had no depression, 41.93% had mild depression, and 16.13% – moderate and severe depression each. Among the patients with neurotic disorders (group 3), no depression was observed only in 5.71% of them, 14.29% had mild depression. Most often, the patients in this group suffered from moderate or severe depression, in 31.43% and 48.57% of people, respectively. Among the patients with affective disorders (group 4), 9.68% had no depression, 32.26% had mild depression, 22.58% had moderate depression, and 35.48% had severe depression (Fig. 2).



	Group 1 (respondents who were not ill)	Group 2 (respondents who were ill)	Group 3 (neurotic patients)	Group 4 (affective patients)
Absent	30,00%	6,45%	0,00%	6,45%
Mild	70,00%	54,84%	28,57%	38,71%
Moderate	0,00%	25,81%	34,29%	32,26%
Severe	0,00%	12,90%	37,14%	22,58%

Fig. 1. Anxiety severity according to HAM-A.

Table 1. Anxiety severity according to HAM-A

Severity of anxiety	Group 3 (neurotic patients) 35 people				Group 4 (affective patients) 31 people			
	Group 3.1 Were ill in 2020 13 respondents		Group 3.2 Were ill in 2021 22 respondents		Group 4.1 Were ill in 2020 13 respondents		Group 4.2 Were ill in 2021 18 respondents	
	No	%	No	%	No	%	No	%
Assessment of anxiety								
Absent	0	0	0	0	1	7.69	0	0
Mild	7	53.85	3	13.64	7	53.85	4	22.22
Moderate	1	7.69	11	50.00	2	15.38	9	50.00
Severe	5	38.46	8	36.36	3	23.08	5	27.78

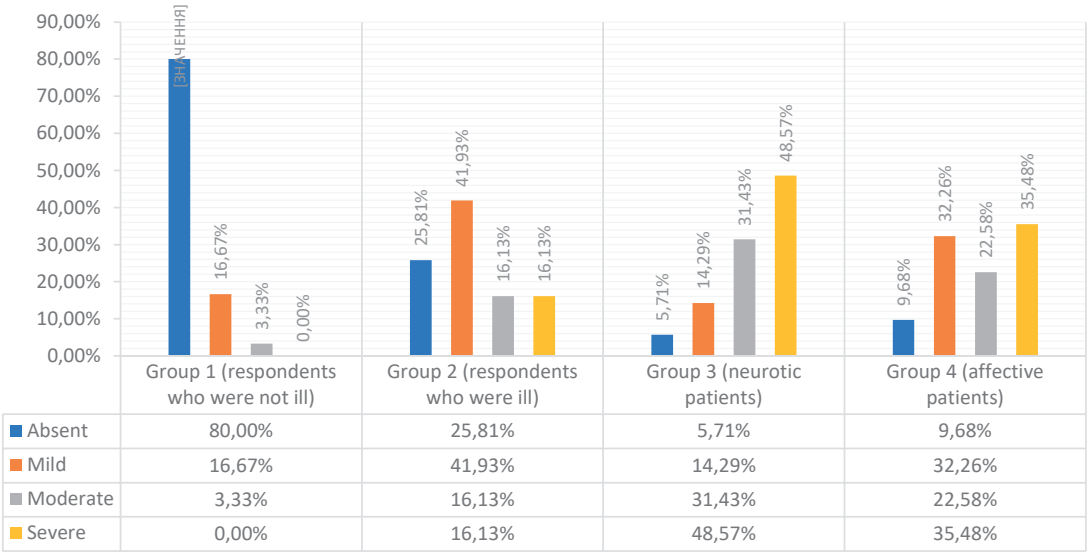


Fig. 2. Depression severity according to HAM-D.

There was an increase in the severity of depression in the respondents and patients, who had COVID-19, compared to the respondents, who were not previously infected. People of the groups 3 and 4 were more likely to experience moderate to severe depression (more severe in the neurotic patients), while the respondents of group 2 were more likely to experience mild depression. Comparing the level of depression severity in the patients of groups 3 and 4, it was noticed that the neurotic patients were more likely to have moderate and severe depression, while the affective patients– mild and severe.

Assessing depression severity in the patients by the date of COVID-19 onset, it was established that the patients, who were ill in 2020, usually experienced mild depression (30.77% of neurotic patients and 46.16% of affective patients), and the patients, who were ill in 2021 – severe depression (54.54% of neurotic patients and 50.00% of affective patients) (Table 2).

The respondents' memory was evaluated using the "Short-term memory study". It was found out that among the respondents of group 1, 6.67% of them had very high memory, 30.00% had high memory, 43.33% had average memory, and 20.00% had low memory. Among the recovered respondents (group 2), only 6.45% of them had high memory, 19.35% – average memory, and low memory was evidenced the most often in 70.97% of people. Among the patients with neurotic disorders (group 3), 48.86% of them had average memory, low memory in 41.94% of patients, and very low memory – in 20.00%. Among the patients with affective disorders (group 4), average memory was found in 12.90% of respondents, low memory – in 51.62%, and very low memory – in 35.48% (Fig. 3).

There was a decrease in memory of the respondents and patients, who recovered from

Table 2. Depression severity according to HAM-D

Depression severity	Group 3 (neurotic patients) 35 people				Group 4 (affective patients) 31 people			
	Group 3.1 Were ill in 2020 13 respondents		Group 3.2 Were ill in 2021 22 respondents		Group 4.1 Were ill in 2020 13 respondents		Group 4.2 Were ill in 2021 18 respondents	
	No	%	No	%	No	%	No	%
Assessment of depression								
Absent	1	7.69	1	4.55	3	23.08	0	0
Mild	4	30.77	1	4.55	6	46.16	4	22.22
Moderate	3	23.08	8	36.36	2	15.38	5	27.78
Severity	5	38.46	12	54.54	2	15.38	9	50.00

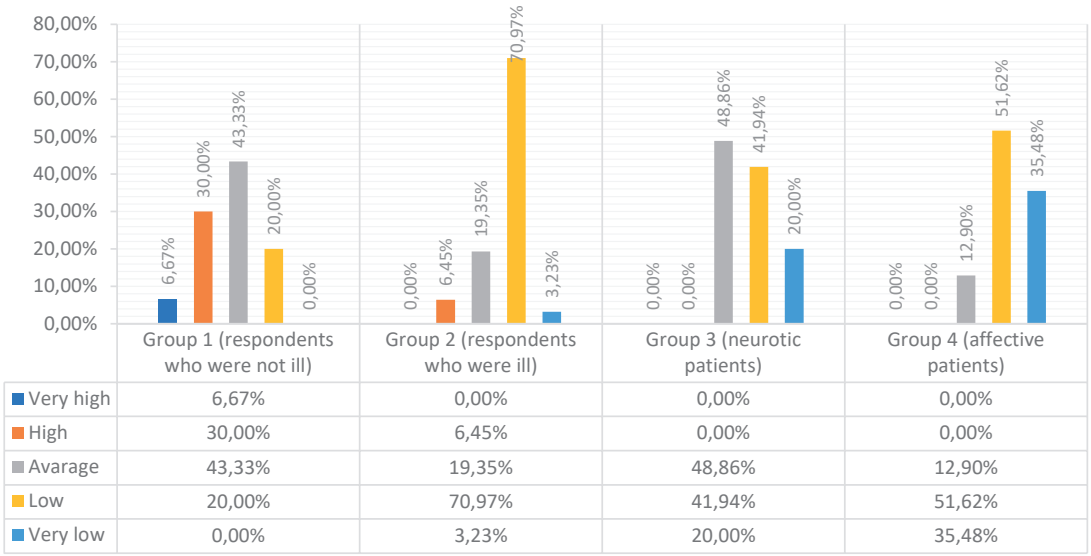


Fig. 3. Assessment of memory according to Short-term memory study.

COVID, compared to the respondents, who were not infected. The people of groups 3 and 4 were more likely to have low and very low memory (more pronounced in the affective patients), while the respondents of group 2 were found to have low memory.

Moreover, the level of attention of respondents according to the "Schulte table" test was evaluated. It was established that 100% of the respondents of group 1 had normal attention, among the people of group 2, 93.50% had normal attention and only 6.45% had reduced attention. Among the neurotic patients, only 17.14% of people had normal attention, while 82.86% had reduced attention. Among the affective patients, only 19.35% of people had normal attention, while 80.65% had reduced attention (Fig.4).

Therefore, the majority of neurotic and affective patients, who were previously infected with COVID-19, had reduced attention, 82.86% and 80.65%, respectively, compared to the recovered respondents without mental illnesses.

Evaluating memory and attention in patients by the date of COVID-19 onset, there was no significant difference in attention changes in the patients, who were ill in 2020 and in 2021. As for memory, the neurotic patients, who were ill in 2021, generally had better memory (45.46% – normal memory, 36.36% – low memory, 18.18% – very low memory) than those, who were ill in 2020 (38.46% – average memory, 38.46% – low memory, 23.08% – very low memory).

Worse results were found in the affective patients, who had COVID-19 in 2021: 5.55% of patients had normal memory, 61.11% – low memory, 33.34% – very low memory, while among the patients, who had COVID-19 in 2020, 15.38% had average memory, 38.46% – low memory and 46.16% – very low memory (Table 3).

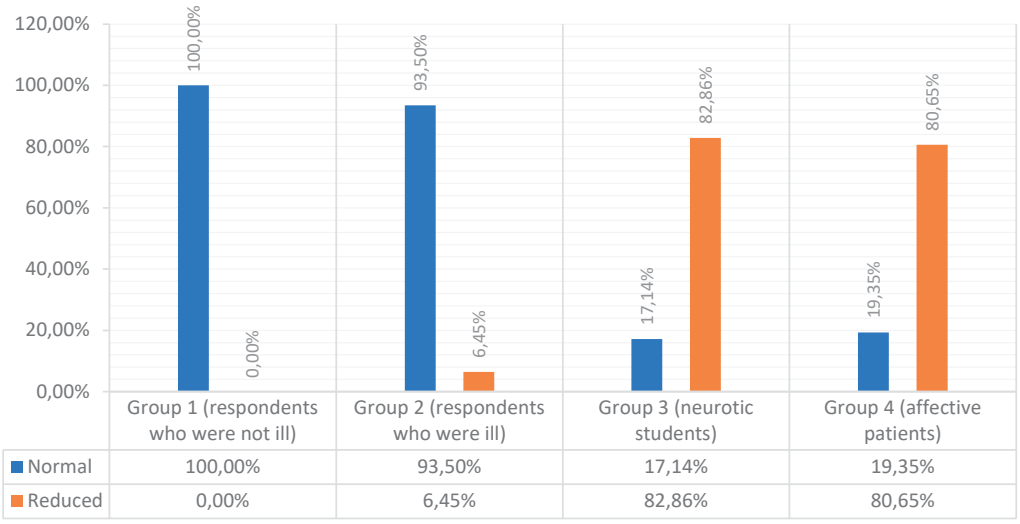


Fig. 4. Assessment of attention according to Schulte table test.

Table 3. Assessment of memory and attention

Severity	Group 3 (neurotic patients) 35 people				Group 4 (affective patients) 31 people			
	Group 3.1 Were ill in 2020 13 respondents		Group 3.2 Were ill in 2021 22 respondents		Group 4.1 Were ill in 2020 13 respondents		Group 4.2 Were ill in 2021 18 respondents	
	No	%	No	%	No	%	No	%
Assessment of attention								
Normal	2	15.38	4	18.18	3	23.08	3	16.67
Reduced	11	84.62	18	81.82	10	76.92	15	83.33
Assessment of memory								
Very high	0	0	0	0	0	0	0	0
High	0	0	0	0	0	0	0	0
Average	5	38.46	10	45.46	2	15.38	1	5.55
Low	5	38.46	8	36.36	5	38.46	11	61.11
Very low	3	23.08	4	18.18	6	46.16	6	33.34

Based on the questionnaire, the Insomnia Severity Index was evaluated. It was found out that 90.00% of the respondents of group 1 had no insomnia, and 10.00% had subthreshold insomnia. Among the respondents, who had COVID-19 (Group 2), only 45.16% of respondents had no insomnia, 38.71% had subthreshold insomnia, 12.90% had moderate insomnia and only 3.23% had severe insomnia. Among the patients with neurotic disorders (group 3), only 8.57% of patients had no insomnia, 25.72% had subthreshold insomnia, 45.71% had moderate insomnia, and 20.00% – severe insomnia.

Among the patients with affective disorders (Group 4), 22.58% had no insomnia, 38.71% had a subthreshold insomnia, 22.58% had moderate insomnia, and 16.13% had severe insomnia (Fig. 5).

Therefore, a higher degree of insomnia was found in the respondents and patients, who were previously infected with COVID-19, compare to the respondents, who did not suffer from the disease. The neurotic patients had moderate insomnia, while the affective patients had subthreshold insomnia. Moderate to severe insomnia was more common in the patients than in the respondents without previous psychiatric history.

Assessing the level of insomnia severity in the patients by the date of COVID-19 onset, it was established that in neurotic patients, who were ill in 2020, subthreshold and moderate insomnia prevailed (30.77% and 53.85%, respectively), and in the patients of this group, who were ill in 2021 – moderate and severe insomnia (40.91% and 27.27%, respectively). Severe insom-

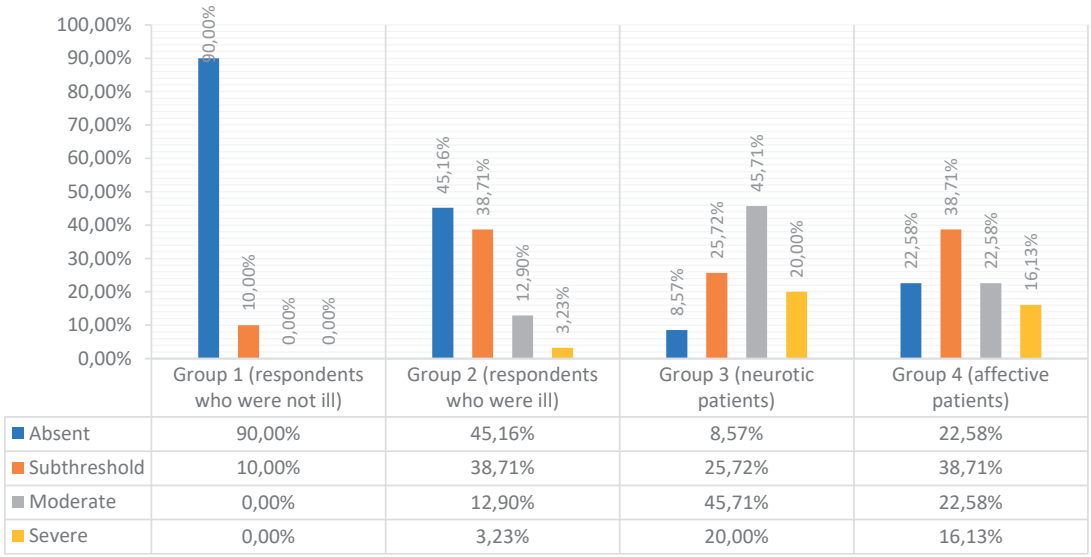


Fig. 5. Assessment of insomnia severity according to ISI.

nia prevailed in the affective patients, who were ill in 2020 (38.46% of people), and subthreshold insomnia prevailed in the patients of this group, who were ill in 2021 (50.00 %) (Table 4).

According to the survey, the severity of mental and cognitive changes in the patients were evaluated depending on the date of COVID-19 onset (2020 or 2021 year). Thus, it was established that 96.15% of patients, who were ill in 2020, and 100% of patients, who were ill in 2021, suffered from anxiety. Therefore, the anxiety severity in the patients, who had COVID-19 in 2021, was higher than in those who had it in 2020.

The respondents, who were ill in 2021, were more likely to have moderate and severe anxiety in 50.00% and 32.50%, respectively. As for the patients, who were ill in 2020, mild and severe anxiety was more common in 53.85% and 30.76% of them, respectively.

Depressive disorders were observed in 84.62% of patients, who were ill in 2020, and in 97.50% of patients, who were ill in 2021. The severity of depression was also higher in the patients, who were ill in 2021. In this group of patients, moderate depression was most often observed in 32.50% of patients and severe depression – in 52.50%. Among the patients, who were ill in 2020, severe depression was observed in 26,92% of them and mild depression – in 38,46% of people.

Attention was reduced in the majority of patients, who were ill in 2020 and 2021, 80.77% and 82.50%, respectively.

Reduced memory was evidenced in 72.50% of patients, who were ill in 2021, and in 73.08% of patients, who were ill in 2020, but the degree of memory loss was higher in those who were ill in 2020 (low memory – in 38.46%, very low memory – in 34.62%). Among the patients, who

Table 4. Assessment of insomnia severity according to ISI

Insomnia severity	Group 3 (neurotic patients) 35 people				Group 4 (affective patients) 31 people			
	Group 3.1 Were ill in 2020 13 respondents		Group 3.2 Were ill in 2021 22 respondents		Group 4.1 Were ill in 2020 13 respondents		Group 4.2 Were ill in 2021 18 respondents	
	No	%	No	%	No	%	No	%
Assessment of insomnia severity								
Absent	1	7.69	2	9.09	1	7.69	5	27.78
Subthreshold	4	30.77	5	22.73	4	30.77	9	50.00
Moderate	7	53.85	9	40.91	3	23.08	4	22.22
Severe	1	7.69	6	27.27	5	38.46	0	0

were ill in 2021, low memory was evidenced in 47.50%, very low – only in 25.00%.

Sleep disorders affected 82.50% of patients, who were ill in 2021, and 92.31% of those, who were ill in 2020. The severity of insomnia was higher in the patients, who were ill in 2020: subthreshold insomnia was observed in 30.77% of people, moderate insomnia – in 38.46%, severe insomnia – in 23.08%.

Among the patients, who were ill in 2021, subthreshold insomnia was evidenced in 35.00% of people, moderate insomnia – in 32.50%, severe insomnia – only in 15.00% (Table 5).

Discussion

It is established that COVID-19 negatively affects mental health of the population around the world. Fear of coronavirus infection associated with the possible risk of infection, unpredictable course of the disease, lack of pathogenetic treatment and total uncertainty causes negative psychological reactions, such as distress and maladaptation [5]. As for patients with a primary psychiatric history, usually after COVID-19, the symptoms of mental disorders were more significant [6].

According to the survey it was found out that 100% of neurotic and 92.31% of affective patients experienced anxiety after COVID-19. Moderate and severe anxiety was more common in the patients with neurotic disorders (in 34.29% and 37.14%, respectively), and mild and moderate anxiety was evidenced in the affective patients (38.71% and 32.26%, respectively).

It was established that 94.29% of neurotic patients and 90.32% of affective patients experienced depression after recovering from COVID-19. The neurotic patients had a higher degree of depression (moderate – in 31.42%, severe – in 48.57%) than the affective patients (mild depression – in 32.26% and severe – in 35.48%)

Table 5. Comparison of the severity of mental and cognitive disorders depending on the date of COVID-19 onset (year 2020 and 2021)

Severity	All patients 65 patients			
	Were ill in 2020 26 patients		Were ill in 2021 40 patients	
	No	%	No	%
Assessment of anxiety				
Absent	1	3.85	0	0
Mild	14	53.85	7	17.50
Moderate	3	11.54	20	50.00
Severe	8	30.76	13	32.50
Assessment of depression				
Absent	4	15.38	1	2.50
Mild	10	38.46	5	12.50
Moderate	5	19.23	13	32.50
Severe	7	26.92	21	52.50
Assessment of attention				
Normal	5	19.23	7	17.50
Reduced	21	80.77	33	82.50
Assessment of memory				
Very high	0	0	0	0
High	0	0	0	0
Average	7	26.92	11	27.50
Low	10	38.46	19	47.50
Very low	9	34.62	10	25.00
Assessment of insomnia				
Absent	2	7.69	7	17.50
Subthreshold	8	30.77	14	35.00
Moderate	10	38.46	13	32.50
Severe	6	23.08	6	15.00

Additionally, impaired cognitive functions were found in the respondents with coronavirus infection, i.e. memory and attention. The memory loss was diagnosed in 61.94% of patients with neurotic disorders and 87.10% of patients with affective disorders. The degree of memory loss was higher in the affective patients (51.62% – low memory, 35.48% – very low memory) than in the neurotic patients (41.94% – low memory, 20.00% – very low memory).

Reduced attention was observed in the majority of the examined patients: 82.86% of neurotic patients and 80.65% of affective patients.

Sleep disorders were evidenced in 91.43% of neurotic patients and 77.42% of affective patients after COVID-19. Subthreshold insomnia and moderate insomnia were more common in both groups of patients. The frequency of their occurrence was higher in the patients with neurotic disorders (25.72% of patients – subthreshold insomnia, 45.71% – moderate insomnia) than in those with affective disorders (38.71% – subthreshold insomnia, 22.58% – moderate insomnia).

We have identified features of mental and cognitive disorders among the patients with a previous psychiatric history, who recovered from COVID-19, depending on the date of COVID-19 onset (2020 and 2021 year):

– depressive disorders and anxiety in the neurotic and affective patients, who were ill in 2020, were mostly mild, and in those, who were ill in 2021 – moderate;

– memory was more worsened in the neurotic patients, who were ill in 2020, than in those, who were ill in 2021. The affective patients had the opposite result – the better memory was in those, who had COVID-19 in 2020;

– sleep disorders also correlated with the date of COVID-19 onset. The neurotic patients, who were ill in 2020, had subthreshold and moderate insomnia, and those, who were ill in 2021, had moderate and severe insomnia. In the affective patients, the results were opposite: those, who were ill in 2020, had severe insomnia, and those, who were ill in 2021, had subthreshold insomnia.

Numerous studies also show that people with psychiatric illnesses are at higher risk of COVID-19 infection and related complications due to a variety of factors [6]. Comorbidities, altered immune functions, sleep problems and various socioeconomic risk factors contribute to an increase in COVID-19 infection rates [6]. Studies [7, 8] from around the world have established a significant association between existing psychiatric disorder and an increased risk of COVID-19 infection and COVID-19-related hospitalization, morbidity and mortality. The prognosis was found to be worse among patients with affective mental illnesses than for patients with neurotic ones [7, 8]. Threats of coronavirus disease, violation of the usual life stereotype, restriction of leisure activity, harmful interest in news about the pandemic, usage of tobacco are important in the mechanisms of distress development. These conditions increase the risk of stress, anxiety and depression [9]. Therefore, patients with mental disorders should be considered a vulnerable group for COVID-19 infection, and the results of this study are of particular significance and value in predicting development of mental disorders and optimizing treatment after an infectious disease in people suffering from neurotic and affective disorders during this pandemic or subsequent ones.

In the perspective of this study, after the survey and interpreting the attained results, a conversation with the respondents took place and a course of cognitive-behavioural and biosuggestive psychotherapy was offered to correct the symptoms of mental disorders and improve resocialization of the patients. The data will be published in the following publications.

Conclusion

Anxiety, depression, insomnia, memory and attention loss were found in examined patients. Anxiety and depression were more severe in the patients with neurotic disorders while the degree of memory loss was higher in the patients with affective disorders. Reduced attention was observed in most of the examined patients with affective and neurotic disorders. Our survey found that 100% of neurotic and 92.31% of affective patients experienced anxiety after COVID-19. Moderate and severe anxiety was more common in the patients with neurotic disorders and mild and moderate anxiety was evidenced in the affective patients. It was established that 94.29% of neurotic patients and 90.32% of affective patients experienced depression after recovering from COVID-19. The neurotic patients had more severe depression than the affective ones. Additionally, impaired cognitive functions in the respondents with coronavirus infection, i.e. memory and attention, were found. Memory loss was diagnosed in 61.94% of patients with neurotic

disorders and 87.10% of patients with affective disorders. Memory loss was more significant in the affective patients than in neurotic ones. Reduced attention was observed in the majority of the examined patients: 82.86% of neurotic patients and 80.65% of affective patients. Sleep disorders were evidenced in 91.43% of neurotic patients and 77.42% of affective patients after COVID-19. Subthreshold insomnia and moderate insomnia were more common in both groups of patients. Their frequency was higher in the patients with neurotic disorders than in those with affective ones. More severe anxiety and depression was observed in the patients, who had COVID-19 in 2021, than in those, who had it in 2020, while severity of insomnia and memory impairment vice versa.

Conflict of Interests
Authors declare no conflict of interest.
Author's Contributions
Olena Venger – conceptualization, methodology, formal analysis, writing – reviewing and editing; *Anna-Maria Koval, Mykola Shved, Tetiana Ivanitska* – data curation, investigation, writing – original draft.

ПОРІВНЯЛЬНА ХАРАКТЕРИСТИКА СИМПТОМІВ У НЕВРОТИЧНИХ ТА АФЕКТИВНИХ ПАЦІЄНТІВ ПІСЛЯ COVID-19

О. Венгер, А. М. Коваль, М. Швед, Т. Іваніцька
ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО, ТЕРНОПІЛЬ, УКРАЇНА

Вступ. *Пандемія COVID-19 негативно вплинула на психічне здоров'я людей і створила нові бар'єри для тих, хто вже страждає на наявні психічні захворювання.*

Мета. *Порівняти симптоми психічних порушень у пацієнтів з невротичними та афективними психічними розладами, які перенесли COVID-19.*

Методи. *Проаналізовано особливості порушень під час пандемії у 35 невротичних і 31 афективних пацієнтів. Було використано: шкалу тривоги та депресії Гамільтона (HAM-A, HAM-D), індекс вираження безсоння (ISI), «Таблиці Шульте», «Дослідження короткотривалої пам'яті за Джекобсоном».*

Результати. *Встановлено, що тривога помірного та тяжкого ступеня частіше розвивається у пацієнтів з невротичними розладами (34,29 % та 37,14% відповідно), а легкого і помірного ступеня – у афективних (38,71% та 32,26% відповідно). Більший рівень вираженості депресії був у невротичних пацієнтів (помірна – у 31,42% осіб, тяжка – у 48,57%), ніж у афективних (переважала легка– у 32,26% та тяжка – у 35,48%). Ступінь зниження пам'яті вищий у афективних пацієнтів (у 51,62% – низька, у 35,48% – дуже низька), ніж у невротичних (у 41,94% – низька, у 20,00% – дуже низька). У більшості обстежених виявлено порушення уваги та безсоння. Частота безсоння більша у пацієнтів із невротичними розладами (у 25,72% осіб – субклінічне, у 45,71% – помірне), ніж в афективних (у 38,71% осіб – субклінічне, у 22,58% – помірне). Вищий рівень тривоги та депресії спостерігався у пацієнтів, які хворіли у 2021, а тяжкість безсоння та порушення пам'яті – у тих, які хворіли у 2020.*

Висновки. *Виявлено тривогу, депресію, безсоння, зниження пам'яті та уваги. Рівень тривоги та депресії більше виражений у невротичних пацієнтів, натомість ступінь зниження пам'яті вищий у афективних пацієнтів. Знижена увага спостерігалася у більшості обстежених пацієнтів із афективними та невротичними психічними розладами.*

КЛЮЧОВІ СЛОВА: **пандемія; психічне здоров'я; депресія; тривога; безсоння.**

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FLUORIDES AND ORAL HEALTH

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Background. *The importance of fluorides in caries prevention is discussed in the article and practical recommendations for the use of fluoride containing products are presented.*

Objectives. *The primary objective of this systematic review is to assess the evidence on the comparative effectiveness of topical fluoride therapy (TFT) in the form of toothpastes, mouth rinses, gels and varnishes in prevention of dental caries in children and adolescents.*

Methods. *A systematic electronic literature search was conducted in the PubMed and Web of Science databases using search terms. Current reports in the literature concerning means and methods of use of fluoride-containing medications are considered.*

Results. *A large number of scientific studies, reviews based on them and meta-analyses conclude that the central element of caries prevention, on which the decrease in caries prevalence and caries experience is based, is the regular topical use of fluoride medications for oral cavity.*

Conclusions. *Topical use of fluorides is a key element in successful caries prevention.*

KEYWORDS: **caries prevention; fluoride; mechanisms of action; fluoride side effects.**

Introduction

Dental caries is the most prevalent chronic disease afflicting a significant proportion of the world population, including around 60% to 90% of school-aged children and the vast majority of adults. Untreated caries causes progressive destruction of the crowns of the teeth, often accompanied by severe pain and suffering, especially in children. Thus, it can result in poorer quality of life and general health [1].

Prevention of caries in children and adolescents is considered a priority for dental services and is more cost-efficient than treatment [2, 3].

Dental caries develops because of demineralization of tooth structure by organic acids formed by oral bacteria present in dental plaque through the anaerobic metabolism of dietary sugars. The causal role of sugars in caries is well established. Most caries lesions in children's permanent teeth progress relatively slowly, with an average lesion taking three years to progress through tooth enamel to dentine [4, 5, 6].

The dental caries process is influenced by the susceptibility of the tooth surface, the bacterial profile, the quantity and quality of saliva and the presence of fluoride, which promotes remineralization and inhibits demineralization of the tooth structure. [7].

The caries process can be affected in several ways. One of the most effective methods to prevent caries is promoting remineralization and slowing down demineralization. This can be accomplished with fluoride therapy [8, 9].

However, it should be emphasized that successful caries prevention is based on the general concept of all caries prevention strategies that have been proven to be effective. In addition to topical fluoride use, this means implementation of adequate oral hygiene to reduce cariogenic biofilm and appropriate diet to reduce the intake of low molecular weight carbohydrates, primarily sucrose.

Review

Mechanisms of action of fluorides on teeth.

Three principal mechanisms by which fluoride is considered to inhibit dental caries have been identified. Fluoride reduces the enamel solubility in acid by pre-eruptive incorporation into the hydroxyapatite crystal. It promotes remineralization and inhibits demineralization of early carious lesions. It inhibits glycolysis, the process by which cariogenic

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bacteria metabolizes fermentable carbohydrates [10].

The hydroxyapatite of tooth enamel is primarily composed of phosphate ions (PO_4^{3-}) and calcium ions (Ca^{2+}). In norm, there is a stable equilibrium between the calcium and phosphate ions in saliva and the crystalline hydroxyapatite that comprises 96 % of tooth enamel. When the pH drops below a critical level (approximately 5.5 for enamel, and 6.2 for dentin), it causes dissolution of tooth mineral (hydroxyapatite) in a process called demineralization. When the natural buffer capacity of saliva elevates pH, the minerals are reincorporated into the tooth through remineralization [12, 13].

Under cariogenic conditions, carbohydrates are converted to acids by bacteria in the plaque biofilm. When the pH drops below 5.5, the biofilm fluid becomes undersaturated with phosphate ion and enamel dissolves to restore balance. When fluoride (F^-) is present, fluorapatite is incorporated into demineralized enamel and subsequent demineralization is inhibited.

When fluoride is present in oral fluids (i.e., saliva), fluorapatite, rather than hydroxyapatite, is formed during the remineralization process. ($Ca_{10}(PO_4)6(OH)_2 \rightarrow Ca_{10}(PO_4)6(F)_2$). Fluoride ions ($F^-$) replace hydroxyl groups (OH^-) in formation of the apatite crystal lattice (Fig. 1). In fact, the presence of fluoride increases the rate of remineralization [11].

Fluoride is available from many sources divided into 3 major categories: tap water (and foods and beverages processed with fluoridated water), home administered, and professionally applied.

Effects of topical fluorides on oral bacteria

In addition to its direct mineralizing effect on enamel, fluoride may affect oral plaque bacteria.

Oral plaque bacteria secrete acids onto tooth surfaces (the byproducts of carbohydrate fermentation), which initiates tooth demineralization. The entry of fluoride into the bacterial cell interferes with acid production, thus reducing, potential enamel destruction. [14, 15, 16].

In addition, fluoride can prevent the attachment of microorganisms to the surface of the tooth. This effect is demonstrated, in particular, by fluorides of tin and amine. This can reduce formation of plaque that contributes to tooth decay.

Streptococci that cause caries bind glucan on tooth enamel surfaces by means of glucan-binding molecules called lectins. Fluoride interferes with this specific binding and thus inhibits bio-film formation by the streptococci that demineralize enamel. The fluoride ion also

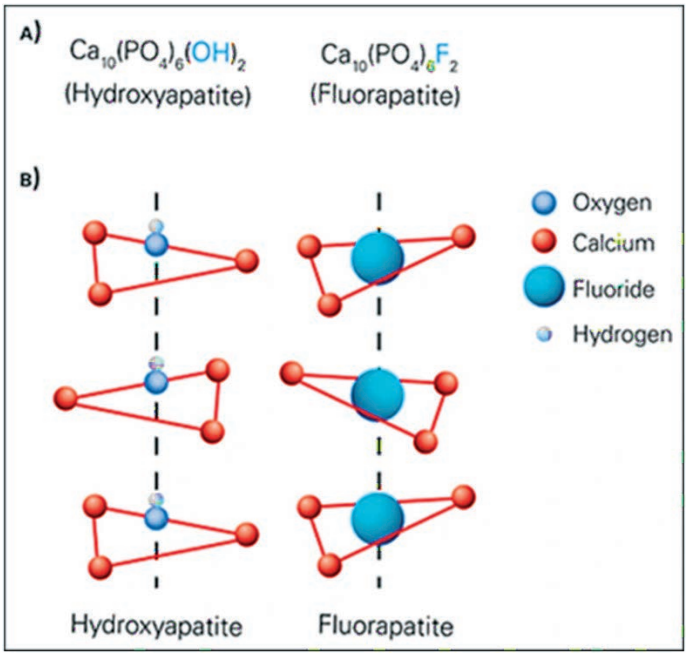

Fig. 1. Fluorapatite formation. (A) Fluoride ions (F^-) replace hydroxyl groups (OH^-) in hydroxyapatite to form fluorapatite in the tooth enamel.
(B) A portion of the apatite crystal lattice shows replacement of hydroxide for fluoride. (Adapted from: Posner, 1985.20).

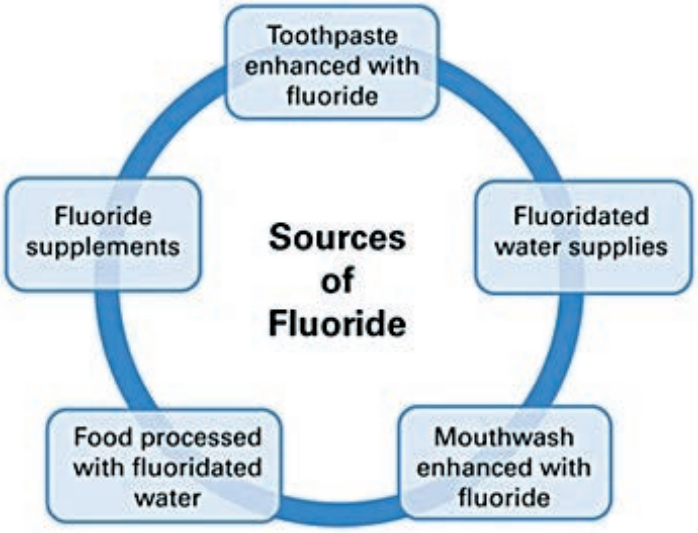

Fig. 2. Sources of fluoride in the environment.

inhibits chain formation (growth) in streptococci and effects physiological capabilities of the micro-organism to metabolize sucrose. However, these effects are manifested only in high fluoride concentrations, making the fluoride an expected process for caries reduction in remineralization [17].

In concentrations of fluoride administered orally via toothpastes or rinses, the clinical effect of inhibiting bacterial metabolism is insufficient to have an appreciable effect on caries development.

Systemic use of fluorides

The correct way to use fluorides is that the body ingests fluorides through the digestive tract and passes them through the gastrointestinal tract. The fluorides are absorbed into the blood circulation and then transferred to the tissues such as teeth and saliva to prevent caries. There are four main methods in the systemic use of fluorides, which are water fluoridation, salt fluoridation, milk fluoridation, and fluoride tablets.

Water Fluoridation. Fluorides are present naturally in all water sources. Community water fluoridation is the process of adjusting the fluoride content of fluoride-deficient water to the recommended level for optimal dental health, which is currently recommended at 0.7 parts fluoride per million parts water. Water fluoridation is an effective and inexpensive means of obtaining the fluoride necessary to prevent tooth decay.

Water fluoridation continues to be effective in reducing tooth decay by 20-40 % in children and adults, even in the era of widespread availability of fluoride from other sources, such as fluoride toothpaste [18, 19, 20].

Table 1 provides some of the fluoride salts that are commonly used for a 'systemic method'.

Local treatment with fluorides

Toothpaste with fluorides

Tooth brushing with fluoride toothpaste is close to an ideal public health method that is convenient, inexpensive, culturally approved, widespread and available [21, 22].

It is scientifically proven and substantiated that fluoride toothpaste has preventive effect of caries for people of all ages.

Table 1. Fluoride compounds and concentrations that are usually used in different 'systemic' fluoride methods (Source: Sampaio & Levy, 2011)

F-methods	F-compounds	F-concentrations
Water fluoridation	Hydrofluorosilicate (FSA), sodium fluorosilicate, sodium fluoride	0.7-1.2 mg/L
Salt fluoridation	Potassium fluoride, sodium fluoride	250-300 mg/kg
Milk fluoridation	Sodium fluoride or disodium monofluorophosphate	5 mg/L
Dietary	F-supplements sodium fluoride, acidulated phosphate fluoride, potassium fluoride, calcium fluoride	0.25-1.0 mg/day

The fluoride concentration of over-the-counter (OTC) toothpaste ranges from 1000 to 1100 mg/kg. This translates into 1 mg of fluoride in a 1-inch (1 g) strip of paste. Therefore, a pea-sized amount of toothpaste containing 1000 to 1100 mg/kg fluoride would have approximately 0.25 mg of fluoride. The use of fluoride toothpaste should begin with the eruption of the first tooth. For children younger than 3 years, the recommended amount is a smear or grain of rice size (approximately 0.1 mg of fluoride) (Table 2) [23].

Table 2. Recommended fluoride toothpastes for children

From Guidelines on the use of fluoride for caries prevention in children: an updated EAPD policy document

Age (years)	(mg/kg F)	Frequency	Amount (g)	Size
First tooth-up to 2 years	1000	Twice daily	0.125	Grain of rice
2-6 years	1000*	Twice daily	0.25	Pea
Over 6 years	1450	Twice daily	0.5–1.0	Up to full length of brush

*Note. *For children, 2-6 years old, 1000+ fluoride concentrations may be considered based on the individual risk of caries.*

Mouthwashes with fluoride

A new strategy developed for toothpastes can also be used to mouthwashes. A new generation of fluoride rinses is expected to contain soluble calcium salts that help retain fluoride in the mouth to release over time. The concept of including soluble calcium in the pre-rinse before a fluoride rinse is proved to increase the amount of fluoride in saliva almost fivefold 1 hour after the rinse compared to a rinse containing NaF at the same fluoride concentration [24, 25, 26].

Over-the-counter (OTC) fluoride rinse provides a lower concentration of sodium fluoride than toothpaste or varnish. The concentration is most commonly 230 mg/kg (0.05% sodium fluoride).

Fluoride varnish is a concentrated topical fluoride applied to the teeth that sets on contact with saliva. Advantages of this modality are that it is well tolerated by infants and young children, has a prolonged therapeutic effect, and can be applied by both dental and nondental health professionals in a variety of settings. The concentration of fluoride in varnish is 22 600 mg/kg (2.26 % fluoride ion), and the active ingredient is sodium fluoride.

There are cogent clinical data that prove anti-caries effectiveness of F-containing varnish. Recent studies have shown that F-containing varnish has long-term effectiveness in preventing caries. [27, 28].

The primary cariostatic effect of F-varnish is caused by the effect of fluoride on the chemical stability of the tooth mineral that converts the enamel to fluorapatite, which is much less susceptible to acid attack than the enamel. For prevention of caries of permanent teeth, it is recommended to use F-containing varnish with an interval of 6 months. For children not at risk of caries, F-varnish may not be useful; however, the risks of therapy are low and the benefits outweigh the risks [29].

Fluoride varnishes are not only effective from the point of view of primary prevention of caries development, but also have a positive effect in terms of secondary prevention in cases of already existing initial caries. At this point, regular use of fluoride varnish combined with regular oral hygiene can often stop caries (preventing further mineral loss) [30].

Side effects of Fluorides

Excessive exposure to Fluorides is associated with a number of health issues:

– Dental fluorosis.
– Skeletal fluorosis.
– Thyroid problems.
– Neurological problems.
– Other health problems.
– Fluoride poisoning.

There is a distinction between acute and chronic effects (Fig. 3).

Acute toxic effect as a result of swallowing a large amount of fluorine-containing oral care products, as well as by children, may cause at least a temporary manifestation of dizziness and nausea.

Infants and preschool children may suffer from enamel fluorosis, the risk of which increases with increased constant fluoride intake. Fluorosis can develop only at the stage of enamel formation; in other age groups, this side effect from the use of fluoride is nor provoked.

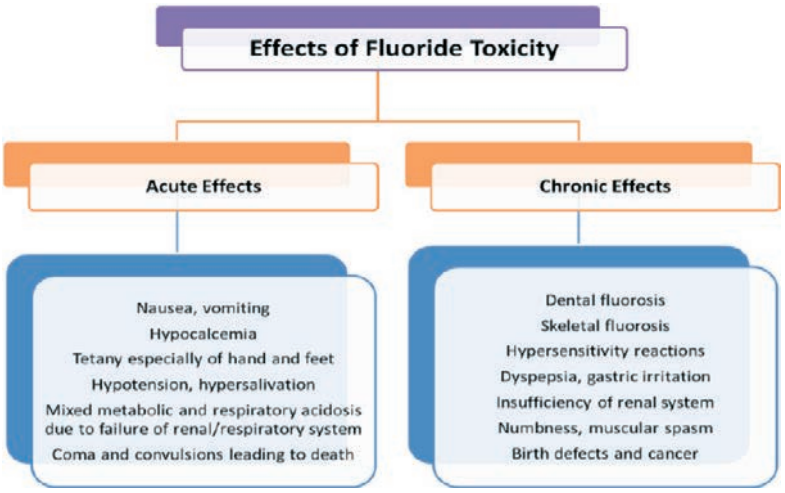

Fig. 3. Effects of fluoride toxicity.

Conclusions

Fluorides are regarded as effective materials for control of dental caries which can benefit both prevention and treatment. Topical application of fluorides is a key element in successful caries prevention.

Conflict of Interests

Authors declare no conflict of interest.

Authors' Contributions

Svitlana Boitsaniuk – investigation, formal analysis, writing – original draft; *Mariana Levkiv* – formal analysis, writing – reviewing and editing, data curation.

ФТОРИДИ І ЗДОРОВ'Я ПОРОЖНИНИ РОТА

С. І. Бойцанюк, *М. О. Левків

ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ, ТЕРНОПІЛЬ, УКРАЇНА.

Вступ. *У статті обговорюється важливість застосування фтору для профілактики карієсу та представлені практичні рекомендації щодо застосування препаратів фтору.*

Мета. *Основною метою цього систематичного огляду є оцінка доказів щодо порівняльної ефективності місцевої фторотерапії (МФП) у вигляді зубних паст, ополіскувачів, гелів та лаків у профілактиці карієсу зубів у дітей та підлітків.*

Методи. *Здійснено систематичний електронний пошук літератури в базах даних PubMed та Web of Science за пошуковими термінами. Розглянуто поточні повідомлення в літературі, які стосуються засобів та методів застосування фторвмісних препаратів.*

Результат. *Велика кількість наукових досліджень, оглядів на їх основі та метааналізів приходять до висновку, що центральним елементом профілактики карієсу, на якому ґрунтується це зниження поширеності карієсу та досвіду розвитку карієсу, є регулярне місцеве застосування препаратів фтору в порожнині рота.*

Висновок. *Місцеве застосування фторидів є ключовим елементом успішної профілактики карієсу.*

КЛЮЧОВІ СЛОВА: **профілактика карієсу; фтор; механізм дії; побічні ефекти фтору.**

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COMMUNICATION OF ONCOLOGICAL PATIENTS WITH ONCOLOGISTS: MAIN PROBLEMS AND PROBLEM-SOLVING STRATEGIES

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Background. *Physician-patient communication is one of the main supportive care provided to oncological patients. It affects treatment outcomes, as well as the interaction of patients within the society, their family and colleagues. Furthermore, COVID-19 and military invasion of Russia into Ukraine makes the issue of improvement of physician-patient communication urgent.*

Objective. *The aim of the study is to develop recommendations based on the analysis of denfined problems in physician-patient communication in of oncological treatment.*

Methods. *The sociological research involved 419 patients during their inpatient treatment in the period from November 2021 to February 2022 using the EORTC QLQ-COMU26 questionnaire.*

Results. *In the pre-war period, in Ukrainian patients with oncological diseases the worst indicators were established for "Active role of a patient" (82.00) and "Correction of misunderstandings by a specialist" (89.19). The best indicators were established for "Skills of the specialist (verbal/non-verbal)" with the score of 93.25 by a 100-point grading scale, as well as "Satisfaction with communication" – 97.04 by a 100-point grading scale.*

Conclusions. *When developing programs for organization of oncological care, mechanisms for providing psychological care to patients through effective communication between patients and specialists regarding providing medical and psychological care must be taken into account.*

KEY WORDS: **communication; quality of life; cancer.**

Introduction

Physician-patient communication is one of the main aspects of care provided to oncological patients. A number of studies have shown that communication focused on a patient can influence patient's satisfaction, decision-making, well-being, compliance with treatment of oncological diseases [1].

Communication focused on a patient is a cornerstone of a high-quality care [2]. Proper communication allows physician to respond better to the patients' needs regarding information and support. For this purpose, recommendations for improving the communication skills of medical workers are available in many countries [3]. The effective physician-patient communication may reduce the anxiety, keep hope [4], and increase satisfaction from communication in patients [5]. Communication focused on a patient has also been developed in order to improve communication skills training of a physician [6]. These measures are aimed at involving a patient into counseling and thus increasing awareness of a physician and timely taking into account patients' expec_ tations.

The present circumstances should also be taken into account. The global crisis caused by COVID-19 outbreak in 2019 has led to unexpected and difficult situations [7]. Physical barriers and non-visitation policy had a significant impact on communication in a hospital settings. Physicians need new strategies to keep in touch with patients and their families/relatives [8, 9]. In the era of COVID-19, in order to solve the challenges for effective physician-patient communication for oncological patients, when physical distancing is required, different solutions have been suggested, particularly, video calls were introduced by using smartphones and tablets [10].

Thousands of oncological patients have suffered in connection with the war in Ukraine, as they lost the opportunity to receive treatment and were left alone with their disease. The necessary medicines are difficult to get, chemotherapy and radiotherapy are carried out irregularly, physicians are often out of the telephone reach. Moreover, cancer patients face psycho-

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logical problems – uncertainty and the inability to plan and control their lives. Most of them have complex depressive, anxiety-depressive and phobic symptoms. Excessively expressed negative emotions (depression, anxiety, phobias) can cause suicidal thoughts in such patients.

The oncologist-patient communication is especially difficult when it comes to information about prognosis and treatment outcomes, which is essential for achieving a shared understanding of disease state and treatment goal between patients and oncologists [11, 12]. The oncologists have frequent difficulties in assessing the patients' information preferences [13]. In patients with advanced cancer, the prognosis information is often missing [14], and patients do not understand that the treatment provided will unlikely cure their oncological diseases [15].

The aim of the study is to develop recommendations based on the analysis of identified problems in physician-patient communication in patients with oncological diseases during treatment.

Methods

The sociological research was perfomed by surveying 419 patients during their inpatient treatment. The required number of participants was calculated according to the Glen's method, and involved 398 individuals. Taking into account the possibility of elimination (10%), 440 questionnaires were sent proportionally to different regions of Ukraine (Northern, Southern, Western, Eastern, Central); 419 questionnaires were received back.

The inclusion criteria were the patients hospitalized with a histologically confirmed cancer diagnosis and received inpatient treatment. Exclusion criteria were lack of written consent to participate in the study.

The research was carried out at oncological institutions in nine regions of Ukraine: Chernihiv, Zaporizhzhia, Dnipropetrovsk, Kyiv, Poltava, Khmelnytskyi, Ivano-Frankivsk, Zakarpattia and Lviv regions. The primary data collection was performed from November 2021 till February 2022. all the patients gave written consents to participate in the trial. The average age of patients who participated in the trial was 59.62±10.33 years old.

The research was conducted according to the unified protocol providing for the use of questionnaires which were designed by the European Organisation for Research and Treatment of Cancer (EORTC). The questionnaire included 26 questions regarding communication of oncological patients with their health workers.

The EORTC-QLQ-COMU26 module was composed of six scales and four separate issues [16, 17, 20].

The following scales are involved in the EORTC-QLQ-COMU26: the ability of the specialist to manage patient's emotions (EMOT), the "specialist-patient" relationships (RELAT), the ability of the specialist to build relationships (QUAL), the active role of the patient (ACT), the skills of the specialist (verbal/non-verbal) (SKILL), the information skills of the specialist (INFO).

The additional issues of EORTC-QLQ-COMU26 are the following: correction of misunderstandings by the specialist (MISUN), sufficient privacy (PRIVA), taking into account patient's preferences (PREF), satisfaction with communication (SATIS).

The permission to use this questionnaire from "EORTC Quality of Life Group" was received in November 2021.

The calculations were carried out according to the EORTC QLQ-COMU26 methodology [16, 17]. The results were calculated according to unified scales or individual indicators. Average score (Raw Score – RS) was presented as M±SD. Besides, all scales and individual indicators of EORTC QLQ-COMU26 questionnaire were calculated by a 100-point grading scale (SS) for easier interpretation according to the formula:

$$SS = ((RS-1)/range)\cdot 100$$

Where RS – raw score, range – scale range which is determined by the difference between the maximum and minimum values of the scale. The low raw score and high score by a 100-point grading scale testified to high quality of communication with a specialist. For scales that consist of 2 or more questions, Cronbach's alpha was calculated as an indicator of scale consistency.

Results

According to the findings of QLQ-COMU26 questionnaire in the patients with oncological diseases, the worst indicators were established for the "Active role of the patient" scale. The score was 82.00 by a 100-point grading scale (Table 1), RS was 3.46±0.82 (Fig. 1). This scale involved questions about sufficient opportunities to communicate with a specialist (physician), opportunity to ask questions freely, opportunity to show emotions.

Table 1. Results of questionnaire of different QLQ-COMU26 scales in oncological patients

Scale issue	Directory code	Score by a 100-point scale	Cronbach's Alpha
Active role of the patient	ACT	82.00	0.63
Information skills of the specialist	INFO	90.75	0.83
Ability of the specialist to manage the patient's emotions	EMOT	91.75	0.64
Specialist-patient relationships	RELAT	91.94	0.66
Ability of the specialist to build relationships	QUAL	93.19	0.78
Skills of the specialist (verbal/non-verbal)	SKILL	93.25	0.67

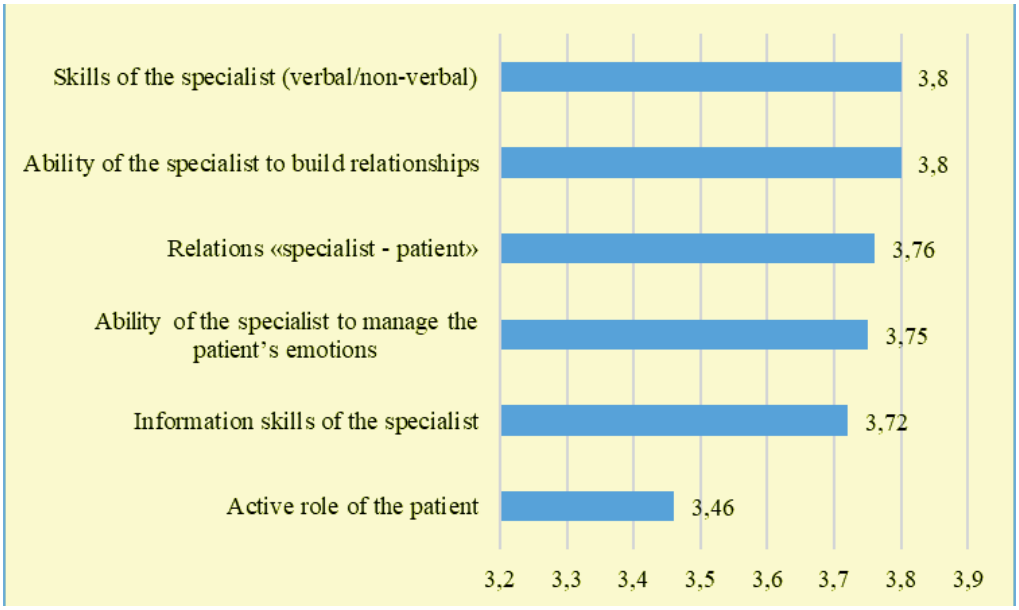

Fig. 1. Raw score of different QLQ-COMU26 scales in oncological patients.

According to the findings of the QLQ-COMU26 questionnaire, a better result was established for the scale of "Information skills of the specialist", where the score was 90.75 a 100-point grading scale. The following questions were included in this scale: whether the specialist was convinced that a patient understood all about the disease before providing any new information, whether the physician specified understanding by a patient the information provided. It is quite natural that the patients with oncological diseases are often worried about their future. Thus, in the scope of this scale, the patients were asked about the specialists' exhaustive replies to difficult questions, as well as whether these answers satisfied the patients. Generally, the sense of completeness of specialists' answers, their explanations are very important, which is also discussed in this scale.

Fewer difficulties happened in the physician-patient communication in the "Ability of the specialist to manage the patient's emotions" scale, where the score was 91.75 by a 100-point grading scale. A cancer patient badly needs support from their family, friends, relatives, but the effort of specialist to understand the current situation of a patient is certainly important as well. In this scale there were questions regarding the specialist's help to master patient's emotions, for example: sadness, anger, fear, anxiety, etc., and also the ability to listen when the patient demonstrated his/her emotions.

The better result was obtained in the scale "Specialist-patient relationships", where the score was 91.94 by a 100-point grading scale. This scale involved questions whether the specialist had spent enough time to communicate, whether there was a mutual trust between the patient and specialist, whether the patient felt that they and the physician had the common understanding of the disease and its treatment.

The highest scores characterized the ability of the specialist to establish the relatioships with the patient. This issue was 93.19 by a 100-point grading scale. This scale described the attitude of the specialist to the patient: whether the physician treated the patient with respect, as an equal, whether the physician showed sincerity, whether it was easy and open to discuss the troubling problems of the patient, whether the physician took them seriously.

The best indicators of the QLQ-COMU26 questionnaire were established for the "Skills of the specialist (verbal/non-verbal)" scale, where the score was 93.25 by a 100-point grading scale. This scale included the following questions: did the specialist use the language understandable to the patient (avoiding medical terminology, using understandable terms), did the specialist openly answer the patient's questions, did the specialist look at the patient during their conversation, did the specialist speak in a calm voice.

It should be mentioned that in the QLQ-COMU26 questionnaire in patients with oncological diseases, the respondents' answers were of the same type in the "Ability of the specialist to build relationships" and "Information skills of the specialist" scales, which was shown by sufficient and high consistency, determined by Cronbach's alpha within 0.78–0.83. For the rest of the indicators, Cronbach's alpha was in the range of 0.63–0.67.

According to the findings of QLQ-COMU26 questionnaire regarding the individual indicators, in the oncological patients the worst indicators were in the "Correction of misunderstandings by a specialist" scale. The score was 89.19 by a 100-point grading scale (Table 2), the raw score was 3.68±0.54 (Fig. 2). This indicator included questions regarding whether the specialist explained again in another way the information which the patient had not understand. This indicates the problem of the physician-patient communication in this scale. One of the probable causes of such misunderstandings may be lack of time allocated per patient, vulnerable emotional state of the patient with a potentially fatal disease, and, in

Table 2. Results of the QLQ-COMU26 questionnaire regarding the individual indicators of oncological patients

Indicators	Directory code	Score by a 100-point scale
Correction of misunderstandings by a specialist	MISUN	89.19
Taking into account the wishes of the patient	PREF	89.62
Sufficient privacy	PRIVA	93.08
Satisfaction from communication	SATIS	97.04

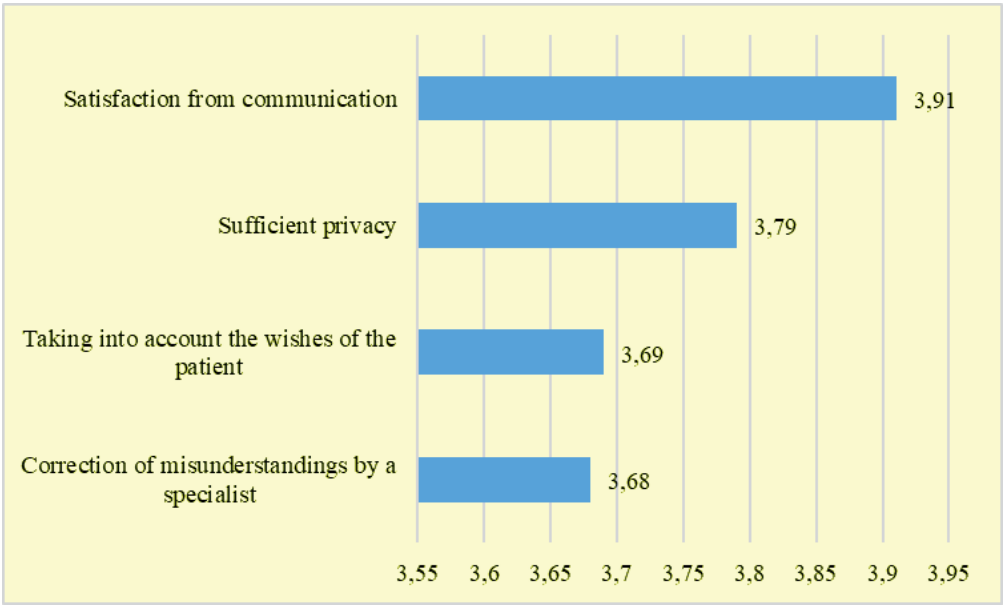

Fig. 2. Average score of individual indicators by QLQ-COMU26 in oncological patients.

the majority of cases, lack of medical literacy to comprehend information, which is difficult for understanding.

The indicator "Taking into account the wishes of the patient" was found to be practically comparable. The score was 89.62 by a 100-point grading scale. For this indicator, the patient was asked whether the specialist took into account the method of obtaining information preferred by the patient.

Slightly better results were established for the indicator "Sufficient privacy". The score was 93.08 by a 100-point grading scale. This indicator included the questions concerning sufficient privacy of the confidential conversation between the patient and specialist.

The best QLQ-COMU26 questionnaire results regarding the individual indicators in oncological patients were established for the issue "Satisfaction from communication", which was 97.04 by a 100-point grading scale.

Discussion

Communication is one of the most important tasks in the professional practice of a clinician, especially for those who deal with the life-threatening diseases. In this case, effective dialogue can be quite challenging, however, clinicians face this daily. In recent decades, clinical communication has been studied a lot, and, several structured approaches have been developed and suggested [8, 18, 19].

Patients with advanced oncological diseases often forget their questions during consultation with a physician, they doubt the legality of the request, indirectly express concern, feel fear of a possibly humiliating answer and physicians do not often encourage them to ask questions [21-23]. Patients may also have different needs and expectations, depending on time of the course of the disease [13, 24, 25]. Discrepancy between the perceptions of the patient and oncologist regarding the goals of treatment, duration of disease treatment can lead to medical decisions that do not meet the life goals which are very important for the patients [26]. It leads to even greater psychological stress in patients [27].

According to the findings of the QLQ-COMU26 questionnaire for the oncological patients, the worst indicators were established for the "Active role of the patient" scale. The score was 82.00 by a 100-point grading scale which was less than the results attained by the German colleagues, where this issue was 85.0 [1]. A possible reason for a low activity of patients could be their self-absorbedness: patients are not able to talk about their problems freely, ask questions about everything concerning them or those they don't completely understand.

The least difficulties for the Ukrainian patients were caused by the scales with nearly comparable indicators for the "Ability of the specialist to build relationships" (93.19 points) and the "Skills of the specialist (verbal/non-verbal)" (93.25 points). These results are higher than the results obtained by the German colleagues: the score of the "Ability of the specialist to build relationships" scale was 89.6 points, while the score of the "Skills of the specialist (verbal/non-verbal)" was 90.3 points [1]. Generally, the European patients need more sincerity and ease, openness in discussing problems during the physician-patient communication.

It should be taken into account that if before COVID-19 the "physicians-patient" consultations were held in person at prearranged time, during the SARS-CoV-2 pandemic communication often took place usually over the phone. In this unprecedented situation often one-way communication cause a feeling of uncertainty and suffering in those who stay at home and have to wait for news [28]. It should be noted that relatives of the seriously ill patients already have the increased risk of anxiety, depression or post-traumatic stress disorder [29]. Moreover, the loss of non-verbal signals, such as eye contact and gestures complicate communication and formation of empathy between the communication provider and the patient. Thus, the uncertainty and experiencing psychological problems by patients make communication between cancer patients and physicians difficult.

According to the findings of the QLQ-COMU26 questionnaire regarding the individual indicators in oncological patients, the worst results were established for the "Correction of misunderstandings by a specialist" indicators. The score was 89.19 by a 100-point grading scale that was less than the results attained by the German colleagues, where this issue was 84.8 [1].

The best indicators for the Ukrainian patients with oncological diseases in the QLQ-COMU26 questionnaire regarding the individual indicators were established for the "Satisfaction with communication" issue, which was 97.04 that was significantly higher compared to the data of the German colleagues, where the indicator was 84.3 [1].

An interesting and important fact should be taken into account for providing high-quality medical care is that communication with critically ill patients is often three-way, rather than two-way involving not only the specialist and the patient but also family members who are often the main support, an important part of the medical team and the component of communication for the health of their relatives. A high level of depression and burden on the caregiver was registered among the patients and relatives of the hospitalised oncological patients [8, 30]. Therefore, targeted intervention in the field of physician-patient communication can improve the quality of life for both patients and their families.

Family and friends can be a great support for an oncological patient. The patient can rely on a family member or a trusted friend in a similar situation for help, for example asking to accompany them to visit a physician. The presence of a supportive person is a reminder that the cancer patient is not alone and it can help them take the initiative to communicate.

Generally, the inappropriate communication leads to unsatisfied patient needs for information and support. Understanding how to improve the physician-patient communication is important for all involved into patient care.

Conclusion

The physician-patient communication is one of the main aspects of support provided to oncological patients. Effective communication of the physician and patient may reduce patient's anxiety, keep hope, increase satisfaction from communication. In today's COVID-19 pandemic, physical barriers and no family visitation policy for patients have significantly affected the physician-patient communication for patients with oncological diseases in the hospital settings, and physicians need new strategies in order to keep contact with the patients.

According to the findings of the QLQ-COMU26 questionnaire for the Ukrainian oncological patients, the worst indicators were established for the "Active role of the patient" scale, its score was 82.00, which was less then the results obtained by the German colleagues (85.0). The best indicators in this questionnaire were established for the issue "Skills of the specialist (verbal/non-verbal)", the score was 93.25 by a 100-point grading scale. According to the findings of the QLQ-COMU26 questionnaire regarding the individual issues, the worst indicators were established for the "Correction of misunderstandings by a specialist" scale. The score was 89.19 by a 100-point grading scale, which was higher the results obtained by the German colleagues (84.8 points). The best results of this questionnaire were established for the "Satisfaction with communication" scale – 97.04 by a 100-point grading scale, which was significantly higher compared to the data of the German colleagues, where the indicator was 84.3.

According to the findings of the QLQ-COMU26 questionnaire, in Ukrainian oncological patients in the pre-war period the worst indicators were established for the issues of "Active role of the patient" and "Correction of misunderstandings by a specialist".

Thus, to provide a high-quality medical care it should be taken into account that communication with critically ill patients is often three-way rather than two-way, where not only the specialist and the patient are involved, but family members, who are often the main support, an important part of the medical team and a significant component of communication for their relatives. When developing programs for organization of oncological care, mechanisms for providing psychological care to these patients through effective communication between patients and specialists regarding providing medical and psychological care should be taken into account.

During the Russia's military invasion of Ukraine, many oncological patients had to go abroad in order to receive specialized treatment. Thus, this information can be used for better communication of the foreign physicians with the Ukrainian patients.

Conflict of Interests

Authors declare no conflict of interest.

Author's Contributions

Valeriy Zub – conceptualization, methodology, formal analysis, writing – original draft, writing – reviewing and editing; *Andrii Kotuza* – conceptualization, methodology, investigation, writing – reviewing and editing; *Oleksandr Tolstanov* – conceptualization, methodology, data curation, writing – reviewing and editing.

КОМУНІКАЦІЯ ОНКОЛОГІЧНО ХВОРИХ ПАЦІЄНТІВ З ЛІКАРЯМИ-ОНКОЛОГАМИ: ОСНОВНІ ПРОБЛЕМИ ТА СТРАТЕГІЇ ЇХ ВИРІШЕННЯ

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1 – НАЦІОНАЛЬНИЙ УНІВЕРСИТЕТ ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ ІМЕНІ П. Л. ШУПИКА, КИЇВ, УКРАЇНА
2 – КЛІНІЧНА ЛІКАРНЯ «ФЕОФАНІЯ» ДЕРЖАВНОГО УПРАВЛІННЯ СПРАВАМИ, КИЇВ, УКРАЇНА

Вступ. *Комунікація "лікар-пацієнт" є одним з основних аспектів підтримки, яка надається хворим на онкологічні захворювання. Вона впливає на результати лікування, а також на взаємодію пацієнтів у суспільстві, з родиною та колегами. Крім того, поширення коронавірусної хвороби COVID-19 та військове вторгнення Росії в Україну зумовлюють необхідність покращення комунікації між лікарем та пацієнтом.*

Мета. *Мета роботи – розробка рекомендацій на основі аналізу виявлених проблем в комунікації "лікар-пацієнт" у хворих на онкологічні захворювання під час лікування.*

Методи. *Соціологічне дослідження проведено за участі 419 пацієнтів, на етапі їхнього стаціонарного лікування, в період з листопада 2021 року по лютий 2022 року з використанням опитувальника EORTC QLQ-COMU26*

Результати. *В українських пацієнтів з онкологічними захворюваннями, у довоєнний період, найгірші показники припали на шкали «Активна роль пацієнта (82.00) та "Корегування фахівцем непорозумінь" (89.19). Найкращі дані встановлено для пункту "Навички фахівця (вербальні-невербальні)", на який припало 93.25 балів за 100-бальною шкалою та "Задоволення від комунікації" – який склав 97.04 балів за 100- бальною шкалою.*

Висновки. *При опрацюванні програм щодо організації онкологічної допомоги повинен бути врахований механізм щодо забезпечення надання психологічної допомоги пацієнтам шляхом ефективної комунікації між пацієнтами та спеціалістами з надання медичної та психологічної допомоги.*

КЛЮЧОВІ СЛОВА: **комунікація; якість життя; онкологія.**

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