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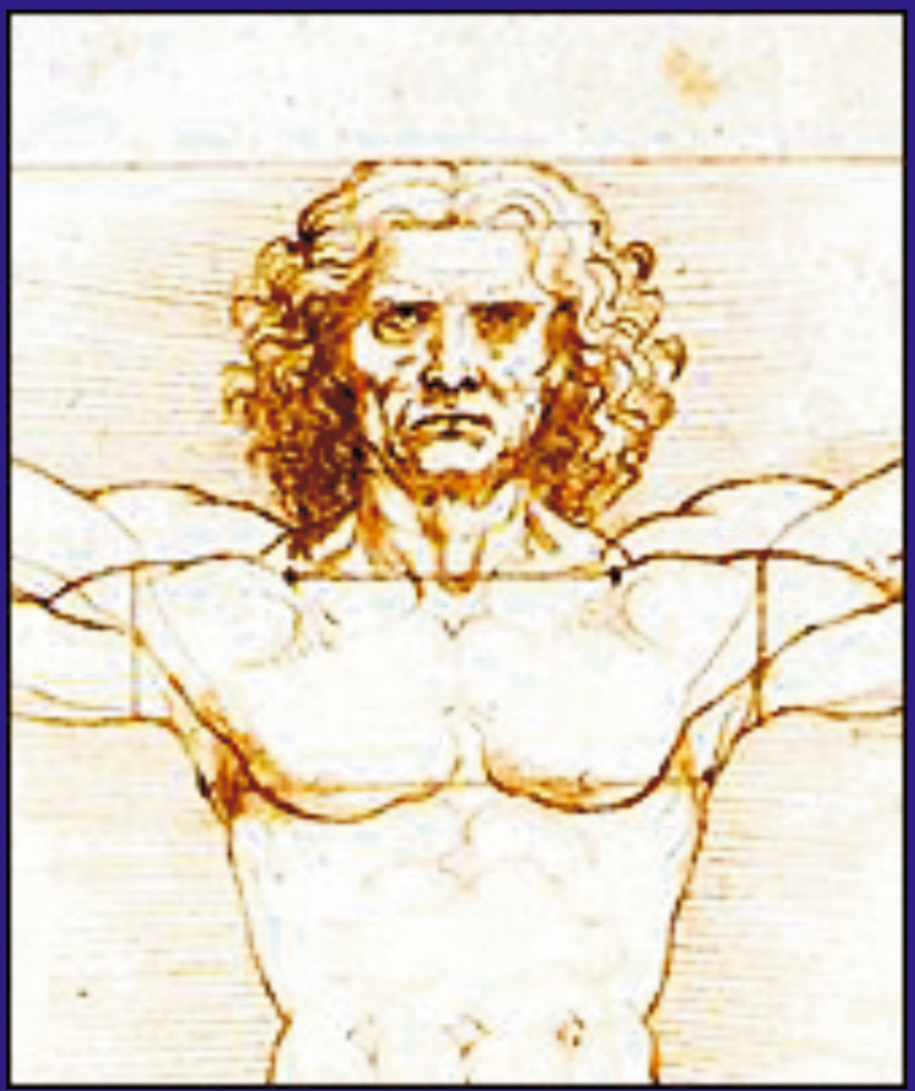

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Letter to editor

THE OPIUM BAN IN AFGHANISTAN AND ITS POSSIBLE CONSEQUENCES FOR THE DRUG MARKET

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Dear Editor,

In this letter, we would like to point out a threatening public health problem and its connection with socio-political processes to the professional public.

According to the United Nations Office on Drugs and Crime (UNODC), opium cultivation in Afghanistan decreased by 95% in 2023 compared to the previous year after the country's de facto authorities imposed a ban on the production, trade, and usage of all drugs on April 3, 2022, including synthetic and semi-synthetic (1). Figure 1 shows the trend of poppy area and opium production annually from 1985 to 2023 (1). According to UNODC data, the area under poppy cultivation plummeted from 233,000 hectares in 2022 to a mere 10,800 hectares in 2023 (1). Notably, the majority of land once dedicated to poppy cultivation is now being utilized for less profitable crops like wheat (1). Most of the remaining poppy fields are located in the province of Kandahar (1). The initial impact of this ban suggests that it could potentially be regarded as one of the most successful anti-drug efforts in modern history.

In his book published by Harvard University Press, Pierre-Arnaud Chouv explained in detail the genesis of the growth of opium production in areas under the rule of the anti-Soviet Mujahideen parties (2). Under the slogan of helping freedom fighters, the intelligence services of the United States and Pakistan were, if not directly, then indirectly involved in the growth of opium production (2).

Claims dating back to the turn of the century that the Taliban were linked to the opium trade proved to be false (3). Since their initial rise to power, the Taliban have maintained a staunchly anti-drug stance (3). The UNODC stands out as one of the few international bodies to collaborate with the de facto authorities in Afghanistan, sharing a mutual commitment to combatting drug trafficking. In 2000, the leader of the Taliban, Mullah Omar, issued a fatwa that poppy cultivation and opium production were against Islamic tradition and, therefore, prohibited in Afghanistan. Local authorities enforced this fatwa, often with brutal efficiency (3). Punishments for violators included imprisonment for up to two years, public floggings, or humiliation in public. Only the northern provinces that were not under the control of the authorities from Kabul during that time increased opium production (3). Merely two months after the fatwa was issued, the UNODC suddenly and without prior notice suspended all activities in Afghanistan, leaving the Taliban regime without any support despite previous cooperation (3). Despite a significant 99% drop in Afghanistan's exports, followed by a 65% drop in world production of opium and heroin in 2001, this measure was neither economically nor politically sustainable (4). Shortly after, the invasion by the United States and its allies exacerbated the country's plight, leading to further destruction and a resurgence in opium production. When Western-backed factions assumed power, billions of dollars were invested in reshaping Afghanistan's governance and agriculture. However, these efforts fell short of expectations, as the profitability of growing poppy outweighed that of other crops (5, 6).

As the production of opium grew, so did the manufacturing of other illicit drugs. Thus, in the second half of the second decade of the 20th century, Afghanistan became the fastest-growing producer of methamphetamine (7). In Afghanistan and its neighboring nations, law enforcement agencies seized nearly 30 tons of methamphetamine in 2021 alone, a stark contrast to the mere three tons seized just four years prior (8). In Afghanistan itself, an increase from 100 kilograms in 2019 to 2,700 kilograms in 2021 was recorded (8). The mass cultivation of Ephedra, from which ephedrine is

directly obtained, has brought down the cost of production to a tenth of that of Southeast Asian producers, making Afghan methamphetamine more competitive with Myanmar's (7).

Opium production represented a crucial economic sector in Afghanistan, contributing to 9-14% of the country's GDP, given its predominantly agrarian economy (1). The decline in production has already yielded adverse economic ramifications at both macro and micro levels (1). There was a drop in Afghanistan's GDP by a fifth in 2022 compared to the year before (9). On a micro level, the reduction in income will economically jeopardize the 15% of the Afghan population involved in illegal trade, putting them in a difficult economic situation (1). The most vulnerable are the poorest communities in Afghanistan, Pakistan, and the surrounding countries through which opium was exported and in which the entire opium ecosystem was built.

The de facto Taliban authorities in Afghanistan are left to their own devices in this endeavor because they are left without official financial aid from other states, banks, or development agencies, with frozen funds from their central bank in the United States, receiving only limited humanitarian aid through the United Nations (9). Concerns about an impending humanitarian crisis have been voiced. Despite these challenges, even American political analysts had to admit that the new regime coped surprisingly well with economic problems (9).

The possible consequences will depend on the Taliban authorities' persistence in this ban. The Taliban must take care not only of the implementation of the decision but also of the stability of their government. Economic problems may contribute to strengthening opposition local leaders, remnants of the Northern Alliance, or the Islamic Republic (5). Suppose the Taliban regime maintains its power and continues implementing the ban, the first effects on the international market can be expected during 2024, once most of the stocks from previous seasons are depleted (10). The drop in the purity of heroin would be the first indication of the effectiveness of the ban (3). For comparison, after the first ban in Estonia, the purity of heroin decreased from 58% in 2000 to only 7% in 2002 (11). Only after the decline in the quality of heroin, one could expect a rise in the price of heroin and other drugs, as well as the spread of harmful alternatives such as fentanyl and other synthetic and semi-synthetic products (1). An escalation in injection frequency could emerge as one of the consequences (3). A greater need for treatment among individuals struggling with substance abuse can also be expected (10). Opium users within Afghanistan, estimated to comprise one-tenth of the population, are projected to be the first affected by these changes. Subsequently, the repercussions will extend to neighboring countries like Pakistan and Iran, followed by former Soviet Union nations, and eventually, Europe. Heroin is the most commonly used opioid in Europe and the drug associated with the highest health burden (10).

It is difficult to predict whether there will be a decline in drug use, even if prohibitions last for years (9). Furthermore, opium production may increase in other countries, such as Myanmar, India, Iran, Central Asian countries, or even further, Mexico and Colombia. If the economic situation in Afghanistan does not improve, a new mass wave of migration of the predominantly rural, young, male population to Europe can be expected (10).

Of these potential consequences, the fentanyl threat is particularly perilous. Synthetic opioids (primarily fentanyl) accounted for over 70,000 deaths in the US in 2021, continuing an upward trend from previous years (12). This rise is especially pronounced among men (12). Fentanyl became widespread in Europe, first in the Baltic states, especially in Estonia, which for almost a decade had the highest drug-related mortality in Europe (11). In Estonia, the popularity of fentanyl surged in 2003, swiftly replacing heroin in the opioid market within a year (11). There is a hypothesis that the increase in the use of fentanyl was caused by the first Taliban ban in 2000 (11). Paradoxically but justifiably, warnings from European Union agencies underscore that the high availability of heroin serves as a deterrent against the proliferation of more hazardous synthetic drugs (13).

Fentanyl functions as an agonist of opioid receptors and is between 50 and 100 times more potent than morphine, in contrast to heroin, which is only 2-5 times more potent than morphine (14). It is used in general and local anesthesia and serves as an effective medicine for chronic, severe pain (15). Being lipophilic, it easily crosses the blood-brain barrier. Fentanyl has a shorter duration of action (half to a third of the action time of heroin), thus requiring more frequent administration, which is associated with HIV and viral hepatitis spreading among users who share injection equipment (11). Fentanyl carries a high risk of fatal overdose in a very short period, a few minutes after injection, much faster than is the case with heroin. The uneven purity of the illegally prepared formulations is an additional risk for death. Fentanyl is 100 times cheaper than heroin when corrected for potency (14). It is added to heroin and sold as heroin and at the price of heroin. That's why it has the name "artificial heroin" (15). It does not require outdoor cultivation but only an improvised laboratory

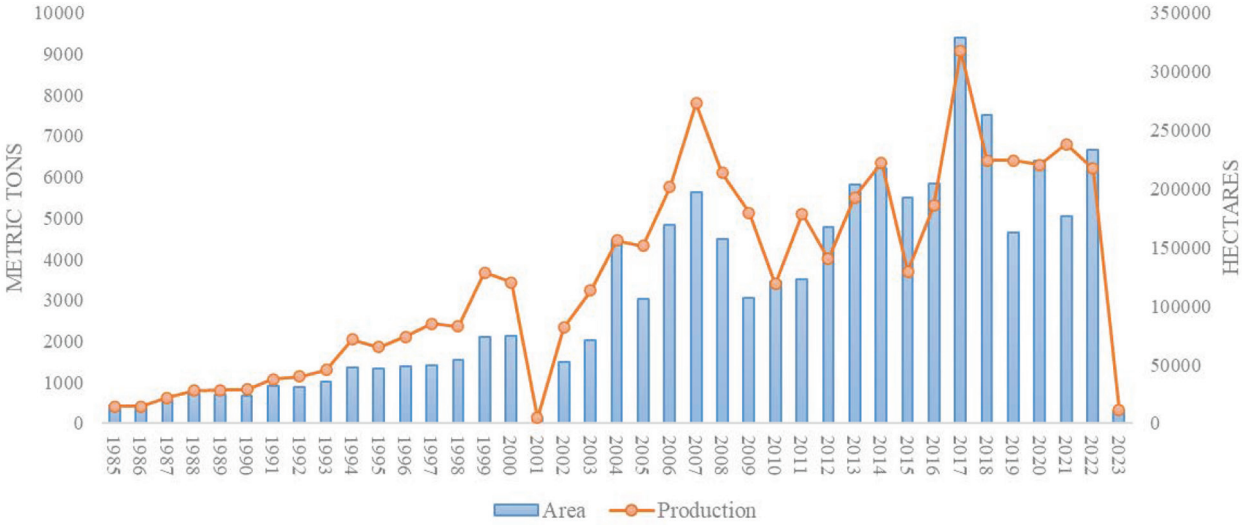

Figure 1. *Annual opium production in metric tons and the area under poppy in hectares in Afghanistan*

(14). Smuggling is easier because of the possibility of transportation in small quantities and the similarity with permitted preparations. To avoid the disastrous effects that the fentanyl epidemic might cause before its appearance on the market, it is necessary to: *a*) Increase the availability of naloxone and educate health professionals and the community about the characteristics of fentanyl and the dangers of its use, *b)* Strengthen low-threshold services, *c)* Prevent the transition of psychoactive substance users to injecting drug use, *d)* Strengthen monitoring of other psychoactive substances and prevent their spread, *e)* Preserve the role of primary health care in prescribing prescription drugs and *f)* Treat the causes of chronic pain whenever it is possible (11). The achievement of these goals requires intersectoral cooperation within and between countries. An integral part of these international efforts is strengthening the surveillance system, which should be more sensitive and based on primary data (15).

Dear Editor, thank you for your attention to this health threat. The consequences of this threat can be mitigated by warning the community and inviting professional bodies to engage in this issue.

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RISK ASSESSMENT IN CORRELATION WITH OBESITY AND LABORATORY MONITORING OF THE MOST COMMON FEMALE BREAST CANCERS IN SARAJEVO CANTON

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Abstract: **Introduction:** Breast cancer (BC) is a malignant disease that predominantly affects women, with known genetic components such as mutations in tumor suppressor genes BRCA1 and BRCA2. Other risk factors include unhealthy lifestyles, lack of physical activity, and consumption of alcohol and cigarettes. Aging also plays a role in BC development, with hormonal influences such as estrogen and progesterone promoting cancer growth.

Material and Methods: Research was conducted using data collection tools for risk factors and tumor markers from primary healthcare unit records. The sample comprised 200 women, divided into two groups based on BC diagnosis, with complete medical documentation. Male BC cases were excluded.

Results: Statistical significance was found between genetic components, family history, aging, obesity, alcohol and cigarette consumption, longer hormone exposure, and female BC development using the Chi-Square test, confirmed by Fisher's Exact test. Tumor markers CA 15-3, CEA, CA 19-9, and CA 125 were useful for BC screening and metastasis detection, as determined by the One Sample T-test. In Sarajevo Canton, invasive ductal BC was the most common type among women, while lobular carcinoma in situ was the least common.

Conclusion: Correlations between risk factors, including aging, unhealthy lifestyles, and hormone exposure, and increased BC risk were confirmed. Tumor markers CA 15-3, CEA, CA 19-9, and CA 125 were effective in diagnosis, screening, and metastasis detection in females, with sensitivity for regression detection at 81.8% and specificity at 100%.

Keywords: breast cancer, tumor markers, risk factors, lifestyles, genetics.

INTRODUCTION

According to data from the World Health Organization (WHO) in 2020, breast cancer (BC) stands as the most common cancer among women globally, and the second most common overall, with 2.3 million newly diagnosed cases among women worldwide, resulting in 685,000 deaths. Additionally, male BC accounts for approximately 0.5 to 1% of cases. Data from the Institute of Public Health FBiH revealed that malignant neoplasm of the breast (C50) ranked seventh among the leading causes of death in 2022, and first among the most common causes of death from malignancies. It was followed by malignant neoplasms of the bronchus and lungs (C34) and malignant neoplasm of the colon (C18).

Genetic components, including family history and carrying mutations of BRCA1 and BRCA2 genes, play significant roles in the development of BC. However, unhealthy lifestyles and environmental factors also exert a considerable influence.

Factors that increase the risk of developing BC include obesity due to an unhealthy lifestyle with a lack

of physical activity after menopause, smoking, and consuming alcohol. Other risk factors include aging, nulliparity, having a first childbirth after the age of 30, never breastfeeding, early menarche, late menopause, use of hormonal replacement therapy and oral contraceptives, and exposure to thoracic radiotherapy before the age of 30. These factors will be further elaborated in this paper (1-4).

Early detection of BC enhances the chances of successful treatment. Therefore, it is crucial for every woman to take responsibility for her healthcare and conduct self-examinations if she is exposed to any of the previously mentioned risks. Screening programs for high-risk groups, including mammography and other examinations, are designed to prevent the disease. In cases of suspected disease, biopsies and tumor markers should be performed as laboratory screenings. Despite their limited sensitivity, tumor markers such as CA 15-3, CEA, CA 19-9, and CA 125 exhibit high specificity, particularly in detecting disease regression or the presence of metastases (5, 6).

The benefit of this research lies in identifying the exposure of women in Sarajevo Canton to BC risk factors. Based on this information, preventive examinations can be planned to detect BC long before it manifests symptoms, thereby reducing mortality rates from the disease and healthcare expenses. **The study aims** to motivate the healthcare sector to further investigate this issue and raise awareness among women about the risk factors associated with BC. One of the study's objectives is to examine the correlation between the rising obesity rates among women in Sarajevo due to depression and unhealthy lifestyles, which hinders physical activity. This correlation aligns with aging, the use of hormonal replacement therapy among postmenopausal women, and the increased risk of developing BC.

MATERIAL AND METHODS

A case-control study was conducted from July to September 2021 at The Public Institution Health Centre of Sarajevo Canton, specifically at the Organisational Unit Health Centre Novi Grad in the Primary healthcare unit located in the central facility. A sample of 200 women was included, consisting of 100 women with BC and 100 women without a BC diagnosis, serving as the control group. Data for the control group were collected from family medical records. A total of 200 family medical records with comprehensive medical documentation were randomly selected and examined. This method was chosen to minimize bias, ensuring the sample adequately represents the population, including all women with BC from Sarajevo Canton.

Inclusion criteria for the research were women diagnosed with BC and women without BC, residing in Sarajevo Canton, and possessing complete medical documentation. Exclusion criteria included men with BC, patients residing outside Sarajevo Canton, and patients lacking complete medical documentation. Data on tumor markers were extracted from family medical records and analyzed using analyzers such as ARCHITECT i2000SR, Vitros 5600, and Vitros ECIQ. Collected risk factors included age, education, marital status, history of BC diagnosis, history of benign breast disease, and any family history of BC, including BRCA mutations. Additional data collected encompassed BMI, age of first menarche, number of pregnancies, breastfeeding history, menopausal status, potential use of hormonal replacement therapy or oral contraceptives, and history of ovariectomy. Lifestyle factors, such as smoking and alcohol consumption, were also recorded.

Statistical analysis was performed using IBM Statistics SPSS v 17.0 and MedCalc software, with results prepared and presented using Microsoft Word and Excel 2019. Prior to analysis, data distribution was tested using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Risk factor data exhibited non-normal distribution, necessitating the use of non-parametric tests including the Chi-Square test and Fisher's exact test. Tumor marker data demonstrated normal distribution allowing for the use of the parametric One Sample T-test. A significance level of $p < 0.05$ was considered statistically significant, with a confidence level of 95%.

RESULTS

For the total sample (N = 200), we analyzed the ages of patients, noting that most women with BC were in the 65+ age group, followed by those in the 41-65 age group. This trend was consistent across both the BC group and the control group, each comprising 100% of the sample, as shown in Table 1 with statistical significance.

In our study, the majority of patients with breast cancer and those in the control group had secondary education. In terms of marital status, most patients, both with BC and in the control group, were married.

Furthermore, the majority of patients with BC and those in the control group did not have a history of benign breast disease. Analysis of family history of BC reveals that most patients with BC had a positive family history, including positive mutations of BRCA 1 and BRCA 2 genes, unlike the control group.

Additionally, most patients with BC were obese, contrasting with the control group. Furthermore, early

Table 1. *Variables frequency distribution*

Variables	Cases (%)	Controls (%)	Chi-Square test value	p value/Fisher's exact test
1	2	3	4	5
Age (years)			31.977	0.000[1]
< 30	0 (0)	9 (9)		
31-40	2 (2)	16 (16)		
41-65	23 (23)	34 (34)		
65+	75 (75)	41 (41)		
Total	100 (100)	100 (100)		
Education			7.230	0.027
Primary or less	10 (10)	3 (3)		
Secondary	65 (65)	58 (58)		
Tertiary	25 (25)	39 (39)		
Total	100 (100)	100 (100)		
Marital status			86.560	0.000
Married	65 (65)	63 (63)		
Divorced	22 (22)	22 (22)		
Never got married	13 (13)	15 (15)		
Total	100 (100)	100 (100)		
History of benign breast disease			14.174	0.000 / 0.000
Yes	27 (27)	7 (7)		
No	73 (73)	93 (93)		
Total	100 (100)	100 (100)		
Family history of BC			72.158	0.000 / 0.000
Yes	66 (66)	8 (8)		
No	34 (34)	92 (92)		
Total	100 (100)	100 (100)		
Obesity (BMI ≥ 25 kg/m^2)			24.921	0.000 / 0.000
Yes	74 (74)	39 (39)		
No	26 (26)	61 (61)		
Total	100 (100)	100 (100)		
Early menstrual cycle (< 13 years)			41.747	0.000 / 0.000
Yes	53 (53)	11 (11)		
No	47 (47)	89 (89)		
Total	100 (100)	100 (100)		
Giving birth			132.280	0.000 / 0.000
Yes	86 (86)	77 (77)		
No	14 (14)	23 (23)		
Total	100 (100)	100 (100)		
Breastfeeding			3.854	0.037 / 0.037
Ever	86 (86)	75 (75)		
Never	14 (14)	25 (25)		
Total	100 (100)	100 (100)		

[1] The Fisher's exact test is displayed only for variables with a 2x2 format.

1	2	3	4	5
Oral contraceptives > 2 months			17.887	0.000 / 0.000
Ever	42 (42)	15 (15)		
Never	58 (58)	85 (85)		
Total	100 (100)	100 (100)		
Menopausal status			35.143	0.000 / 0.000
Pre-menopausal	8 (8)	45 (45)		
Post-menopausal	92 (92)	55 (55)		
Total	100 (100)	100 (100)		
Hormonal replacement therapy > 2 months			49.818	0.000 / 0.000
Ever	65 (65)	16 (16)		
Never	35 (35)	84 (84)		
Total	100 (100)	100 (100)		
Ovariectomy			147.920	0.000 / 0.000
Yes	6 (6)	8 (8)		
No	94 (94)	92 (92)		
Total	100 (100)	100 (100)		
Smoking (consuming at least 2 years)			30.420	0.000 / 0.000
Yes	32 (32)	29 (29)		
No	68 (68)	71 (71)		
Total	100 (100)	100 (100)		
Alcohol (> 44g per day for at least 2 years)			131.220	0.000 / 0.000
Yes	8 (8)	11 (11)		
No	92 (92)	89 (89)		
Total	100 (100)	100 (100)		

menarche was more prevalent among patients with BC compared to the control group, where women mainly experienced menarche between the ages of 13 and 15.

Regarding the variable number of pregnancies, it is notable that the majority of patients with BC had given birth one or two times, mirroring the distribution seen in the control group. Additionally, most patients with BC who had given birth were also breastfeeding their babies, in contrast to the control group where a small proportion of women had never breastfed their children. Conversely, women in the control group were less likely to use oral contraceptives compared to women with BC, with approximately half of the latter group reporting usage for at least two months.

A significant portion of patients with BC were post-menopausal, whereas the control group was evenly split between pre-menopausal and post-menopausal women. Concerning the variable use of hormonal replacement therapy, most patients with BC reported using hormonal replacement therapy for at least two months, contrasting with the control group where usage was less common. Similarly, the majority of patients with BC and those in the control group had not undergone ovariectomy. Most patients with BC reported not smoking or consuming alcohol, a pattern also observed in the control group.

In this study, we monitored the tumor markers CA 15-3, CEA, CA 19-9, and CA 125. The reference ranges for these markers were as follows: < 25 kIU/L for CA 15-3, < 4.6 ng/mL for CEA in non-smokers and < 10 ng/mL for smokers, < 27 kIU/L for CA 19-9, and < 35 IU/mL for CA 125.

Among our sample of patients with BC (N = 100), the most commonly utilized combination of tumor markers for follow-up and metastasis detection was CA 15-3 and CEA, comprising 78% of cases. This was followed by a combination of CA 15-3, CEA, CA 19-9, and CA 125, utilized in 13% of cases. The least utilized combination was CA 125, CA 15-3, and CEA, accounting for 9% of the total sample.

Comparison of our data for these tumor markers with data from the literature conducted using One Sample T-tests demonstrated statistical significance.

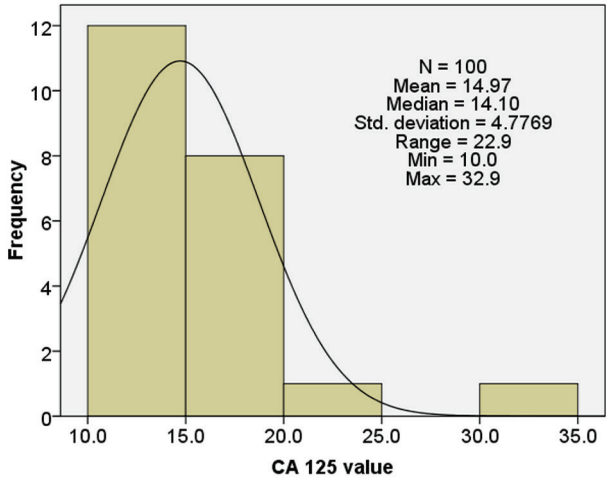

Figure 1. *Histogram of distribution and descriptive presentation of CA 125 values*

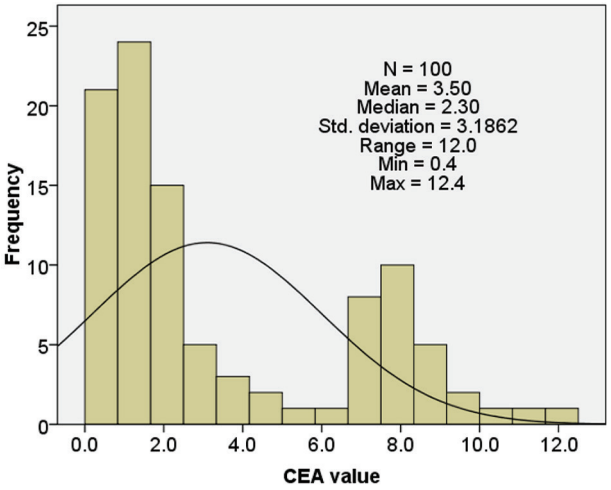

Figure 2. *Histogram of distribution and descriptive presentation of CEA values*

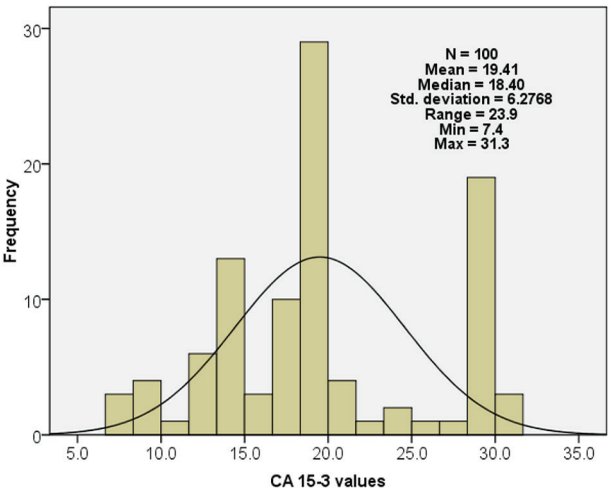

Figure 3. *Histogram of distribution and descriptive presentation of CA 15-3 values*

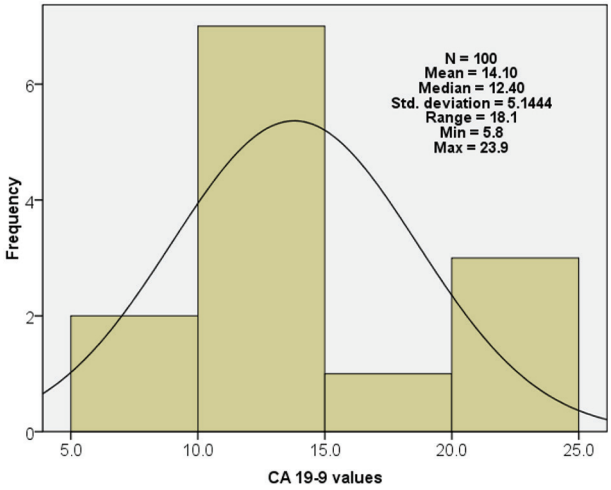

Figure 4. *Histogram of distribution and descriptive presentation of CA 19-9 values*

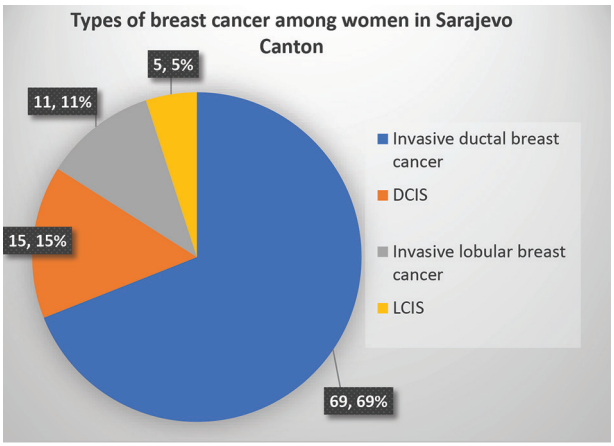

Figure 5. *Types of BC among women in Sarajevo Canton*

Descriptive presentations of CA 125 values (Figure 1) and CEA values (Figure 2) according to our sample are provided in the accompanying figures.

Comparison of our data for tumor markers CA 15-3, specific for BC, and CA 19-9, specific for pancreatic cancer, with data from the literature, followed by One Sample T-tests, revealed statistical significance for their use in detecting BC. Descriptive presentations of CA 15-3 values (Figure 3) and CA 19-9 values (Figure 4) for our sample are provided below. The sensitivity achieved for CA 15-3 in detecting regression was 81.8% with a specificity of 100% at a cutoff value of 19.55 kIU/L.

Among the group of women with BC from our study (N=100), the most prevalent type of BC in Sarajevo Canton was invasive ductal BC, accounting for 69 cases or 69% of the total sample. This was followed by ductal carcinoma in situ (DCIS) with 15 cases or 15%, and invasive lobular BC with 11 cases or 11% of the total sample. The least common type of BC observed among women in Sarajevo Canton was lobular

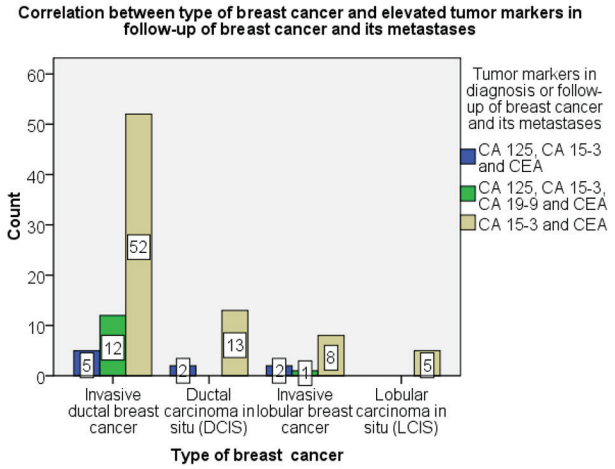

Figure 6. *Correlation of type of breast cancer with tumor markers*

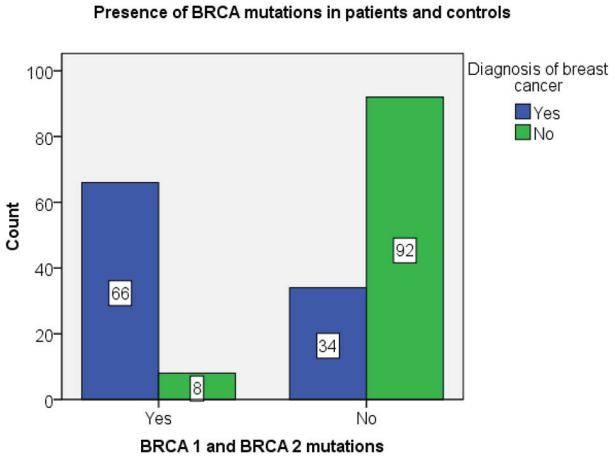

Figure 7. *Presence of BRCA mutations in patients and controls*

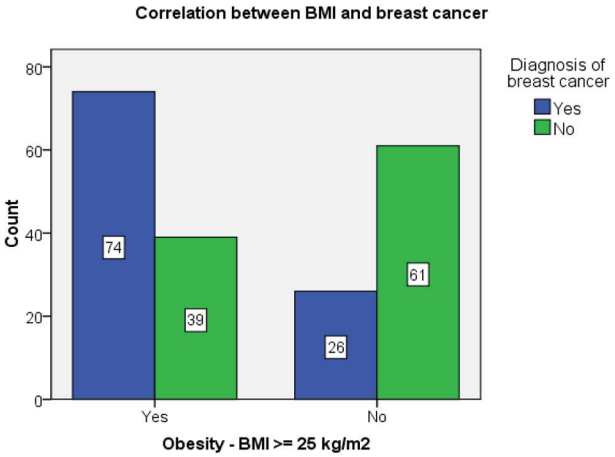

Figure 8. *Correlation between obesity and BC*

carcinoma in situ (LCIS), comprising 5 cases or 5% of the total sample. Additionally, the correlation between the type of cancer and tumor markers is depicted in the figures below (Figure 5 and 6).

It is well-established that genetic components play a significant role in the development of BC, notably through mutations in tumor suppressor genes such as BRCA 1 and BRCA 2. In our sample, we gathered data on the presence of BRCA 1 and BRCA 2 mutations among patients with BC, the majority of whom had mutations, contrasting with controls without BC, who predominantly lacked mutations in these genes, as illustrated in Figure 7.

Because of the modern lifestyle, some women spend extended periods of time living a sedentary way of life. Coupled with reduced physical activity, this can contribute to obesity, as individuals may consume more food than necessary or can process. Our study revealed that obesity is more prevalent among postmenopausal women corroborating its status as a risk factor for developing BC, as depicted in Figure 8.

Significant statistical correlations were observed between obesity, menopausal status, and the use of hormonal replacement therapy as risk factors for developing BC as indicated in the accompanying table.

DISCUSSION

The findings from Wahidin et al.'s research in Indonesia align with our study, highlighting statistically significant correlations between several risk factors and BC development, including age, oral contraceptive use, early menarche, childbirth, breastfeeding, obesity, and history of benign breast tumors (7). In our sample, we also observed statistically significant associations for these risk factors. However, it's noteworthy that some of the results reported by Wahidin et al., such as non-significant associations for family history of BC and menopausal status, were not consistent with our findings. This variation may be attributed to differences in sample characteristics, methodology, or other contextual factors between the studies.

Similarly, research conducted by the Hong Kong BC Registry in Hong Kong identified significant associations between family history of BC, early menarche, childbirth, breastfeeding, smoking at a younger age, alcohol consumption, obesity, and oral contraceptive use. These findings are consistent with the results obtained from our analysis, as most of the risk factors were found to be statistically significant in both studies. However, unlike our findings, menopausal status and hormonal replacement therapy were not found to be statistically significant in the research conducted by the Hong Kong BC Registry. This discrepancy may stem from variations in sample characteristics, methodology, or other contextual factors between the studies (8).

In Malaysia, Kamarudin et al (9). found significant correlations between breastfeeding, obesity, and BC risk. However, they reported non-significant associations for variables such as marital status, education,

menopausal status, childbirth, oral contraceptive use, hormonal replacement therapy, smoking status, and age. Our results, on the other hand, indicated that the aforementioned risk factors were statistically significant, which is not consistent with their findings. This inconsistency may be attributed to differences in sample characteristics, study design, or other contextual factors between the two studies (9).

Hing et al.(5) conducted a study in 2020, wherein tumor markers CEA and CA 15-3 were monitored for the diagnosis, follow-up, and detection of regression and metastasis of BC. They found that 23 patients (34%) with regression exhibited elevated levels of tumor markers, serving as the first indicator of disease regression before clinical symptoms appeared or were detected by any other diagnostic method. Specifically, the elevated level of CEA in patients with regression was found to be 10 ng/ml compared to 6 ng/ml in the control group. The sensitivity of elevated CA 15-3 alone was 71.6% with a specificity of 97%, while the sensitivity of CEA alone was 75% with a specificity of 92.5%. Moreover, the combination of elevated levels of CEA and CA 15-3 for monitoring regression showed a sensitivity of 93.9% with a specificity of 89.6%. Our study yielded consistent results with theirs, particularly regarding the sensitivity of CA 15-3 in detecting regression, which was 81.8% with a specificity of 100% (5).

In the study conducted by Li et al. (10) in 2019, they established statistical significance between women with low and high levels of carcinoembryonic antigen (CEA) and cancer antigen 125 (CA 125). Their findings suggest that CEA and CA 125 levels reflect different aspects of BC in young women. Specifically, groups with high and low CEA levels exhibited differences in tumor size, lymph node status, and HER-2 status, while groups with high and low CA 125 levels showed significant differences in TNM stage, hormonal receptor status (ER and PR), molecular type of BC, and the use of endocrine therapy, all with p values < 0.05. Our results also demonstrated that CEA and CA 125 were useful in detecting BC and its metastases, consistent with their findings (10).

In the research conducted by Zalenski et al. (11), tumor markers including CEA, CA 15-3, CA 19-9, and CA 125 were analyzed using automatic immunoassays. They found that the best combination of tumor markers was CA 15-3 and CEA, with a sensitivity of 90% and specificity of 95%. However, their study did not demonstrate the usefulness of the combination of CA 125 and CEA in the early detection of BC and its metastases. Despite this difference, their study yielded results similar to our findings regarding the use of tumor markers, although they achieved higher sensitivity and specificity (11).

In the study conducted by Sun et al., it was demonstrated that approximately 16% of BC deaths in females in China were associated with excess weight and obesity, while 11.6% of BC deaths were attributed to physical inactivity. Our results similarly indicate a correlation between obesity and a higher risk of developing BC (12).

CONCLUSION

Based on our findings, we conclude that a correlation exists between various risk factors and an increased risk of developing female breast cancer (BC) in Sarajevo Canton. Furthermore, the tumor markers assessed in this study, namely CA 15-3, CEA, CA 19-9, and CA 125, demonstrated statistical significance, indicating their potential as a combined screening tool for detecting BC and its metastases. Invasive ductal BC was identified as the most prevalent type. The sensitivity for regression detection was found to be 81.8%, with a specificity of 100% at a cutoff value of 19.55 kIU/L.

Note: Artificial intelligence was not used as a tool in this study.

Authors contribution: BH: conceived the idea for the study, participated in writing the paper; **AK:** conceived the idea for the study**,** article writing; **LH:** designed the figures and contributed to the research implementation;**LI and VS:** verified the analytical methods and encouraged further investigation into the correlation between obesity and BC; **MS:** verified the numerical results and supervised the project. All authors discussed the results and contributed to the final manuscript.

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Sažetak

PROCENA RIZIKA U KORELACIJI SA GOJAZNOŠĆU I LABORATORIJSKIM MONITORINGOM NAJČEŠĆIH TIPOVA KARCINOMA DOJKE KOD ŽENA U KANTONU SARAJEVO

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Uvod: Karcinom dojke je maligno oboljenje, češće se javlja ženaa, a jedan od najpoznatijih uzroka je mutacija tumor supresorskih gena BRCA 1 i BRCA 2 što predstavlja genetičku komponentu. Drugi rizikofaktori uključuju nezdrave životne stilove uključujući manjak fizičke aktivnosti i konzumiranje alkohola i cigareta. Starenje također ima ulogu u razvoju karcinoma dojke sa uticajem hormona s obzirom da mnogi od ovih karcinoma za svoj rast koriste ženske hormone uključujući estrogen i progesteron.

Materijal i metode: Istraživanje je sprovedeno uz pomoć alata za prikupljanje podataka o rizikofaktorima i tumorskim markerima iz kartona porodične medicine. Naš uzorak je uključivao 200 žena koje su podeljene u dve grupe, jedna sa i druga bez dijagnoze karcinoma dojke sa potpunom medicinskom dokumentacijom. Muškarci sa karcinomom dojke su isključeni iz studije.

Rezultati: Sa Pirsonovim χ^2testom je dokazano da postoji statistička značajnost između genetičke komponente, porodične istorije, starenja, pretilosti, konzumiranja alkohola i cigareta i dužeg izlaganja **ženskim** hormonima i povećanog rizika za razvoj karcinoma dojke kod **žena. Potvrdili** smo rezultate sa Fisherovim egzaktnim testom. Za tumorske markere korišten je One Sample T-test i potvrđeno je da tumorski markeri CA 15-3, CEA, CA 19-9 i CA 125 su korisni u skriningu karcinoma dojke i njegovih metastaza. Najčešći tip karcinoma dojke kod **žena u Kantonu Sarajevo** je invazivni duktalni karcinom, dok najmanje zastupljen je lobularni karcinom in situ.

Zaključak: Korelacija između rizikofaktora uključujući: starenje, nezdrave životne stilove i duže izlaganje ženskim hormonima i povećan rizik za razvoj karcinoma dojke je dokazana. Tumorski markeri koji su korišteni uključujući CA 15-3, CEA, CA 19-9 i CA 125 su bili korisni u dijagnozi, skriningu i otkrivanju metastaza kod žena. Senzitivnost koju smo dobili za ove tumorske markere u otkrivanju recidiva je bila 81.8% sa specifičnošću koja je iznosila 100%.

Ključne reči: karcinom dojke, tumorski markeri, faktori rizika, životni stilovi, genetika.

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Original article

A COMPARATIVE STUDY OF MELATONIN WITH PLACEBO IN ATTENUATION OF HEMODYNAMIC RESPONSES TO LARYNGOSCOPY AND INTUBATION

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Abstract: **Introduction:** An increase in blood pressure and heart rate is observed during laryngoscopy and insertion of the endotracheal tube. Melatonin is used for sedation in the Intensive Care Unit. Our study was based on the hypothesis that administrating 3 mg and 6 mg of melatonin 90 minutes before induction attenuates hemodynamic responses encountered during laryngoscopy and intubation.

Materials and Methods: Seventy-five adult patients scheduled for elective surgical procedures, ASA I and II, were assigned into 3 groups (25 patients in each group) to receive oral placebo, melatonin 3 mg, or melatonin 6 mg 90 minutes prior to induction of anesthesia. Hemodynamic variables were recorded at baseline, before induction, and at 3, 6, 9, 12, 15, and 30 minutes after induction. Analysis of variance (ANOVA) was used for intergroup analysis of data. Categorical variables were compared using non-parametric tests like the Chi-square test or Fisher's exact test. Bonferroni correction was applied for intergroup analysis. Statistical significance was considered when $p < 0.05$.

Results: An increase in heart rate and blood pressure at 3, 6, and 9 minutes after induction of general anesthesia was observed in the control group compared to the melatonin 3 mg and 6 mg groups administered 90 minutes prior to induction. Oral administration of 6 mg of melatonin was found to provide greater attenuation than 3 mg of melatonin.

Conclusion: Oral administration of 3 mg and 6 mg melatonin effectively attenuates the hemodynamic pressor changes observed during laryngoscopy and tracheal intubation.

Keywords: Laryngoscopy, pressor response, melatonin, pre-operative anxiety, hemodynamic changes.

INTRODUCTION

Laryngoscopy and endotracheal intubation elicit profound hemodynamic changes characterized by increased heart rate and blood pressure. These responses can be particularly detrimental in individuals with limited cardiorespiratory reserve (1), highlighting the importance of attenuating sympathetic stimulation (2).

Various pharmacological approaches, including beta-adrenergic blockers, hypotensive agents, calcium channel blockers, and opioids, have been assessed for their ability to mitigate the hemodynamic pressor response during premedication or induction. However, these interventions may carry risks such as bradycardia, hypotension, and postoperative respiratory depression (3).

Preoperative anxiety, arising from concerns about the disease, anesthesia, and surgery, can lead to altered analgesic responses and may benefit from pharmacological intervention (4, 5).

Melatonin influences the sleep cycle by impacting the sleep-wake cycle and facilitating sleep induction (6). Upon oral administration, melatonin modulates gamma-aminobutyric acid ($GABA_A$) receptors, leading to sedation (7, 8). This sedative and hypnotic action of melatonin may help decrease heart rate and

blood pressure during laryngoscopy and intubation (9, 10).

Our research question was based on the hypothesis that the oral administration of 6 mg of melatonin 90 minutes before anesthesia induction may attenuate noxious stimuli (hypertension and tachycardia) more effectively than oral premedication with 3 mg of melatonin during laryngoscopy and intubation. In our study, the primary objective was to compare the impact of oral melatonin 6 mg and oral melatonin 3 mg versus placebo on blood pressure variation during laryngoscopy and intubation. The secondary objectives included comparing heart rate, anxiety scores, and analgesia between the two melatonin dosage regimens and placebo.

MATERIALS AND METHODS

Approval from the institutional ethical committee (IEC/SKIMS Protocol # RP 20/2019 dated 9 July 2019) was obtained, and the study was conducted in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki, following informed written consent from the patients. Seventy-five patients were allocated to one of three study groups, with each group comprising 25 patients at the discretion of the attending anesthesiologist.

Group M3 (n = 25): Received oral melatonin 3 mg, 90 minutes prior to anesthesia administration with a sip of water.

Group M6 (n = 25): Received oral melatonin 6 mg, 90 minutes before induction of anesthesia with a sip of water.

Group P (n = 25): Received a placebo tablet (sugar-free tablet consisting of lactose, aspartame, croscarmellose sodium, magnesium stearate, colloidal silicon dioxide, and polyvinyl pyrrolidone), 90minutes before induction of anesthesia with a sip of water.

All patients classified as American Society of Anesthesiologists (ASA) physical status I and II, aged between 18 and 65 years, of either sex, undergoing elective surgeries for supratentorial tumors requiring general anesthesia were included in the study.

Exclusion criteria included patients with any psychiatric disorders, history of allergies, use of antiepileptic or sedative agents, pregnancy, lactation, or coagulopathy, as well as patients with anticipated difficult airways, requiring more than one attempt at laryngoscopy, or where laryngoscopy time exceeded 20 seconds, and those with artificial airways in situ or accompanying spinal cord lesions. All enrolled patients underwent a pre-operative evaluation including relevant history, physical examination, and airway assessment. Routine pre-operative investigations and procedure-specific investigations were conducted according to institutional protocol. Patients followed nil per oral instructions for 6 hours prior to surgery.

Before administration of melatonin or placebo, baseline values of heart rate, mean, systolic, and diastolic blood pressures were noted. On the morning of surgery, after recording baseline vitals and assessing anxiety levels, melatonin or placebo was administered with sips of water approximately 90 minutes before anesthesia induction. An 18-gauge intravenous cannula was established, and a 0.9% NaCl solution was infused at 100-150 ml/h. In the operation theatre, essential monitors were applied, and vitals were recorded. General anesthesia was induced with fentanyl 2 μg/kg, preservative-free lidocaine hydrochloride (1.5 mg/kg), and propofol administered incrementally (20 mg increments) until loss of verbal response. Endotracheal intubation was performed after administration of atracurium 0.5 mg/kg. Maintenance anesthesia comprised a mixture of oxygen, nitrous oxide, and isoflurane. Heart rate, noninvasive blood pressure, and arterial oxygen saturation were recorded before induction and at 3, 6, 9, 12, 15, and 30 minutes after induction. Neostigmine (0.06 mg/kg) and glycopyrrolate (0.01 mg/kg) were administered at the end of surgery to reverse residual neuromuscular blockade. Tracheal extubation occurred after ensuring recovery of neuromuscular blockade. Patients were transferred to the recovery room where vitals were monitored, and appropriate interventions were initiated if necessary. Undesirable postoperative events such as blurred vision, nausea, vomiting, and persistent sedation were noted.

Anxiety levels were assessed using the Beck Anxiety Inventory (BAI)score before medication administration, at induction, and at intervals of 15 and 30 minutes, 3, 6, and 24 hours after extubation.

The BAI scores were classified as low anxiety (0-21), moderate anxiety (22-35), and severe anxiety (> 35) (11). While calculating BAI score 21 parameters related to anxiety were taken into consideration assigning a score of 0 (absent), 1 (mild), 2 (moderate) and 3 (severe). The behavioral rating scale for pain consisted of 5 factors for face, restlessness, muscle tone, vocalization and consolability with a scoring system of 0 for absent, 1 for moderate and 2 for severe symptoms (12).

Data collection was performed by an independent attending anesthetist. Sample size was calculated using OpenEpi software version 3.01(Centers for Disease Control and Prevention (CDC), Atlanta,Georgia, USA Atlanta, GA, USA) based on a previous study by Gupta et al.(9), aiming for a confidence interval of 95% and power of 90% to detect a clinically significant reduction in mean blood pressure with 6 mg

melatonin. Considering potential dropouts due to intraoperative complications, 25 patients were recruited in each group. Data was entered into a Microsoft Excel spread sheet (developed by Microsoft for Windows, Washington USA) and analyzed using SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were presented as Mean ± SD, and categorical variables as percentages. Intra-group comparisons were made using analysis of variance (ANOVA), and categorical variables were compared using the Chi-square test or Fisher's exact test. A p-value < 0.05 was considered statistically significant.

RESULTS

All three groups exhibited comparable demographic characteristics, ASA grade, and Mallampati grading (MPG) (Table 1). At baseline and before induction, the mean heart rate among patients receiving placebo, 3 mg, and 6 mg melatonin was similar. However, at 3, 6, and 9 minutes after induction, the observed mean heart rate differed significantly among patients receiving placebo, 3 mg, and 6 mg of melatonin. As the duration of anesthesia progressed, from 12 to 30 minutes, there were no significant differences in heart rate ($p \geq 0.05$) (Figure 1). Intergroup comparison following Bonferroni correction demonstrated significantly lower heart rates at 3, 6, and 9 minutes after induction among patients administered 6 mg melatonin compared to placebo (Table 2, Figure 1).

The mean systolic blood pressure (BP) baseline values and values before induction among the three groups were comparable. However, at 3, 6, 9, and 12

Table 1. *Demographics*

Variable	Group M3 (n = 25)	Group M6 (n = 25)	Group P (n = 25)	p value
Age (in years), mean ± S.D	37.6 ± 12.39	40 ± 2.46	42.6 ± 14.49	0.403
Sex (male/female) (n = 25)	13/12	10/15	11/14	0.771
ASA grade (I/II) (n = 25)	18/7	17/8	16/9	0.951
MPG (I/II/III/IV) (n = 25)	7/15/2/1	7/13/5/0	6/12/6/1	0.754
Comorbidities				
Smoker n (%)	4 (16)	8 (32)	6 (24)	0.416
Hypertension n (%)	7 (28)	4 (16)	8 (32)	0.401
Diabetes n (%)	1 (4)	2 (8)	3 (12)	0.581
Hypothyroid n (%)	2 (8)	3 (12)	5 (20)	0.446

n = number of patients, % = percentage; M3 = Melatonin 3mg, M6 = Melatonin 6 mg, P = Placebo, MPG = Mallampati grading

Table 2. *Intergroup comparison of hemodynamic parameters between the three groups at different intervals (p values with Bonferroni correction)*

Time interval	M3 vs M6	M3 vs P	M6 vs P
1	2	3	4
Baseline HR	1.000	1.000	1.000
Baseline SBP	1.000	1.000	1.000
Baseline DBP	1.000	1.000	1.000
Baseline MAP	1.000	1.000	1.000
Before Induction HR	1.000	1.000	1.000
Before Induction SBP	1.000	1.000	1.000
Before Induction DBP	1.000	1.000	1.000
Before Induction MAP	1.000	1.000	1.000
3 Minutes after induction HR	0.486	0.708	0.033*
3 Minutes after induction SBP	0.517	0.776	0.042*
3 Minutes after induction DBP	1.000	1.000	0.942
3 Minutes after induction MAP	1.000	0.996	0.304
6 Minutes after induction HR	0.466	0.563	0.022*
6 Minutes after induction SBP	0.009*	1.000	0.004*

1	2	3	4
6 Minutes after induction DBP	0.394	1.000	0.049*
6 Minutes after induction MAP	0.090	1.000	0.021*
9 Minutes after induction HR	0.818	0.169	0.010*
9 Minutes after induction SBP	0.098	1.000	0.012*
9 Minutes after induction DBP	0.610	0.492	0.027*
9 Minutes after induction MAP	0.265	0.610	0.011*
12 Minutes after induction HR	1.000	0.408	0.202
12 Minutes after induction SBP	0.474	0.191	0.004*
12 Minutes after induction DBP	1.000	0.027*	0.013*
12 Minutes after induction MAP	1.000	0.038*	0.033*
15 Minutes after induction HR	1.000	0.413	0.626
15 Minutes after induction SBP	1.000	0.323	0.131
15 Minutes after induction DBP	0.888	0.083	0.707
15 Minutes after induction MAP	1.000	0.094	0.311
30 Minutes after induction HR	1.000	1.000	1.000
30 Minutes after induction SBP	1.000	1.000	0.622
30 Minutes after induction DBP	0.697	0.524	1.000
30 Minutes after induction MAP	1.000	0.582	1.000

Legends: *Statistically Significant Difference; P-value by Bonferroni correction; M3 = Melatonin 3 mg, M6 = Melatonin 6 mg, P = Placebo, HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure.

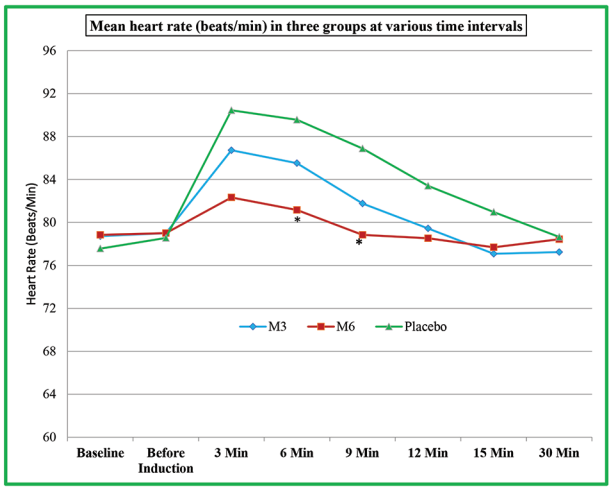

Figure 1. *Line diagram showing mean heart rate (beats/minute) M3 = Melatonin 3 mg; M6 = Melatonin 6 mg; P = Placebo*

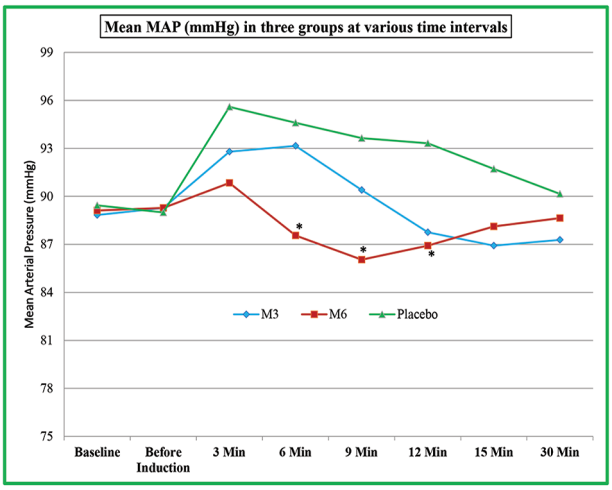

Figure 2. *Line diagram showing mean arterial pressure (mmHg) M3 = Melatonin 3 mg; M6 = Melatonin 6 mg; P = Placebo*

minutes after induction, there were significant differences in mean systolic BP among the three groups. As the duration of anesthesia progressed to 15 and 30 minutes, there were no significant differences in mean systolic blood pressure values ($p \geq 0.05$). Intergroup comparison revealed that mean systolic blood pressure was significantly lower at 3, 6, and 9 minutes after induction in patients administered 6 mg melatonin compared to placebo (Figure 2). Similarly, systolic blood pressure was significantly lower at 6 and 9 minutes after induction between patients administered 3 mg and 6 mg melatonin.

At baseline, before induction, and 3 minutes after induction, there were no differences in mean diastolic BP between the three groups. However, at 6, 9, and 12 minutes after induction, the difference in mean diastolic BP among the three groups was statistically significant. As the duration of anesthesia progressed, at 15 and 30 minutes, the differences in mean diastolic BP values became comparable ($p < 0.05$). A similar trend was observed in mean arterial pressure ($p < 0.05$). Intergroup comparison showed that mean diastolic blood pressure was significantly lower at 6, 9, and 12 minutes after induction in patients administered 6 mg

Table 3. *Intergroup comparison based on interoperative BAI score among three groups at various time intervals*

Time Interval	P-value		
	M3 vs M6	**M3 vs Placebo**	**M6 vs Placebo**
Before giving premedication	1.000	1.000	1.000
At time of induction	0.047*	0.923	0.006*
15 minutes after extubation	0.001*	1.000	< 0.001*
30 minutes after extubation	0.162	0.162	0.001*
3 hours	0.544	0.851	0.053
Intergroup comparison based on perioperative pain score among three groups at various time intervals			
Before giving premedication	1.000	1.000	1.000
At time of induction	1.000	1.000	1.000
15 minutes after extubation	0.043*	< 0.001*	< 0.001*
30 minutes after extubation	0.009*	< 0.001*	< 0.001*
3 hours	0.760	< 0.001*	< 0.001*
6 hours	1.000	0.008*	0.008*
24 hours	1.000	0.297	0.297

**Statistically Significant Difference (P-value < 0.05); P-value by* Bonferroni correction. BAI = Beck Anxiety Inventory

melatonin compared to placebo. After Bonferroni correction in intergroup comparison, significantly lower mean arterial blood pressure was observed at 3, 6, and 9 minutes after induction in patients administered 6 mg melatonin compared with placebo (Table 2, Figure 2).

Before administering premedication with melatonin, the mean Beck Anxiety Inventory (BAI) scores among the three groups were comparable (Table 3). However, at the time of induction, and 15 minutes and 30 minutes after extubation, the differences in mean BAI scores among the three groups were statistically significant. As time progressed, the differences in mean BAI scores became comparable again 3 hours after extubation. No significant differences in mean BAI scores were observed at 6 hours and 24 hours after extubation (Figure 3).

Before premedication and at the time of induction, there were no differences in mean pain scores among the three groups. However, at 15 minutes, 30 minutes, 3 hours, and 6 hours after extubation, there were statistically significant differences in mean pain scores among patients receiving placebo, 3 mg, and 6 mg of melatonin (Table 3).

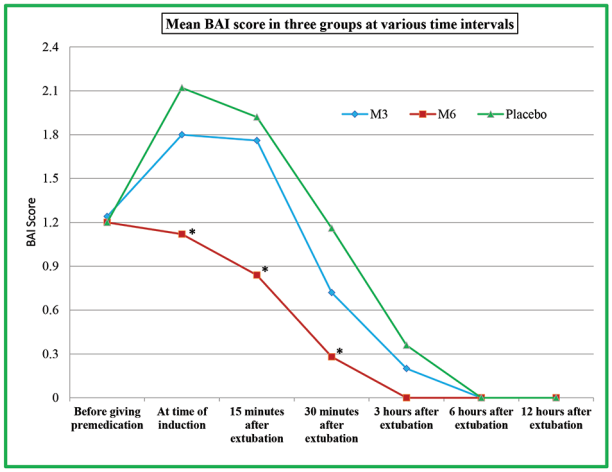

Figure 3. *Line diagram showing Beck Anxiety Inventory score M3 = Melatonin 3 mg; M6 = Melatonin 6 mg; P = Placebo*

Additionally, lower mean anxiety scores at the time of induction and in the postoperative period, as well as lower mean pain scores in the postoperative period, were noted with melatonin administration compared to the control group.

DISCUSSION

In our study, we observed that administration of melatonin at doses of 6 mg and 3 mg (given 90 minutes prior to induction of general anesthesia) effectively attenuated hemodynamic responses up to 12 minutes after induction compared to the control group.

Effect on Hemodynamic Parameters

Our results align with findings from Gupta et al. **(9)** who reported an increase in heart rate during laryngoscopy, with the increase lasting up to 10 minutes in the control group. However, with oral melatonin administration, the heart rate increase was transient during laryngoscopy and returned to baseline within

1 minute. Kumar **et al.** (13) also observed a notable reduction in heart rate 1 minute following intubation with melatonin 3 mg compared to the control group.

In our study, we observed an increase in systolic, diastolic, and mean blood pressure at 3, 6, 9, and 12 minutes in the control group. However, with progression in the duration of anesthesia, at 15 and 30 minutes, there were no significant differences in the values of mean systolic blood pressure ($p \geq 0.05$). This finding is similar to that observed by Gupta et al. (9), who found higher systolic blood pressure during laryngoscopy and intubation compared to baseline values in the control group, whereas oral administration of 6 mg of melatonin attenuated this response.

Similar findings were reported by other studies. For example, oral melatonin at doses of 6 mg and 9 mg administered one hour before the preoperative period resulted in a significant decrease in blood pressure at 1, 2, 3, 5, and 10 minutes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) compared to the control group (11).

These studies collectively support the role of melatonin in mitigating hemodynamic responses during laryngoscopy and intubation, possibly through its sedative and anxiolytic effects.

Effects on Anxiety

Our study observed lower mean Beck Anxiety Inventory (BAI) scores with the administration of 6 mg of melatonin compared to the control group and 3 mg of melatonin. This finding is consistent with previous research. Abbasivash et al. (14) reported that melatonin administration decreased perioperative anxiety levels compared to control subjects, aligning with our results. Similarly, Rosas-Luna **et** al. (15) found that oral administration of melatonin at a dose of 5 mg was associated with anxiolysis compared to control groups. Brignardello-Petersen et al. (16) also demonstrated preoperative anxiolysis with melatonin administration compared to placebo, similar to our findings. Additionally, Yılmaz (17) reported that melatonin was associated with less postoperative anxiety compared to placebo. Etedali et al. (18) observed a 33% reduction in anxiety scores after administration of oral melatonin. Furthermore, Jouybar et al. (19), Shahrokhi et al. (20), and Saneet et al. (21) found that melatonin premedication effectively reduced perioperative anxiety in adults and improved patient comfort.

Effects on Analgesia

In our study, we observed statistically significant higher mean pain scores in patients receiving placebo compared to those receiving 3 mg and 6 mg of melatonin at 15 minutes, 30 minutes, 3 hours, and 6 hours after extubation. These findings are consistent with previous research. Kiabi et al. (22) reported that melatonin premedication (10 mg) reduced postoperative analgesic requirement in patients undergoing caesarean section, similar to our study. Javaherforooshzadeh et al. (23) demonstrated that pre-treatment with melatonin decreased anxiety and pain in lumbar surgery compared to placebo. Additionally, in patients receiving intravenous regional analgesia, melatonin was shown to have postoperative analgesic effects (24), aligning with our study findings.

Our study compared the effects of two doses of melatonin (6 mg and 3 mg) with a control group, whichis a unique contribution to the existing literature. However, limitations of our study include the lack of randomization of patients into different treatment arms, potentially introducing selection bias due to subjective considerations of the attending anesthesiologist during allocation. Furthermore, the size and location of supratentorial tumors could have influenced postoperative recovery characteristics.

Future studies should be conducted to further assess the efficacy of melatonin in reducing hemodynamic responses and providing adequate analgesia, and to establish dose-response relationships to achieve desired effects. Randomized controlled trials with larger sample sizes and standardized methodologies will contribute to a better understanding of the therapeutic potential of melatonin in perioperative care.

CONCLUSION

Premedication with oral melatonin at doses of 3 mg and 6 mg administered before induction of anesthesia in elective surgical procedures effectively reduces the pressor response to intubation and laryngoscopy. Additionally, melatonin provides analgesic and anxiolytic effects, with oral melatonin 6 mg showing greater effectiveness compared to 3 mg.

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Author contribution: All authors have contributed equally.

Sažetak

KOMPARATIVNO ISPITIVANJE MELATONINA SA PLACEBOM U SMANJENJU HEMODINAMIČKIH ODGOVORA NA LARINGOSKOPIJU I INTUBACIJU

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Uvod: Povećanje krvnog pritiska i srčane frekvencije primećuje se tokom laringoskopije i intubacije. Melatonin se koristi za sedaciju u jedinicama intenzivne nege. Naše istraživanje se baziralo na hipotezi da primena melatonina u dozama od 3 mg i 6 mg 90 minuta pre uvoda u anesteziju smanjuje hemodinamičke odgovore tokom laringoskopije i intubacije.

Materijal i Metode: 75 odraslih pacijenata zakazanih za elektivne hirurške procedure, ASA I i II, podeljeni su u 3 grupe (25 pacijenata u svakoj grupi) koje su primile, 90 minuta pre indukcije anestezije, oralni placebo, melatonin 3 mg i melatonin 6 mg, redom. Hemodinamički parametri su mereni pre anestezije, i nakon indukcije anestezije u intervalima od 3, 6, 9, 12, 15 i 30 minuta. Analiza varijanse (ANOVA) je korišćena za međugrupnu analizu podataka. Kategoričke varijable su upoređivane primenom neparametrijskih testova Chi-kvadrat ili Fisherovog egzaktnog testa. Bonferronijeva korekcija je korišćena za međugrupnu analizu. Statistička značajnost je uzeta u obzir kada je $p < 0,05$.

Rezultati: Primećeno je povećanje srčane frekvencije i krvnog pritiska u 3, 6 i 9 minuta nakon indukcije opšte anestezije u kontrolnoj grupi, u poređenju sa grupama koje su primile melatonin u dozama od 3 mg i 6 mg 90 minuta pre indukcije opšte anestezije. Melatonin u dozi od 6 mg oralno je izazvao veće smanjenje nego melatonin u dozi od 3 mg.

Zaključak: Oralna primena melatonina u dozama od 3 mg i 6 mg efikasno smanjuje hemodinamičke promene tokom laringoskopije i intubacije.

Ključne reči: Laringoskopija, odgovor na podražaj, melatonin, preoperativna anksioznost, hemodinamske promene.

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Original article

PERFORMANCE EVALUATION OF VERI-Q RED HAEMOGLOBIN METER FOR POINT-OF-CARE HAEMOGLOBIN AND PACKED CELL VOLUME ESTIMATIONS

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Abstract: **Introduction:** Haemoglobin (Hb) and packed cell volume (PCV) are tests used in the assessment of anaemia. The Veri-Q haemoglobin meter is a new device in the point-of-care market used for the quantitative measurement of haemoglobin and packed cell volume. This study aimed to evaluate the performance of the Veri-Q haemoglobin meter for the assessment of haemoglobin and packed cell volume.

Materials and Methods: Haemoglobin and packed cell volume estimations of one hundred and eleven participants were determined using the Veri-Q Red haemoglobin meter and statistically compared with those obtained from the conventional method (gold standard).

Results: One hundred and eleven undergraduate students participated in this study, of whom 72 (64.9%) were females and 39 (35.1%) were males. The mean haemoglobin values calculated using the Veri-Q haemoglobin meter (11.97 ± 1.95 g/dl) were significantly lower than the values obtained with the conventional method (12.35 ± 1.66 g/dl) (t = 4.7549; p = 0.0001). Similar results were obtained with packed cell volume estimation. The performance indices of the Veri-Q haemoglobin meter were as follows: sensitivity (75.41% for Hb and 77.05% for PCV), specificity (28.0% for Hb and PCV), positive predictive value (PPV) (56.1% for Hb and 56.63% for PCV), negative predictive value (48.28% for Hb and 50% for PCV). The prevalence of anaemia in this study was 54.05%. Positive Likelihood Ratio (1.05 for Hb and 1.07 for PCV), Negative Likelihood Ratio (0.88 for Hb and 0.82 for PCV), Accuracy (54.05% for Hb and 54.95% for PCV). The Receiver Operative Characteristics (ROC) Area Under Curve (AUC) was 0.996 for Hb and 0.984 for PCV. A significant but weak positive correlation was found to exist between haemoglobin estimations using conventional and Veri-Q methods (r = 0.3013, P = 0.01); PCV (R = 0.2512, P = 0.07). The sensitivity of the device can be described as moderate while the specificity is low. The accuracy of the device is just average.

Conclusion: The Veri-Q haemoglobin meter demonstrates an average level of accuracy and a high AUC, making it potentially useful for field epidemiological studies.

Keywords: Veri-Q, performance indices, haemoglobin, packed cell volume, anaemia, point of care.

INTRODUCTION

Haemoglobin (Hb) is a crucial protein found in red blood cells, responsible for transporting oxygen from the lungs to tissues throughout the body. Each gram of haemoglobin can carry approximately 1.4 ml of oxygen, comprising 96% of the red blood cell's weight (1-3).

Measurement of Hb and packed cell volume (PCV) is routinely included in complete blood counts, essential for diagnosing and monitoring anaemia in patients. Anaemia can result from various pathological processes, including bleeding, micronutrient deficiencies, hydration imbalance, organ diseases, and hemolysis (4-7).

The VERI-Q Instrument (Manufacturer-Diaprax GmbH (sold by Micobiomed, South Korea), Wesel, Deutschland, 2015) is utilized for quantitatively measuring Hb levels. This device is suitable for both professional and self-testing purposes. It provides results within 5 seconds, offering precision, reliability, and ease of use. The Veri-Q-Red device boasts advantages such as quick results, requiring only a small blood sample (7 µl full blood), a measuring range of 5 - 25 g/dl,

including haematocrit indication, PC interface, affordability, and convenient storage of test strips at room temperature without the need for cooling (7).

Veri-Q haemoglobin test strips measure both Hb and haematocrit values in blood samples. However, the performance characteristics of this point-of-care machine have not been extensively documented in the literature, and its reliability and utility remain to be validated. Given that Hb and packed cell volume are commonly requested tests in hospitals, there is a critical need to compare the performance of the Veri-Q machine with conventional methods of Hb and packed cell volume estimations for patient management and field epidemiological studies.

Therefore, this study aimed to determine Hb and packed cell volume levels using the Veri-Q Red Point-of-Care device and compare the results with those obtained from conventional laboratory methods. The study seeks to assess the performance indices of the Veri-Q Red device to ascertain its reliability and utility in clinical and epidemiological settings.

Figure 1. *Veri-Q RED Haemoglobin meter*

MATERIAL AND METHODS

Study Setting

This study was conducted at Rivers State University (RSU) in Port Harcourt, Nigeria, a government-owned university located in the heart of Port Harcourt metropolis. The study population consisted of apparently healthy students of the university.

Study Design

The study adopted a cross-sectional design to collect data from participants.

Ethical Considerations

Informed consent was obtained from all participants before blood collection. Ethical approval was obtained from the Office of the Research Ethics Committee at the Rivers State University Teaching Hospital. All procedures were conducted in accordance with the institutional and/or national research committee's ethical standards and with the principles outlined in the 1964 Helsinki declaration and its later amendments.

Sample Collection

Three milliliters of venous blood were collected from each participant into ethylene diamine tetraacetic acid (EDTA) anticoagulant bottles. These samples were used for Veri-Q Red point-of-care device testing and conventional methods for haemoglobin and packed cell volume estimations.

Procedure for Packed Cell Volume Estimation by Microhematocrit Method

A capillary tube was immersed in the venous blood sample, allowing the blood to enter the tube via capillary action. The last 15mm of the tube was left unfilled.

The tube was sealed with sealant, ensuring no air was trapped between the sealant and the column of blood. The sealed tube was placed in a microhematocrit centrifuge with the sealed end facing the outer rim and centrifuged at 12000 g for 5 minutes.

The packed cell volume was determined using a microhematocrit reading device.

Procedure for Haemoglobin and Packed Cell Volume by Veri-Q Method

The pipette lip was securely inserted into the pipette.The top button of the pipette was pushed down to the first stage to collect the blood sample from the finger.

Subsequently, the top button of the pipette was carefully and slowly released to draw the blood into the lip. The top button was then pushed down to release the blood into the strip.

The results for haemoglobin and packed cell volume were read within 5 seconds using the Veri-Q Red device.

Procedure for Haemoglobin Estimation by Haemiglobincyanide Method

25 µl of blood was added to 5.0 mL of reagent, mixed, and left for 5 minutes. Absorbance was measured at 540 nm against a reagent blank. The absorbance of the HiCN standard was measured similarly.

The haemoglobin concentration was calculated using the formula: (Absorbance of test / Absorbance of standard) × Concentration of standard in g/dl.

Statistical Analysis

The data obtained were analyzed using GraphPad Prism software version 6.00 produced by GraphPad

Software Inc., USA. Data were presented as means and standard deviations, and comparison between means was done using t-test analysis. Performance indices were calculated using standard formulae.

RESULTS

A total of one hundred and eleven subjects participated in the study, comprising 72 (64.9%) females and 39 (35.1%) males. The mean Hb values measured using the Veri-Q haemoglobin meter (11.97 ± 1.95 g/dl) were significantly lower than those obtained from the conventional method (12.35 ± 1.66 g/dl) (t = 4.7549; p = 0.0001). Similar results were observed for Packed Cell Volume estimation (Table 1).

Table 2 presents the performance indices of the Veri-Q Red haemoglobin meter. The sensitivity of the point-of-care (POC) machine was 75.41%, specificity was 28.0%, positive predictive value (PPV) was 56.1%, and negative predictive value was 48.28%. The prevalence of anaemia in this study was found to be 54.05%.

Figures 2-5 depict the Receiver Operating Characteristic (ROC) curve of Veri-Q Red for haemoglobin and Packed Cell Volume (PCV). The Area Under Curve (AUC) was 0.996 for HB and 0.984 for PCV.

Figures 6 and 7 illustrate the Pearson correlation between haemoglobin and Packed Cell Volume estimations using the Veri-Q Red meter and conventional methods. A significant positive correlation was found to exist between haemoglobin estimations using conventional and Veri-Q Red methods (r = 0.3013, p = 0.001); PCV (R = 0.2512, p = 0.007) (Figure 6). Similar results were obtained for PCV and the Veri-Q Red haemoglobin meter (Figure 7).

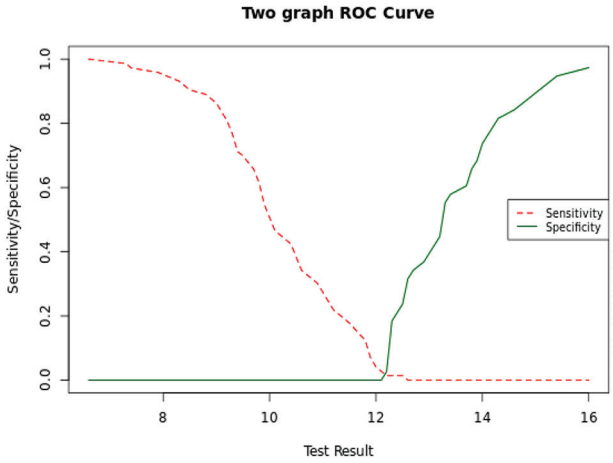

***Figure 2**. Sensitivity and Specificity ROC curve for Veri-Q haemoglobin estimation*

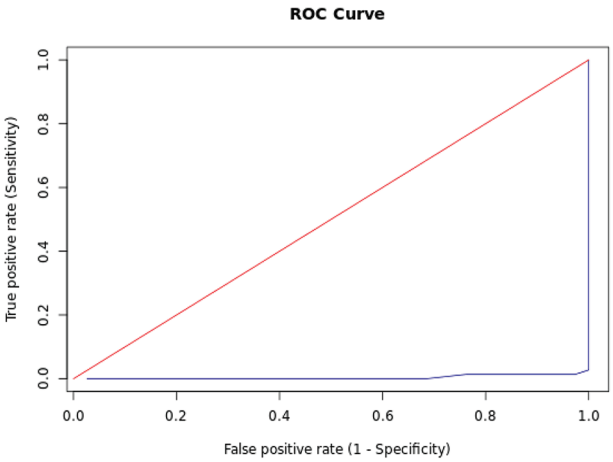

***Figure 3.** Graph of ROC curve for haemoglobin estimation using Veri-Q meter*

***Table 1.** Mean values of Haemoglobin and Packed Cell Volume of the conventional and Veri-Q methods*

Methods	Hb(g/dl) Mean ± SD	PCV (%) Mean ± SD
Conventional	12.35 ± 1.66	36.48 ± 4.91
Veri-Q	11.97 ± 1.95	33.18 ± 6.43
T-test	4.7549	4.2951
P-values	0.0001***	0.0001***

***Table 2.** Performance indices of Veri-Q haemoglobin meter using conventional methods as gold standard*

Statistic	Hb Value	Hb 95% CI	PCV Value	PCV 95% CI
Sensitivity	75.41%	62.71% to 85.54%	77.05%	64.50% to 86.85%
Specificity	28.00%	16.23% to 42.49%	28.00%	16.23% to 42.49%
Positive Likelihood Ratio	1.05	0.84 to 1.31	1.07	0.86 to 1.33
Negative Likelihood Ratio	0.88	0.47 to 1.64	0.82	0.43 to 1.55
Disease prevalence (*)	54.95%	45.22% to 64.41%	54.95%	45.22% to 64.41%
Positive Predictive Value (*)	56.10%	50.51% to 61.53%	56.63%	51.15% to 61.94%
Negative Predictive Value (*)	48.28%	33.31% to 63.55%	50.00%	34.54% to 65.46%
Accuracy (*)	54.05%	44.33% to 63.55%	54.95%	45.22% to 64.41%

(*) These values are dependent on disease prevalence.

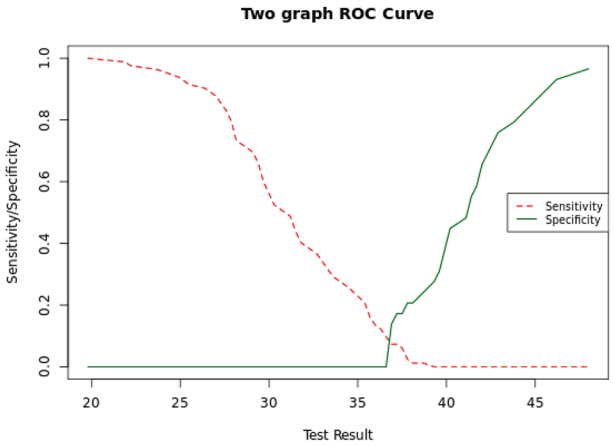

Figure 4. *Sensitivity and Specificity ROC curve for Veri-Q Packed Cell Volume estimation*

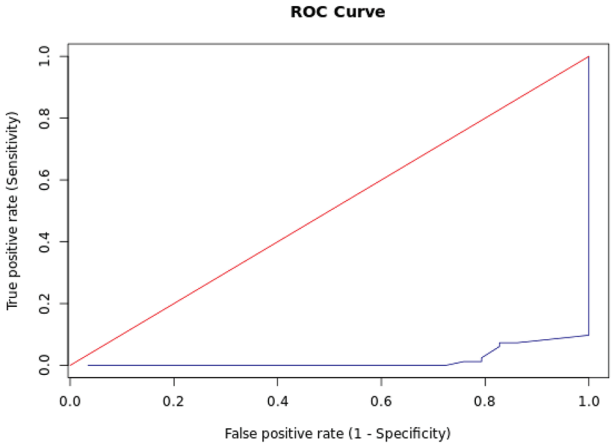

Figure 5. *Graph of ROC curve for packed cell volume estimation using Veri-Q meter*

DISCUSSION

The Veri-Q haemoglobin meter is a new device designed for point-of-care testing, field studies, diagnostic, and clinical use in hospital emergencies, as well as for quick diagnoses of anaemia at home. The performance characteristics of this new device have not been encountered in the literature. This study represents the very first attempt to validate the equipment and determine its performance characteristics.

The sensitivity of the Veri-Q Red haemoglobin meter was found to be 75.4% for Haemoglobin and 77.0% for Packed Cell Volume. Sensitivity indicates the likelihood that a diseased patient has a positive result, meaning it will correctly give positive results for those with the disease condition. A sensitivity of 75% implies that out of one hundred people who have the disease, in this case, anaemia, seventy-five of them will be correctly diagnosed with this test device. In epidemiological or diagnostic studies, high sensitivity is useful to exclude a diagnosis because it will render few results that are falsely negative. To rule out anaemia, clinicians

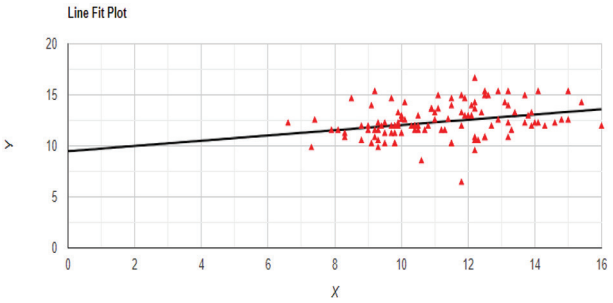

Figure 6. *Pearson correlation of haemoglobin estimation using Conventional versus Veri-Q methods*

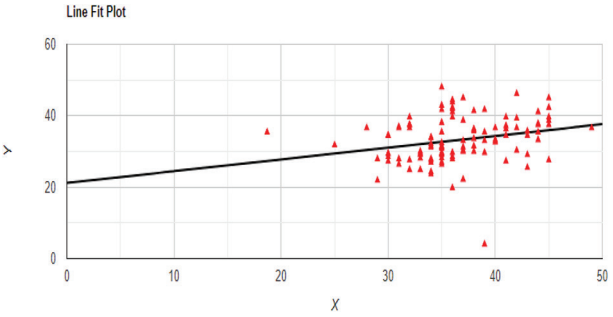

Figure 7. *Pearson correlation of Packed cell volume values using Conventional versus Veri-Q methods*

might prefer a test with high sensitivity. The sensitivity of this device could be regarded as very good.

The specificity of the Veri-Q Red haemoglobin meter was found to be 28.0% for both haemoglobin and packed cell volume. Specificity refers to the likelihood that a healthy person has a negative test result. If one hundred persons do not have anaemia and the test is capable of giving a negative result for all of them (100% specificity), then the test is highly specific. A highly specific test is useful to confirm a diagnosis because it will have few results that are falsely positive. In this study, the specificity of the Veri-Q Red haemoglobin meter is as low as 28.0%. This means that the device can correctly identify 28% of true negative cases. In other words, if the testing device is used on a sample of individuals who do not have a certain condition or trait, it will correctly identify 28% of them as negative. The higher the specificity, the better the testing device is at accurately ruling out the presence of a specific condition or trait in individuals without it. Thus, it is not suitable to be used to confirm disease among apparently healthy subjects.

Receiver Operative Characteristics (ROC), which is a logistic regression model, is often employed to determine the best cutoff value for predicting whether a new observation is a failure (0) or a success (1). In this study, the AUC for haemoglobin is 0.996 while that of PCV is 0.984. This indicates that the Veri-Q Red haemoglobin meter is efficient and will be able to discriminate between positives and negatives.

The accuracy of the Veri-Q Red machine was determined to be 54.05% for Hb and 54.95% for PCV. The accuracy of the Veri-Q Red haemoglobin meter can be maximized by calibrating the equipment with reference material and by participating in external quality control programmes.

The positive predictive value (PPV) of the Veri-Q Red machine in this study was obtained as 56.10% for Hb and 56.63% for PCV. On the other hand, the negative predictive value for Hb was 48.28% and 50% for PCV. PPV is capable of predicting how likely it is for someone to truly be a patient in case of a positive test result, while Negative Predictive Value (NPV) can predict how likely it is for someone to truly be healthy in case of a negative test result (8).

In this study, the positive likelihood ratio (LR^+) for Hb was 1.05 and for PCV 1.07, while the negative likelihood ratio (LR^-) was 0.88 for Hb and 0.82 for PCV. The prevalence of anaemia was 54.95%. The study population consisted of apparently healthy adult students of both sexes. This prevalent rate of anaemia among the students of this University corroborates the study of Shill *et al*. (9), where a prevalent rate of 55.3% was reported among university students in Bangladesh. However, the prevalence of anaemia in this study is quite high compared with 28.9% reportedly recently among adults in a selected population in Lagos, Nigeria (10). In Ghana, a prevalence rate of anaemia was reported to be 45.1% among University students (11). The high prevalence of anaemia among students may be attributed to poor dietary habits, menstrual blood loss, and lack of awareness of iron deficiency and nutritional status (12).

CONCLUSION

In conclusion, this study revealed a high prevalence rate of anaemia when using the Veri-Q Red haemoglobin meter. Despite this, a significant positive correlation was found to exist between haemoglobin estimations using conventional and Veri-Q Red methods. However, the sensitivity of the Veri-Q device can be described as moderate, while the specificity is quite low. Additionally, the accuracy of the device was found to be average.

If properly validated, the Veri-Q-Red device has the potential to be an ideal point-of-care device for various medical settings, including blood banks, blood donation centers, general practitioners' offices, internists' practices, gynecologists' and perinatologists' clinics, as well as laboratory and home use. Further validation and quality control measures are necessary to ensure its reliability and effectiveness in clinical practice.

RECOMMENDATION

It is recommended that the Veri-Q Red haemoglobin meter undergo thorough validation and quality control measures to ensure its reliability and accuracy. If these measures are implemented successfully, the device can serve useful purposes in field epidemiological surveys and point-of-care settings.

Abbreviations

AUC - Area Under Curve
ROC - Receiver Operative Characteristics
PCV - Packed Cell Volume

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Authors' Contributions: ZJ contributed to conceptualization, detailed review, and statistical analysis. VA conducted literature reviews and laboratory analyses. RJ participated in manuscript review and editing. All authors have reviewed and approved the final manuscript.

Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

EVALUACIJA PERFORMANSI VERI-Q HEMOGLOBINSKOG MERAČA ZA PROCENU HEMOGLOBINA I HEMATOKRITA NA MESTU PRUŽANJA POMOĆI

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Uvod: Hemoglobin (Hb) i hematokrit (Ht) su testovi koji se koriste u proceni anemije. Veri-Q hemoglobin merač je nov uređaj na tržištu za brzo testiranje, koji se koristi za kvantitativno merenje hemoglobina

i hematokrita. Ova studija ima za cilj procenu performansi Veri-Q hemoglobin merača za procenu hemoglobina i hematokrita.

Materijali i metodi: Procena hemoglobina i hematokrita kod sto jedanaest učesnika izvršena je pomoću Veri-Q hemoglobinskog merača i statistički upoređena sa vrednostima dobijenim konvencionalnom metodom (zlatni standard).

Rezultati: U ovoj studiji je učestvovalo sto jedanaest studenata osnovnih studija, od kojih je 72 (64,9%) bilo ženskog pola, a 39 (35,1%) muškog pola. Srednje vrednosti hemoglobina izračunate korišćenjem Veri-Q hemoglobinskog merača (11,97 ± 1,95 g/dl) bile su značajno niže od vrednosti dobijenih konvencionalnom metodom (12,35 ± 1,66 g/dl) (t = 4,7549; p = 0,0001). Slični rezultati dobijeni su i kod procene hematokrita. Performanse Veri-Q hemoglobinskog merača bile su kako sledi: osetljivost (75,41% za Hb i 77,05% za PCV), specifičnost (28,0% za Hb i PCV), pozitivna prediktivna vrednost (PPV) (56,1% za Hb i 56,63% za PCV), negativna prediktivna vrednost (48,28% za Hb i 50% za PCV). U ovoj studiji, prevalencija anemije je bila 54,05%, pozitivni odnos verovatnoće (1,05 za Hb i 1,07 za PCV), negativni odnos verovatnoće (0,88 za Hb i 0,82 za PCV), a tačnost (54,05% za Hb i 54,95% za PCV). AUC-ROC je bila 0,996 za Hb i 0,984 za PCV. Primećena je značajna, ali slaba pozitivna korelacija između procene hemoglobina korišćenjem konvencionalne i Veri-Q metode (r = 0,3013, P = 0,01); PCV (R = 0,2512, P = 0,07). Osetljivost uređaja može se opisati kao umerena, dok je specifičnost niska. Tačnost uređaja je samo prosečna.

Zaključak: Veri-Q hemoglobinski merač pokazuje prosečnu tačnost i visok AUC, što ga čini potencijalno korisnim za terenske epidemiološke studije.

***Ključne reči**:* Veri-Q, performansni indeksi, hemoglobin, puni volumen eritrocita, anemija, „Point-of-Care“ ispitivanje.

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DEVELOPMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA AND INVASIVE CERVICAL CANCER DUE TO OXIDATIVE STRESS

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Abstract: **Background:** Cervical cancer (CC) ranks third among all malignant diseases of the female reproductive system. CC arises through a series of pathological changes called cervical intraepithelial neoplasia (CIN). Timely diagnosis and treatment of CIN are essential in the prevention of CC. Oxidative stress (OS) presents a major risk factor in the pathogenesis of both CC and CIN. This study aimed to determine the association between OS and the pathohistological severity of cervical lesions.

Materials and Methods: The research was conducted at the Clinical Center of the University of Sarajevo on 240 female respondents divided into two groups. The experimental group consisted of 200 women with changes consistent with CIN, carcinoma in situ (CIS), and CC determined by biopsy, divided into 5 subgroups (CIN 1, CIN 2, CIN 3, CIS, and CC) with 40 respondents per group. The control group (N = 40) had biopsy findings that were non-pathological. The concentration of acid thiobarbituric reactive substances (TBARS) was determined for all subjects from bioptic samples using the spectrophotometric method and according to standard laboratory practice.

Results: Our results showed a significant difference in age between patients with CIN 1, CIN 2, and CIN 3 and the control group as well as when compared to patients with CC. The oldest group comprised patients with CC. Tissue TBARS levels in the CIS group were significantly higher than that of the control group ($p < 0.001$), CIN 1 group ($p < 0.001$), CIN 2 group ($p < 0.001$), CIN 3 group ($p = 0.033$), as well as CC group ($p = 0.002$). Likewise, tissue TBARS levels in the CIN 3 group were significantly higher than those of the control group ($p = 0.023$), and CIN 1 group ($p = 0.024$).

Conclusion: Compared to healthy controls, patients with CIN and CC have increased oxidative stress. Tissue TBARS levels represent a significant differentiation marker of the clinical stage of the disease and can be a useful diagnostic tool influencing the selection of therapeutic procedures.

Keywords: oxidative stress, cervical intraepithelial neoplasia, cervical cancer.

INTRODUCTION

Cervical cancer (CC) stands as the third most prevalent malignancy affecting the female reproductive system, accounting for approximately 12% of all malignant neoplasms in women (1, 2). Its precursor, cervical intraepithelial neoplasia (CIN), marks a spectrum of pathological changes that vary in severity, with higher-grade CIN posing an increased risk for the development of CC. The incidence of CC and CIN is influenced by a myriad of factors, including human papillomavirus (HPV) infection, early initiation of sexual activity, smoking, and socioeconomic status (3).

The successful implementation of screening programs significantly impacts the frequency of CC, emphasizing the importance of early detection and intervention (4). Diagnosis typically involves a combination of gynecological examinations, Pap smears, colposcopy, and biopsies to confirm CC. Treatment modalities vary based on disease stage, ranging from surgical interventions for early-stage disease to radiotherapy and chemotherapy for advanced cases. Prognosis hinges largely on disease stage and lymph node involvement (5, 6).

Early diagnosis and treatment of CIN are very important in the prevention of CC, and today, special attention is paid to screening examinations of women and HPV vaccination of the younger population of girls.

In the last decade, a series of discoveries indicate oxidative stress (OS) asanmayor risk factor in CC and

CIN pathogenesis (7). Oxidative stress induced peroxidation of membrane lipidscreates a broad range of oxidation products, among which the most common one is malondialdehyde (MDA), which binds to proteins and phospholipids of the membrane, thereby deepening oxidative cell damage (7). Today, MDA is used in many scientific studies as oxidative stress marker, more precisely for the assessment of lipid peroxidation. Another oxidative stress marker that quickly and strongly binds to malondialdehyde is Acid thiobarbituric reactive substances (TBARS). The involvement of lipid peroxidation in pathogenesis in female reproductive system malignant diseases has been proven (8).

AIM

The aim of this study was to determine the association between OS and pathohistological severity of cervical lesions.

MATERIAL AND METHODS

The study was conducted at the Clinical Center of the University of Sarajevo and received approval from the Ethics Committee (number: 0901-2-390/17) in accordance with the principles outlined in the Declaration of Helsinki.

Two hundred and forty female respondents were recruited and divided into two groups: an experimental group and a control group. The experimental group comprised 200 women with confirmed indications for biopsy based on colposcopy findings and Pap test results, showing changes consistent with cervical intraepithelial neoplasia (CIN), carcinoma in situ (CIS), or cervical cancer (CC). This group was further subdivided into five subgroups (CIN 1, CIN 2, CIN 3, CIS, and CC), each consisting of 40 respondents.

The control group comprised 40 women with non-pathological findings, excluding CC and CIN. Biopsy indication in this group was determined for other medical reasons.

Participants underwent physical, gynecological, and colposcopic examinations, as well as Pap tests, to establish the biopsy indication. TBARS concentration was determined from bioptic samples using a spectrophotometric method following standard laboratory protocols.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 16.0. Data were presented as mean ± standard deviation (SD) or as median and interquartile range (IQR). Analysis of variance (ANOVA) test was used for variables following a normal distribution, while non-parametric Kruskal-Wallis and Mann-Whitney U tests were applied as appropriate. A significance level of $p < 0.05$ was considered statistically significant.

RESULTS

The age statistics and tissue TBARS levels among the study groups are summarized in Table 1.

Table 1. *Descriptive statistics for age and TBARS according to study groups*

Group	N	Age (years)	TBARS-tissue (µM)
Controls	40	50.0 (42.0-57.0)	4.80 ± 0.22
CIN 1	40	44.0 (35.5-51.0)	4.78 ± 0.25
CIN 2	40	45.0 (36.0-51.67)	4.94 ± 0.24
CIN 3	40	41.0 (36.5-50.0)	5.94 ± 0.23
CIS	40	45.0 (40.0-61.5)	7.06 ± 0.31
CC	40	54.0 (38.5-62.25)	5.65 ± 0.24

A significant difference in age was found between the control group and patients with CIN 1 ($p = 0.042$), CIN 2 ($p = 0.036$) and CIN 3 ($p = 0.005$). Likewise, significant age differences were found between patients with CC and those with CIN 1 ($p = 0.015$), CIN 2 ($p = 0.022$) and CIN 3 ($p = 0.010$) (Figure 1).

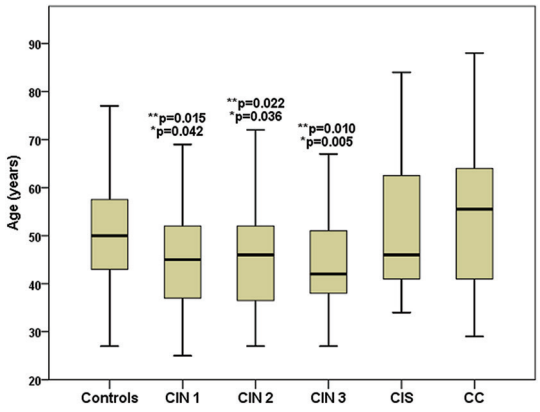

Figure 1. *Age of patients with CIN,CC and subjects of the control group*

(Results are shown as median and interquartile range /25-75 percentiles/; *compared to control group; **compared to group with CC).

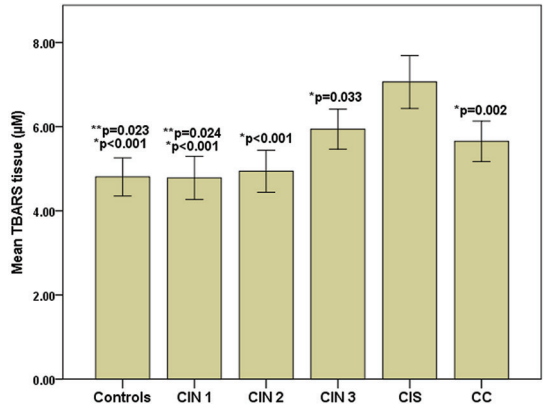

Figure 2. *Tissue TBARS levels in patients with CIN, CC and subjects of the control group*

(Results are shown as mean ± standard error of the mean (x ± SEM); *compared to CIS; **compared to CIN 3).

Tissue TBARS levels were significantly elevated in patients with CIS compared to the control group ($p < 0.001$), as well as compared to patients with CIN 1 ($p < 0.001$), CIN 2 ($p < 0.001$), CIN 3 ($p = 0.033$), and CC ($p = 0.002$). Additionally, tissue TBARS levels in patients with CIN 3 were significantly higher than those in the control group ($p = 0.023$) and in patients with CIN 1 ($p = 0.024$) (Figure 2).

DISCUSSION

Cervical carcinoma is often preceded by CIN. It can spontaneously regress or progress if not treated immediately. CIN stages 2 and 3 are associated with the risk of developing CC and are usually treated with rest. There is a certain chance that these lesions will resolve, and observation and follow-up may be chosen for certain patients. This is a particular option for women planning to give birth, as excisional procedures are followed by an increased risk of poor pregnancy outcomes.

Our results showed a significant difference in age between the control group and patients with CIN 1 ($p = 0.042$), CIN 2 ($p = 0.036$) and CIN 3 ($p = 0.005$). The same significant age difference has been noted between CC patients and patients CIN 1 ($p = 0.015$), CIN 2 ($p = 0.022$) and CIN 3 ($p = 0.010$). The oldest group were patients with CC.

In a study by Chang et al. (9), it was shown that CIN 3 and CC incidence rates decrease with time, while CIN 1 and CIN 2 increase significantly ($p < 0.001$). The peak age of incidence was 25–29 and 30–34 years for CIN 1 and 2, respectively, and 70–74 years for CIN 3 and CC. The frequency of CIN 1 and 2 showed an increasing trend in all age groups. CC was significantly reduced in all age groups, except for the 35-39 age group.

The study by Wang et al. (3), where the researchers monitored age, spouse occupation, hygiene after intercourse, and average daily folate intake as predictors of CIN, yielded interesting data. The 56-65year-old group was at the highest risk for developing CIN, while the risk of CIN in the group aged 36-45 was determined to be 61.4% of the risk in the older group.

CIN and uterine cancer can also be associated with other risk factors, such as marked OS. Oxidative damage in the human body is a daily occurrence, but most oxidative lesions can be significantly repaired by specific DNA glycosylases. The repair of damage, however, is never complete, so it accumulates with age. As the organism ages, during the division of such cells, damage becomes permanent, along with the development of mutations and malignant diseases. (10, 11).

OS holds an important place in the pathogenesis of many malignant diseases such as cancer of the kidney, bladder, lung, colon, etc (12).

A number of researchers believe that selective OS, i.e. free radicals at the local level (in the malignant tissue itself) could have a beneficial effect on the apoptosis of carcinomatous cells and prevent their proliferation (13).

OS is an understudied factor when it comes to its role in CC, where the main questions are whether it acts synergistically or independently of HR-α-HPV infection. HPV-positive cervical lesions show higher levels of oxidative DNA damage when compared to control HPV-negative samples. The extent of damage is closely related to high-risk HPV types (14).

OS and lipid peroxidation already appear in the early stages of carcinogenesis when it comes to CIN. MDA, as lipid peroxidation product, is highly cytotoxic and acts as a cancer promoter. Patients with CC were shown to have significantly higher levels of MDA (15).

Previous studies have shown inconsistent results when examining the levels of OS markers in patients with CIN and CC.

Srivastava et al. (16) showed that the level of lipid peroxidation was increased in patients with CC compared to the control group, but in relation to different stages of carcinoma, lipid peroxidation levels in these patients did not differ.

Carrero et al. (17) showed a positive correlation between the increase in the cellular level of superoxide anions and the progression of CIN. According to this research, the increased production of superoxide anions in CIN lesions can lead to oxidative DNA damage, which can lead to CC. According to this study, measuring the level of cellular superoxide anions can have a predictive role in monitoring the progression of premalignant changes on the cervix. Lipid peroxidation levels and OS monitored in other malignant diseases showed mostly their higher levels compared to the healthy population.

Our results showed significantly higher tissue TBARS levels in patients with CIS compared to levels of other groups (controls, CIN 1, CIN 2, CIN 3, CC). The level of TBARS in the tissue of patients followed the level of changes in the cells. TissueTBARS levels in CIN 3 group were significantly higher than those in controls and patients with CIN 1.

These results are similar to the results of Jelić et al. (15), who showed that the lipid peroxidationlevel is higher in cervical precancers, as well as in uterine cancer compared to the control group. Their research concluded that TBARS as an OS marker was higher in all study groups compared to controls, especially in women with advanced CC.

The same authors also showed that the activity of other markers such as superoxide dismutase, catalase, glutathione-S-transferase were significantly higher in cervical pre-cancers, as well as in uterine cancer compared to the control group.

It is believed that disease progression followed by production of oxygen radicals and increase in lipid peroxidation causegreater degree ofcell membrane degeneration in patients with advanced CC when compared to patients with lower stages, indicating that lipid peroxidation can cause CC progression. Tissue degeneration can be caused by increased lipid peroxidation and this process can spread from primary sites through the circulation.OS is probably involved in the pathogenesis of CC due to increased lipid peroxidation and changes in the antioxidant defense system (18).

The data obtained in the study by Zahra et al. (7) also show OS involvement in CC pathogenesis, demonstrated by increased lipid peroxidation, higher of 8-OhdG levels and alteration in the antioxidant defense system. The authors believe that OS can be considered a dominant risk factor even in the initial stage of carcinogenesis. Cancer cells produce oxidants, deplete antioxidants and establish a vicious stress multiplication cycle. This cycle is characteristic in advanced stages because of increase in cancer burden. The disruption of oxidant-antioxidant levels leading to oxidative lipid damage and promotion of cancer initiation and progression is hypothesised by Zahra et al.

A study by Visalli et al. (19) that included 202 samples from colpo-cytopathology examinations found much higher OS levels in patients with more severe squamous intraepithelial lesions (SIL)compared to the control group. Higher OS levels were also found among patients with intraespithelial lesions of lower grade.

This is also backed by Carneiro et al. study (20), where it was shown that women with SIL had higher levels of MDA compared to women with normal histopathological findings.

Lipid peroxidation products could indeed be one of the possible causes of uterine cancer progression. Sahah et al. (21) showed that the mean concentration of total antioxidant capacity (TAC) was significantly lower in the group of patients with CC compared to healthy subjects.

Taking into account that the results of our research showed the highest TBARS concentrations in the CIS group, compared to the control group, patients with premalignant lesions, and patients with uterine cancer, we are of the opinion that the increase in lipid peroxidation in this stage of the disease can be used as a potential differentiation biomarker indicating transition of the disease from premalignant to malignant form. A possible increase in TBARS levels at this stage may be a consequence of disease progression, but it is not excluded that the organism at this very stage responds with pronounced lipid peroxidation at the local and systemic level as a potential defense, because it is known that oxygen radicals can be harmful to cancer cells.

The fact is that most studies classify OS as a risk factor for the pathogenesis and progression of the disease,meaning that the increase in TBARS in the CIS stage may indicate the risk of disease progression. In any case, the results of this study open new perspectives in the diagnosis and therapy of the disease. Lipid peroxidation can serve as a possible biomarker of disease staging, and as such can be a useful diagnostic tool (22).

CONCLUSION

Patients with CIN and CC have increased levels of oxidative stress.Tissue TBARS levels in patients with the CIS stage were significantly higher compared to subjects with CC and subjects with any of the lower CIN stages. TBARS level is a significant marker of differentiation of the clinical stage of the disease and can be a useful diagnostic tool influencing the selection of therapeutic procedures, but its application in screening is also possible.

Abbreviations

CC - Cervical Cancer
CIN - Cervical Intaepithelial Neoplasia
CIS - Carcinoma in Situ
DNA - Deoxyribonuceic acid
HPV- Human papillomavirus
MDA - Malondialdehyde
OS - Oxidative stress
TBARS - Acid tiobarbituric reactive substances

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Note: Artificial intelligence was not used as a tool in this study.

Sažetak

RAZVOJ INTRAEPITELNIH NEOPLAZIJA I INVAZIVNOG KARCINOMA GRLIĆA MATERICE ZBOG OKSIDATIVNOG STRESA

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Uvod: Karcinom grlića materice (CC) zauzima treće mesto među svim zloćudnim bolestima ženskog reproduktivnog sistema. CC nastaje kroz seriju patoloških promena nazvanih intraepitelne neoplazije grlića materice (CIN). Pravovremena dijagnoza i lečenje CIN su ključni u prevenciji CC. Oksidativni stres (OS) predstavlja glavni faktor rizika u patogenezi kako CC,tako i CIN. Cilj ovog istraživanja bio je utvrditi povezanost između OS-a i patohistološke ozbiljnosti cervikalnih lezija.

Materijali i metode: Istraživanje je sprovedeno na Kliničkom centru Univerziteta u Sarajevu na 240 ženskih ispitanica podeljenih u dve grupe. Eksperimentalnu grupu činilo je 200 žena s promenama koje su bile u skladu s CIN-om, karcinomom in situ (CIS) i CC-om utvrđenim biopsijom, podeljenim u 5 podgrupa (CIN 1, CIN 2, CIN 3, CIS i CC) sa po 40 ispitanica u svakoj grupi. Kontrolnu grupu (N = 40) činile su biopsije koje nisu bile patološke. Koncentracija reaktivnih supstanci tiobarbituratne kiseline (TBARS) određena je za sve ispitanice iz bioptičkih uzoraka koristeći spektrofotometrijsku metodu i prema standardnoj laboratorijskoj praksi.

Rezultati: Naši rezultati pokazuju značajnu razliku u uzrastu između pacijentkinja s CIN 1, CIN 2 i CIN 3 i kontrolne grupe, kao i u poređenju s pacijentkinjama s CC. Najstariju grupu činile su pacijentkinje s CC. Nivoi TBARS-a u tkivu u CIS grupi bili su značajno viši nego u kontrolnoj grupi ($p < 0,001$), CIN 1 grupi ($p < 0,001$), CIN 2 grupi ($p < 0,001$), CIN 3 grupi ($p = 0,033$), kao i u CC grupi ($p = 0,002$). Isto tako, nivoi TBARS-a u tkivu u CIN 3 grupi bili su značajno viši nego u kontrolnoj grupi ($p = 0,023$), i CIN 1 grupi ($p = 0,024$).

Zaključak: U poređenju s zdravim kontrolama, pacijentkinje s CIN i CC imaju povećani oksidativni stres. Nivoi TBARS-a u tkivu predstavljaju značajan diferencijalni marker kliničkog stadijuma bolesti i mogu biti korisno dijagnostičko sredstvo koje utiče na izbor terapijskih postupaka.

Ključne reči: oksidativni stres, cervikalna intraepitelna neoplazija, karcinom grlića materice.

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Original article

SWITCHING BIOLOGICS IN PSORIASIS: CHALLENGES AND EXPERIENCE FROM A SMALL TERTIARY HEALTH-CARE CENTER

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Abstract: **Objective**: Psoriasis, a chronic inflammatory skin disease, significantly impacts patients' quality of life. Over the last decade, therapeutic goals have aimed to complete skin clearance and restore normal patient activities, minimizing the disease's impact on social, family, and work activities. Biologics have emerged as a promising solution to achieve better disease control without organ-specific side effects, helping meet these therapeutic goals. However, it was soon noticed that approximately 30% of patients do not sufficiently react to the therapy in the long term, and the need for switching biologics emerges.

Findings: We present our experience with biologic switching over a specific period. Seventeen patients required a switch in biologic agents, with three undergoing a second switch. The cohort predominantly consisted of males (14 out of 17), with an average BMI of 29.81. The primary reasons for switching were secondary failure (loss of initial treatment efficacy), followed by primary failure. Adverse reactions were the least common cause, highlighting the satisfactory safety profile of biologics. One patient underwent dose escalation of secukinumab due to efficacy failure but ultimately ended up switching the biologic.

Conclusion: Biologic agents approved for the treatment of psoriasis showed a favorable safety profile without compromising efficacy. The increasing demand for higher efficacy in psoriasis treatment aims to alleviate the disease's multifaceted impact on patients. It is anticipated that biologic switching, primarily due to inadequate therapeutic response and less frequently due to adverse reactions, will become more prevalent in clinical practice. Literature and our clinical experience suggest that constitutional factors influence treatment success. As new agents and targets emerge, the established standards for biologic switching may require ongoing revision.

Keywords: psoriasis, biologics, switch, primary failure, secondary failure, inefficacy.

INTRODUCTION

Psoriasis is a chronic inflammatory disease affecting approximately 1 to 3% of the general population and significantly impacting patients' quality of life (1, 2). It is estimated that more than 30% of patients develop psoriatic arthritis. Furthermore, studies have confirmed a strong correlation between psoriasis and metabolic syndrome, posing a high risk for cardiovascular events (3, 4, 5). Physical and emotional discomforts related to psoriatic skin changes are common causes of sick leave and work absenteeism, highlighting the multisystemic nature of the disease.

Despite the availability of various treatment modalities for psoriasis, systemic agents often present organ-specific toxicity. The introduction of biologics for moderate to severe clinical forms of psoriasis brought new hope for patients and healthcare providers, initially observed for their lack of organ-specific side effects. However, approximately 30% of patients do not respond adequately to long-term therapy, necessitating a switch in biologics.

The need to alter biological treatment primarily arises due to four reasons: (I) inefficacy due to primary failure (not achieving a ≥ 50% Psoriasis Area and Severity Index [PASI] score improvement at 24 weeks of treatment); (II) inefficacy due to secondary failure (losing the efficacy that was present after commenc-

ing treatment, also known as biologic fatigue); (III) adverse events; and (IV) other factors such as lack of compliance and unhealthy lifestyle habits (6-9).

AIM

The increasing trend in biologic switching is due to the arrival of new agents with higher efficacy and potency, as well as patients' growing demands for complete skin clearance. The aim of our study is to assess the reasons for switching biologics and to analyze our previous experiences with these treatments. To our knowledge, there are few reports on this topic; therefore, we believe our study, even with a smaller sample, could contribute to a better understanding and potentially serve as a foundation for further research.

PATIENTS AND METHODS

As of 2019, three biologic agents have been available in Montenegro, a small Mediterranean country with a population of approximately 619,000, for the treatment of psoriasis. Adalimumab was first introduced in 2019, followed by secukinumab in 2020, and guselkumab at the end of 2021.

This retrospective study was conducted to evaluate patient characteristics necessitating biologic agent switching, as well as the frequency and reasons for treatment alteration. All patients undergoing biologic treatment in Montenegro must receive approval from three dermatologists at the Clinic of Dermatovenereology, Clinical Center of Montenegro. This center is the only site in the country authorized to approve biologic treatment. We collected data on patients who switched treatments, including age, gender, smoking habits, body mass index, initial PASI score, and number of biologic alterations. Clinical efficacy was assessed using the PASI (Psoriasis Area and Severity Index) score. This report is in alignment with the Statement of Human Rights stated by the Helsinki Declaration.

RESULTS

From the initiation of biologic treatments in 2019 until March 2022, we observed 17 patients who required alteration of their treatment. Tables 1 and 2 present the demographic and clinical characteristics of these patients, including the first-line biologic used before switching and the reasons for treatment alteration.

It is noteworthy that three patients underwent biologic switching twice. Each of these patients transitioned from adalimumab to secukinumab, and subsequently from secukinumab to guselkumab. All three patients switched both times due to secondary failure.

One patient required dose escalation of secukinumab due to primary failure but ultimately switched to a different biologic.

Table 1. *Characteristics of the Patients Observed in the Study*

Parameter	**Results**
Gender	Nº of patients (percent of patients)
Male	14 (82.3%)
Female	3 (17.7%)
Age	
Mean	51.58 years old (y.o.)
Range	28 y.o.-75 y.o.
BMI	
Mean	29.81
Range	22.2-40.7
Initial PASI	
Mean	26.17
Range	10-60
Smoking habit	Nº of patients (percent of patients)
Yes	10 (59%)
No	7 (41%)

Table 2. *Reasons for switching the biologics divided according to different agents*

Reasons for Switching	Adalimumab	Secukinumab	Guselkumab
Number of patients	9	8	0
Inefficacy due to primary failure	1	2	/
Inefficacy due to secondary failure	6	9	/
Infection/ inflammation	2	0	/

We did not observe any biologic switching due to serious or unforeseen adverse reactions. However, one patient, who was administered an anti-TNF agent, experienced reactivation of latent tuberculosis infection (LTBI). Additionally, there was one case where a patient experienced joint swelling after each dose of adalimumab. Upon reporting this to the dermatologist, we recommended an evaluation for potential underlying internal diseases. Consequently, she discontinued the treatment and opted not to switch to another biologic while undergoing further examination.

DISCUSSION

In recent years, switching biologics has become an important issue for discussion as new targets have been discovered and new biologics with higher efficacy introduced. The most common reasons for switching biologics relate to primary and secondary inefficacy (10, 11). In this regard, our study confirms such

findings, as the most common reasons in our patients were due to lack of efficacy. Regarding adverse reactions, they were not frequently observed. This underscores the favorable safety profile of the biologics (7, 8). We did not observe any other reasons for switching, such as lack of compliance.

The global prevalence of latent tuberculosis infection (LTBI) was estimated at 23.6% in 2019 (12). Although the exact reactivation rate is uncertain, around 5% are believed to experience reactivation (13, 14). Medications that interfere with patients' immune systems, particularly anti-TNF-alpha agents, pose a higher risk for reactivating LTBI and developing active tuberculosis. This is due to the necessity of TNF in forming granulomas to contain M. tuberculosis (15, 16). Our findings indicate no LTBI reactivation associated with anti-IL-17 and -23 agents (8).

Regarding gender prevalence, according to our observation, switching biologics was more prevalent in males. This is in accordance with the study conducted by Honda H et al., but the actual reason for such gender disparity is not known. According to the same study, the mean initial PASI of our cohort aligns with their results (7).

A smoking habit does not significantly influence the outcome of therapy in our cohort. The average body mass index in our patients was 29.81. A recent study by Pirro F et al. reported that obesity adversely affects the clinical response of biologics in psoriatic patients, with anti-interleukin agents being more affected by body mass index compared to anti-tumor-necrosis agents (17). A meta-analysis by Wu MY et al. stated that treatment with anti-TNF-alpha inhibitors appears to be associated with an increase in body weight and BMI, whereas treatment with anti-IL-12/23 and anti-IL-17 biologics does not. This association should be considered before initiating biologics in overweight patients (18).

An important discussion point is the timing of commencing a new biologic agent. According to guidelines published by Tsai YC et al. a washout period is recommended when switching is due to side effects, but not necessary for lack of efficacy (8). In our clinical practice, we temporarily ceased biologic administration until resolving infections and observed the washout period prior to starting new biologic treatment.

The same guidelines affirm that switching to the same class of biologics can still be effective, with firm evidence shown in biologics targeting IL-17. However, when switching is due to side effects, it is advisable to switch to a biologic targeting a different molecule. In our cases, we always transitioned to an agent with a different target molecule, due solely to the availability of just one agent from the same class (8).

Regarding dose escalation, a research study by Honda H et al. showed that some patients needed a subsequent biologic switch mainly due to inefficacy after dose escalation. The study emphasized the presence of refractory cases needing a biologic switch ultimately (7). In our experience, we did not attempt dose escalation, except in one case which resulted in efficacy failure and ultimately led to a biologic switch. Based on available data, if inefficacy occurs (both primary and secondary), dose escalation often does not bring PASI improvement. Thus, in our previous clinical practice, we preferred to immediately change the biologic agent rather than trying dose escalation.

CONCLUSION

Biologic agents approved for the treatment of psoriasis have shown a favorable safety profile without compromising efficacy. Furthermore, there is an increasing demand for higher efficacy to mitigate the various negative impacts of psoriasis. It is anticipated that the practice of switching biologics will become increasingly common in clinical settings, primarily due to inadequate therapeutic response, and less frequently due to infections and adverse reactions.

Studies have shown that after switching biologics, the subsequent agent is often administered at the scheduled time without a washout period. Our experience indicates that switching biologics often leads to better efficacy and more satisfactory clearance of skin lesions, aligning with recent studies on this topic. It is worth noting that correction of lifestyle habits helps achieve a better response to medications.

As presented in our results, there was no switch from guselkumab. Given its recent introduction into our clinical practice, it is likely the reason we did not observe any switches from this agent. Therefore, our report has a notable limitation regarding data on switching from guselkumab. Furthermore, the limitation of our report is the small sample size of observed patients, so reports on larger samples should be performed.

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Sažetak

ZAMENA BIOLOŠKIH LEKOVA KOD PSORIJAZE: IZAZOVI I ISKUSTVO IZ MALOG TERCIJARNOG ZDRAVSTVENOG CENTRA

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Uvod: Psorijaza je hronična inflamatorna bolest kože koja negativno utiče na kvalitet života pacijenata. U poslednjoj deceniji, terapijski ciljevi za pacijente obolele od psorijaze su visoko postavljeni, a to su postizanje čišćenja kože i omogućavanje pacijentu obavljanje svakodnevnih aktivnosti, tako da uticaj bolesti na društvene, porodične i radne aktivnosti bude minimalan ili nepostojeći. U smislu takve potrebe, biološki lekovi su se pokazali kao nada i obećanje za postizanje bolje kontrole bolesti. Međutim, ubrzo je uočeno da oko 30% pacijenata ne reaguje u dovoljnoj meri na terapiju dugoročno i javlja se potreba za zamenom bioloških lekova.

Rezultati: Ovde predstavljamo naše iskustvo za određeni vremenski period u vezi sa potrebom za zamenu bioloških lekova. Do sada je sedamnaest pacijenata bilo u potrebi za zamenom biološkog leka, a tri od njih su dva puta menjala lek. Od sedamnaest pacijenata, četrnaest su bili muškarci i tri žene. Prosečan BMI pacijenata bio je 29,81. Jedan pacijent je podvrgnut eskalaciji doze sekukinumaba zbog primarnog neuspeha, ali je ipak na kraju promenio biološki lek. Glavni razlozi za zamenu bioloških lekova bili su usled sekundarnog neuspeha (gubitak efikasnosti koji je bio prisutan nakon početka lečenja, biološki zamor) i nakon toga usled primarnog neuspeha. Srećom, zamena zbog neželjenih reakcija nije česta. Ovo dokazuje zadovoljavajući bezbednosni profil bioloških lekova.

Zaključak: Biološki agensi odobreni za lečenje psorijaze pokazali su povoljan bezbednosni profil, bez ugrožavanja efikasnosti. Potrebna je veća efikasnost lečenja psorijaze kako bi se smanjili svi negativni uticaji koje psorijaza ima na različite aspekte zdravlja i života pacijenata. Procenjuje se da će biološka promena biti sve češća u kliničkoj praksi. Javlja se uglavnom zbog neadekvatnog terapijskog odgovora, a ređe zbog neželjenih reakcija (kao što su infekcije). Podaci iz literature, kao i naše kliničko iskustvo sugerišu da konstitucionalni faktori mogu da utiču na uspeh lečenja. Sve u svemu, uspostavljeni su neki standardi i preporuke u zameni bioloških lekova, međutim kako se pojavljuju novi agensi i terapijske mete, potrebno je razmotriti potrebu za njihovom stalnom i kontinuiranom korekcijom.

***Ključne reči**:* psorijaza, biološki lekovi, zamena, primarni neuspeh, sekundarni neuspeh, neefikasnost.

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ELEVATED MEAN CELL VOLUME IN SICKLE CELL ANAEMIA: ONE STORY, TOO MANY?

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Abstract: **Introduction:** Sickle cell disease is a hereditary blood disorder characterized by defective hemoglobin. Red cell indices are proposed as potential tools for diagnosing and managing sickle cell disorders.

Materials and Methods: This study aimed to assess the utility of red cell indices as screening tools for sickle cell anemia. One hundred consenting adults of both sexes participated. Haematological parameters, including packed cell volume, hemoglobin values, hemoglobin electrphoretic patterns, and red blood cell count, were examined. Mean cell volume (MCV), mean cell hemoglobin concentration (MCHC), and mean cell hemoglobin (MCH) were calculated. Data analysis was performed using GraphPad Prism Software Version 9, with statistical significance set at $p < 0.05$ (95% confidence interval).

Results: Haemoglobin values were significantly lower in Hb SS subjects (5.68 ± 1.7g/dl) compared to Hb AA (11.30 ± 1.5 g/dl) and Hb AS groups (11.03 ± 1.4 g/dl) ($F = 32.279$; $p < 0.00001$). The pattern was consistent with PCV and RBC values. Among the red blood cell indices assessed, only MCV showed a significant elevation (95.7 ± 2.4 fl) in the HbSS group compared to other groups ($F = 4.165$; $p = 0.0183$). No statistically significant difference was observed in MCHC and MCH values between the three groups ($F = 0.5373$, $p > 0.586$ for MCHC; $F = 0.607$, $p > 0.546$ for MCH). The prevalence of haemoglobin variants was as follows: HbAA (77%), HbAS (19%), and HbSS (4%).

Conclusion: This study highlights significant reductions in haemoglobin values in Hb SS subjects and a notable elevation in MCV values in the Hb SS blood group. Elevated MCV in sickle cell anemia, where red cells are typically microcytic, warrants further investigation for differential diagnosis.

Keywords: Mean Cell Volume, Sickle Cell Anemia, Haemoglobinopathies, Port Harcourt, Nigeria.

INTRODUCTION

Haemoglobinopathies are the most common genetically inherited disorders. According to the World Health Organization (WHO), approximately 5% of the world's population carries genetic haemoglobin (Hb) disorders. Each year, over 42 million individuals are carriers, and more than 12,000 infants are born with major and clinically significant haemoglobinopathies. The worldwide migration of human populations and the relatively higher frequency of consanguineous marriages in many countries have contributed to the increased burden of haemoglobinopathies (1-4).

These disorders primarily affect populations in malaria-endemic regions and those with a history of consanguineous marriages, posing a significant public health burden. The clinical spectrum of haemoglobinopathies varies widely, ranging from asymptomatic carriers to severe anaemias and life-threatening complications such as acute chest syndrome and organ damage (3).

Early diagnosis and accurate classification of haemoglobinopathies are crucial for appropriate clinical management and genetic counseling. Traditionally, laboratory tests including haemoglobin electrophoresis and DNA analysis have been the gold standard for definitive diagnosis. However, these methods are often costly, time-consuming, and require specialized equipment and expertise, thereby limiting their utility in resource-limited settings (5, 6). There is, therefore, a growing interest in exploring alternative screening tools that are cost-effective, easily accessible, and capable of providing rapid results.

Red cell indices, including mean cell volume (MCV), mean cell hemoglobin (MCH), and mean cell hemoglobin concentration (MCHC), have been proposed as potential screening parameters for haemoglo-

binopathies. Mean Corpuscular Volume (MCV) measures the average volume or size of a red blood cell, calculated by dividing the total volume of packed red blood cells by the total number of red blood cells in the sample, and is expressed in femtolitres (fl) (7, 8). Mean Cell Hemoglobin (MCH) represents the average amount of hemoglobin in a single red blood cell, calculated by dividing the total amount of hemoglobin by the total number of red blood cells in the sample, and is measured in picograms (pg) (8). Mean Cell Hemoglobin Concentration (MCHC) measures the concentration of hemoglobin in a given volume of packed red blood cells, calculated by dividing the total amount of hemoglobin by the total volume of packed red blood cells, and is expressed in grams per litre (g/L) (8).

These indices are routinely measured as part of full blood counts (FBC) in clinical practice, making them readily available and integrated into standard laboratory procedures (9). The rationale behind their potential usefulness lies in the fact that different types of haemoglobinopathies manifest with distinct erythrocyte morphologies and hemoglobin content, leading to alterations in the red cell indices.

Anaemia is characterized by a reduction in hemoglobin (Hb) or hematocrit (HCT) or red blood cell count (RBC) and can be subdivided into macrocytic, microcytic, or normocyticanaemia (10).

Mean Cell Volume (MCV) classifies anaemia into three main categories: microcytic (small cells), normocytic (normal-sized cells), and macrocytic (large cells). These classifications help in identifying potential underlying causes of anaemia. For example, microcyticanaemia is caused by iron deficiency or thalassaemia, while macrocyticanaemia is caused by vitamin B_{12} or folate deficiency (11).

Mean Cell Haemoglobin (MCH) assesses the amount of haemoglobin present in the cells, aiding in the classification of anaemia. Low MCH levels may suggest iron deficiency anaemia, thalassaemia, vitamin B_{12}, or folic acid deficiency, as well as macrocyticnormochromicanaemias (8, 11).

Mean Cell Haemoglobin Concentration (MCHC) provides information about the colour or colour intensity of the red blood cells and is useful in diagnosing certain types of anaemia like hypochromicanaemia, which characterizes iron deficiency (11).

Using these red cell indices, healthcare professionals can diagnose anaemia and differentiate between different types of anaemia. This differentiation is crucial for determining the underlying cause of the anaemia and guiding appropriate treatment strategies (11).

There is a need to systematically assess the usefulness of these red cell indices in detecting and characterizing haemoglobinopathies to determine their reliability and clinical significance.

Aim

This study aims to evaluate the diagnostic potentials of red cell indices as a screening tool for the identification of sickle cell anaemia.

MATERIALS AND METHODS

Study Area

This study was conducted at the Rivers State University Teaching Hospital (RSUTH) (formerly Braithwaite Memorial Specialist Hospital) in Port Harcourt, a government-owned hospital located at 5-8 Harley Street, Old GRA, Port Harcourt, Rivers State, Nigeria. Its GPS coordinates are 4.7843°N 7.0104°E. The hospital, ranked among the largest in the Niger Delta, has a capacity of 375 beds and accreditation in most clinical departments. Port Harcourt, the capital and largest city in Rivers State, Nigeria, has a population of about 1,148,665 (12). It is a major hub of activities and a new frontier of opportunity for various economic, social, and political interests.

Study Population

The study population comprised patients attending the sickle cell clinic at RSUTH who were referred to the haematology laboratory for confirmation of their sickle cell status. One hundred adults of both sexes who consented to participate were included in the study.

Study Design

This study was a cross-sectional observational study designed to assess the usefulness of red cell indices as screening tools for haemoglobinopathies.

Sample Size Calculation

The minimum sample size was determined using the global prevalence of haemoglobinopathies (7%) as reported by Wendt *et al* (13). The formula used for calculation was:

$$n = \frac{Za^2 pq}{d^2}$$

Where n = Minimum sample size

Z = Standard normal deviation corresponding to 95% confidence level set at 1.96

p = 7% = 0.07

q = 1 – p = 0.93

d = desired precision, 5% (0.05)

$$n = \frac{1.96(0.07 \times 0,93)}{(0.05)^2}$$

$$n = 51$$

Ethical Considerations

Ethical approval was obtained from the Office of the Research Ethics Committee, Rivers State University Teaching Hospital. All procedures were performed in accordance with institutional and national research committee ethical standards and with the 1964 Helsinki declaration and its later amendments.

Sample Collection and Storage

Five milliliters (5ml) of blood were aseptically collected from each patient by venipuncture of the cubital vein using sterile disposable vacutainer blood collection needles and bottles. Samples were placed in Ethylenediaminetetraacetic acid (EDTA) bottles and stored at 4-8 °C until analyzed.

Procedures for the Estimation of Complete Blood Count Parameters:

Two (2) ml of blood was placed in another EDTA tube for automated analysis using the hematology auto analyzer Sysmex KX-21N, following the manufacturer's operational guidelines. All samples were analyzed within 30 minutes of collection.

Red Cell Indices Calculations:

The red cell indices were calculated using the standard formulae.

$$MCV = \frac{\text{Hematocrit}(\%)\text{x}10}{\text{RBC}\ (\text{x}10^{12}/\text{L})}$$

$$MCH = \frac{\text{Hb}(\text{g/dL})\text{x}10}{\text{RBC}\,(\text{x}10^{12}/\text{L})}$$

$$MCH = \frac{\text{Hb}(\text{g/dL})\text{x}100}{\text{Hematocrit}(\%)}$$

Determination of Haemoglobin Electrophoretic Pattern by Cellulose Acetate Method

Principle

This method is based on the principle of electrophoresis. Under an electric current, at an alkaline pH (8.4 - 8.6), haemoglobin is a negatively charged molecule and migrates towards the anode (the positively-charged pole of the gel). Haemoglobin variants have alterations in their surface charge due to changes in surface amino acids. This alters the speed of their migration, resulting in characteristic separation based on set mobility patterns.

Procedures

Wash 100µl of EDTA whole blood three times with normal saline using a centrifuge. Carefully decant the supernatant after each wash. Lyse the washed cells with 300 µl of distilled water and allow for 5 minutes. Fill each compartment of the electrophoretic tank with 50ml of Tris-EDTA borate buffer solution at pH 8.6.

Soak the cellulose acetate paper in Tris-EDTA borate buffer for 5 minutes. Remove the impregnated cellulose acetate strip from the buffer with forceps and blot gently between two clean sheets of blotting paper.

Place a wick of filter over each bridge, dipping into the buffer in the tank.

Place a tile on a horizontal surface. Place a drop of the control sample on the tile and a test sample beside it.

Use an applicator to load the control and test samples onto the cellulose acetate paper. Transfer the cellulose acetate paper and place it across the bridge of the tank on the wick of the filter, dipping into the buffer solution.

Close the lid of the tank and switch on the electric power for 10-15 minutes.

Switch off the power, remove the lid, and interpret the result based on the movement of loaded samples from the point of origin.

Statistical analysis

The data generated from this study were analyzed using GraphPad Prism Software Version 9. Statistical significance will be defined as a p-value less than 0.05 at a 95% confidence interval.

RESULTS

This study aimed to assess the usefulness of red cell indices as screening tools for sickle cell anaemia. One hundred subjects participated in the study, with 86% being females and 14% males. The prevalence of haemoglobin variants in the study population was as follows: Haemoglobin AA (HbAA) (77%), Haemoglobin AS (Sickle cell trait) (HbAS) (19%), and Haemoglobin SS (Sickle cell haemoglobin variant) (HbSS) (4%).

Table 1. *Mean ± SD of the haematological indices and association with the haemoglobin electrophoretic patterns*

Haemoglobin Electrophoretic pattern	Sex		Hb (g/dl) Mean ± SD	PCV (%) Mean ± SD	RBC x 10^{12}/dl Mean ± SD	MCHC (g/l) Mean ± SD	MCV (fl) Mean ± SD	MCH (pg) Mean ± SD
	F	M						
HbAA	67	11	11.30 ± 1.5^{a}	34.17 ± 4.2^{a}	3.61 ± 0.4^{a}	33.17 ± 0.3^{a}	94.55 ± 0.7^{a}	3.10 ± 0.02
HbAS	15	2	11.03 ± 1.4^{a}	33.24 ± 4.3^{a}	3.51 ± 0.4^{a}	33.11 ± 0.3^{a}	94.48 ± 0.7^{a}	3.11 ± 0.03
HbSS	4	1	5.68 ± 1.7^{ab}	17.14 ± 5.2^{ab}	1.8 ± 0.4^{ab}	33.04 ± 0.3^{a}	95.7 ± 2.4^{ab}	3.12 ± 0.04
Total	86	14	–	–	–	–	–	–
Mean ± SD			10.981	33.15 ± 5.6	3.505 ± 0.6	33.16 ± 0.4	94.59 ± 0.9	3.10 ± 0.05
F-value			32.27908	36.19111	35.9207	0.53732	4.16529	0.60759
P = value			< .00001***	< .00001.***	< .00001.**	0.586044^{ns}	0.0183*	$0.546724.^{ns}$

Abbreviations: **SD** - Standard deviation; **HbAA** - Haemoglobin AA (Normal haemoglobin); **HbAS** - Haemoglobin AS (Sickle cell trait); **HbSS** - Haemoglobin SS (Sickle cell haemoglobin variant); **Hb** - Haemoglobin; **PCV** - Packed Cell Volume; **MCHC** - Mean Cell Haemoglobin Concentration; **MCV** - Mean Cell Volume; **MCH** - Mean Cell Haemoglobin

Note: Significant differences are denoted as follows: 'a', 'b' for Hb levels, '' for P-values.*

DISCUSSION

This study aimed to evaluate the diagnostic potential of red cell indices as screening tools for haemoglobinopathies. The prevalence of haemoglobin variants observed in this study was Hb AA (77%), Hb AS (19%), and Hb SS (4%). This prevalence rate aligns with the findings of Gboeloh *et al*. (14), where the prevalence of SS subjects was reported as 62.1%, 33%, 4.4%, and 0.5% for HbAA, HbAS, HbSS, and HbAC, respectively. However, the prevalence of sickle cell trait was higher in the study by Gboeloh *et al.* (14). Similarly, Jeremiah (15) reported Hb AA as 80.32% and Hb AS as 19.68%, indicating that the prevalence of haemoglobin variant Hb AS has remained relatively stable over eighteen years.

Another significant finding in this study was a notable reduction in haemoglobin values in the Hb SS blood group. This finding is consistent with the research results of Valavi *et al*. (16), who also observed significantly lower haemoglobin values in individuals with the SS haemoglobin genotype. The pronounced reduction in haemoglobin values observed in individuals with sickle cell anaemia (SCA) is a central haematological hallmark of this inherited blood disorder.

Sickle cell anaemia is characterized by a point mutation in the beta-globin gene, resulting in the substitution of glutamic acid for valine at position 6 of the beta-globin chain of chromosome 11. This genetic alteration leads to the formation of abnormal haemoglobin known as haemoglobin S (HbS), which, under conditions of reduced oxygen tension, triggers the characteristic sickling of red blood cells.

Normal red blood cells typically circulate for approximately 120 days before undergoing natural senescence. In contrast, sickled cells exhibit a significantly shortened lifespan, contributing to a diminished red blood cell count in circulation. This accelerated turnover is a consequence of the increased fragility and vulnerability of sickled cells, rendering them more prone to haemolysis.

Haemolysis, or the premature breakdown of red blood cells, plays a pivotal role in the reduction of haemoglobin values in sickle cell anaemia. The rigid, sickle-shaped cells are more susceptible to rupture as they navigate through the microvasculature, particularly in regions of the body experiencing low oxygen levels. This chronic haemolysis leads to a continuous loss of red blood cells, creating a persistent state of anaemia in affected individuals.

Furthermore, the process of haemolysis in sickle cell anaemia is associated with the release of free haemoglobin into the bloodstream. This free haemoglobin can then undergo oxidation, leading to the formation of methaemoglobin and haemosiderin. The removal and recycling of these byproducts place an additional burden on the body's physiological systems, contributing to the overall depletion of haemoglobin and the downstream consequences of anaemia.

The cyclical nature of haemolysis in sickle cell anaemia results in recurrent drops in haemoglobin levels, often precipitating acute episodes known as haemolytic crises. These crises can be triggered by various factors, including infections, dehydration, or exposure to low oxygen levels. During a haemolytic crisis, there is a rapid and substantial reduction in haemoglobin, exacerbating the symptoms of anaemia and potentially leading to life-threatening complications (17-23).

The study recorded a significant elevation in MCV values in the Hb SS blood group, which is con-

sistent with the study of Akodu et al. (21), where elevated MCV values were reported in Hb SS subjects. The observation of macrocytosis in sickle cell anaemia (SCA) represents a significant haematological phenomenon with multifaceted implications. Macrocytosis, characterized by an elevated Mean Cell Volume (MCV), is attributed to an increase in reticulocytes, which are young, immature red blood cells. This process serves as a crucial adaptive response in the context of SCA, and its underlying mechanisms shed light on the dynamic interplay between haemolysis, haematopoiesis, and the unique pathophysiology of sickle cell disease.

The primary driver of macrocytosis in SCA is the heightened production of reticulocytes, which replace damaged red blood cells in circulation. Reticulocytes, being larger than mature red cells, contribute to the overall elevation in MCV values. This phenomenon is reflected in an MCV greater than 100fl, serving as a distinctive marker of macrocytosis.

The intricate relationship between macrocytosis and ongoing haemolysis in SCA is pivotal to understanding this phenomenon. Haemolysis, the premature breakdown of red blood cells, is a characteristic feature of SCA, primarily driven by the abnormal sickle-shaped morphology of red cells. As these sickled cells navigate through the circulation, they become more susceptible to rupture, leading to a continuous release of haemoglobin into the bloodstream and a subsequent increase in free reticulocytes.

The surge in reticulocyte production can be viewed as a compensatory mechanism initiated by the body in response to the chronic loss of red blood cells through haemolysis. The stimulation of haematopoiesis, the process of blood cell formation, becomes heightened to counteract the ongoing depletion of mature red cells. This heightened haematopoietic activity results in an increased supply of young red cells, characterized by their larger size and elevated MCV values.

The pivotal role of reticulocytes in macrocytosis is further underscored by the fact that young red cells inherently possess higher MCV values compared to their mature counterparts. This physiological characteristic contributes to the overall elevation in MCV observed in individuals with SCA. The increased MCV values in the SS blood group, indicative of macrocytosis, thus emerge as a consequence of the intricate interplay between ongoing haemolysis, heightened haematopoiesis, and the production of young, larger red blood cells.

The insights from Sembulingam et al (19) lend support to the proposed mechanism, emphasizing the dynamic nature of erythropoiesis in response to the unique challenges posed by sickle cell anaemia. The observed macrocytosis in sickle cell anaemia not only serves as a diagnostic indicator but also offers valuable insights into the adaptive responses of the hematopoietic system to the chronic haemolytic stress characteristic of this genetic disorder. Understanding these intricate relationships contributes to a more comprehensive comprehension of the haematological manifestations in sickle cell anaemia and may inform targeted therapeutic interventions aimed at modulating haematopoietic responses in affected individuals.

CONCLUSION

This study concluded as follows: 1) significant reductions in haemoglobin values in the Hb SS subjects. 2) significant elevation in MCV values in the Hb SS blood group. Ideally, MCV is decreased in sickle cell anaemia as the red cells are predominantly microcytes, but when the reverse is the case and MCV becomes elevated, it necessitates further investigations for the purpose of differential diagnosis.

Abbreviations

MCV - Mean Cell Volume
MCHC - Mean Cell Haemoglobin Concentration
MCH - Mean Cell Haemoglobin
ANOVA - Analysis of Variance
GPS - Global Positioning System
RSUTH - Rivers State University Teaching Hospital
WHO - World Health Organization
EDTA - Ethylene Diamine Tetraacetic Acid

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Authors' Contributions: ZJ contributed to conceptualization, detailed review, and statistical analysis. MA contributed to literature review and laboratory analysis. All authors have critically reviewed and approved the final manuscript for submission.

Note: Artificial intelligence was not utilized as a tool in conducting this study.

Sažetak

POVIŠENA SREDNJA ZAPREMINA ERITROCITA U ANEMIJI SRPASTIH ĆELIJA: JEDNA PRIČA, PREVIŠE?

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Uvod: Anemija srpastih ćelija je nasledni poremećaj krvi karakterisan defektnim hemoglobinom. Pokazatelji crvenih krvnih zrnaca se predlažu kao potencijalni alati za dijagnostikovanje i tretiranje poremećaja srpastih ćelija.

Materijali i metodi: Ova studija imala je za cilj procenu korisnosti indeksa crvenih krvnih zrnaca kao alata za pretragu anemije srpastih ćelija. Učestvovalo je 100 odraslih osoba oba pola koje su pristale na učešće. Hematološki parametri, uključujući hematokrit, vrednosti hemoglobina, elektroforetske obrasce hemoglobina i broj crvenih krvnih zrnaca, ispitan je. Izračunate su srednje vrednosti zapremine eritrocita (MCV), srednje koncentracije hemoglobina u eritrocitima (MCHC) i srednje količine hemoglobina u eritrocitima (MCH). Analiza podataka izvršena je korišćenjem softvera GraphPad Prism verzije 9, sa statističkom značajnošću postavljenom na $p < 0,05$ (interval poverenja od 95%).

Rezultati: Vrednosti hemoglobina bile su značajno niže kod osoba sa SS genotipom (5,68 ± 1,7 g/dl) u poređenju sa AA (11,30 ± 1,5 g/dl) i AS grupama (11,03 ± 1,4 g/dl) ($F = 32,279$; $p < 0,00001$). Ovaj obrazac bio je u skladu sa vrednostima hematokrita (PCV) i broja eritrocita (RBC). Među procenjenim indeksima eritrocita, samo MCV je pokazao značajno povećanje (95,7 ± 2,4 fl) u HbSS grupi u poređenju sa drugim grupama ($F = 4,165$; $p = 0,0183$). Nije primećena statistički značajna razlika u vrednostima MCHC i MCH između tri grupe ($F = 0,5373$, $p > 0,586$ za MCHC; $F = 0,607$, $p > 0,546$ za MCH). Učestalost varijanti hemoglobina bila je kako sledi: HbAA (77%), HbAS(19%) i HbSS (4%).

Zaključak: Ova studija ističe značajna smanjenja vrednosti hemoglobina kod osoba sa SS genotipom i primetno povišene vrednosti MCV u krvi osoba sa SS grupom. Povišen MCV u anemiji srpastih ćelija, gde su crvena krvna zrnca tipično mikrocitna, zahteva dalje istraživanje u svrhu diferencijalne dijagnoze.

Ključne reči: Hematokrit, Anemija srpastih ćelija, Hemoglobinopatije, Port Harcourt, Nigerija.

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Case report

MULTIFACTORIAL ETIOLOGY OF ATIPICAL HEMOLYTIC UREMIC SYNDROME - CASE REPORT

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Abstract: **Introduction:** Hemolytic uremic syndromes are characterized by the simultaneous occurrence of hemolytic anemia, microangiopathy, thrombocytopenia, and acute renal insufficiency. In terms of the clinical prodrome, they can be classified as typical, which is more common and occurs in 90% of cases, often preceded by diarrheal syndrome induced by enterohemorrhagic Escherichia coli. Alternatively, there is an atypical and rarer form associated with pneumococcal infection, dysregulation of the alternative complement pathway, and cases involving the use of cyclosporine. Hemolytic anemia is confirmed in laboratory analyses (presence of fragmented red blood cells, decreased hemoglobin, undetectable haptoglobin values, and elevated LDH values), along with thrombocytopenia and an increase in nitrogenous substances (urea and creatinine).

Case report: The report details the case of an 18-month-old girl who experienced acute renal insufficiency subsequent to a respiratory infection. Ten days preceding admission, the patient exhibited nasal discharge, and during the seven days leading up to hospitalization, she presented with fever. Furthermore, two days prior to admission, the onset of persistent vomiting and abdominal pain occurred. Suspected of bowel intussusception, the patient underwent a surgical assessment where acute surgical pathology was ruled out. The absence of urination, coupled with heightened urea and creatinine levels, prompted consideration of hemolytic-uremic syndrome, later confirmed as atypical during hospitalization. This was grounded in the clinical presentation, devoid of diarrhea syndrome but marked by nasal discharge over the preceding ten days. The administration of fresh frozen plasma yielded no improvement, and there were decreased values of the C3 complement component, H factor, and reduced ADAMTS13 activity. The lack of verotoxins from enterohemorrhagic Escherichia coli further supported the diagnosis of atypical hemolytic-uremic syndrome. After the first dose of eculizumab, a terminal complement C5 component inhibitor, the girl recovered renal function and established diuresis.

Conclusion: The prompt diagnosis of atypical hemolytic-uremic syndrome is challenging due to nonspecific symptoms like nasal discharge, vomiting, fatigue, and abdominal pain. Laboratory analyses, lacking specific criteria, make it difficult to conclusively identify aHUS at the disease's onset. In Serbia, pneumococcal immunization is recommended as a preventive measure, administered through a conjugated vaccine in three doses starting from the second month of life. Rapid and accurate differentiation between typical and atypical HUS is crucial for effective treatment and prognosis. Typical HUS requires hemodialysis and plasmapheresis, whereas atypical HUS is managed with plasmapheresis, immunosuppressive therapy, and eculizumab. Administering eculizumab heightens the risk of meningococcal infection by inhibiting the C5 complement component. Therefore, it is crucial not to disregard the importance of meningococcal immunization.

Keywords: atypical hemolytic uremic syndrome, pneumococcus, renal failure, complement system, eculizumab.

INTRODUCTION

Atypical Hemolytic Uremic Syndrome (aHUS) represents a complex and rare disorder characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. Unlike its more common counterpart, aHUS is associated with diverse etiologies, including dysregulation of the alternative complement pathway, pneumococcal infections, and drug-induced cases, necessitating a comprehensive understanding for accurate diagnosis and targeted therapeutic interventions (1).

Among all aHUS cases, 40% are induced by an invasive strain of pneumococcus that secretes neuraminidase, an enzyme breaking down neuraminic acid coating renal endothelium, red blood cells, platelets, and hepatocytes. This results in the exposure of the Thomsen-Friedenreich (TF) antigen, subsequently triggering the activation of the immune system and coagulation cascades. Other forms of atypical HUS result from dysregulations in the alternative complement pathway activation, specifically mutations in genes encoding complement regulatory factors H (CFH) and I (CFI), which inactivate the C3b complement component (2).

The rarest form of atypical HUS involves a mutation in the gene responsible for synthesizing the liver protease ADAMTS13 (a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13). This protease acts enzymatically on von Willebrand factor (vWF), cleaving it into smaller peptides. In the absence or reduced activity of ADAMTS13, von Willebrand factor circulates as a large polypeptide, facilitating platelet adhesion and contributing to the formation of microthrombi in circulation (3, 4). This case report shows the simultaneous occurrence of pneumococcal infection, reduced activity of the ADAMTS13 protease, and activation of the alternative complement pathway.

CASE REPORT

An 18-month-old girl, conscious but visibly unwell, arrived at the surgical ward presenting with fever, tachypnea, lethargy, and widespread edema. The primary concerns leading to admission were persistent vomiting and abdominal pain, raising suspicion of an acute surgical condition. Symptom onset occurred ten days prior, marked by escalated nasal discharge and, over the preceding seven days, the patient exhibited ongoing fever along with a notable episode of vomiting greenish contents observed the day before admission.

Despite the implementation of intravenous rehydration protocols, the patient's condition showed no improvement, and alongside continuous vomiting, anuria was diagnosed. Acute surgical pathology was effectively ruled out. Biochemical analyses revealed elevated urea levels at 21.8 mmol/L, creatinine at 261 µmol/L, thrombocytopenia at 81.4 x 10^9, and anemia with hemoglobin at 81.7 g/L and Red Blood Cell count at 3.06 x 10^{12}/L. This constellation of findings raised suspicion of hemolytic-uremic syndrome. With diuretic stimulation proving ineffective and anuria persisting, a dual-lumen catheter was inserted into the right femoral vein, initiating venovenous hemodialysis. Simultaneously, a fifteen-day regimen of fresh frozen plasma infusions was initiated. Unfortunately, during this period, a satisfactory diuretic response was not achieved, as it did not exceed 50 ml in 24 hours.

During the course of hospitalization, a series of examinations were undertaken to further assess the patient's condition:

Biochemical Analysis: Glucose: 4.36 mmol/L,- Total CO2: 16, Potassium (K): 4.9 mmol/L, Sodium (Na): 131 mmol/L, Chloride (C): 94 mmol/L, Calcium (Ca): 1.94 mmol/L, Magnesium (Mg): 0.82 mmol/L, Phosphorus (P): 2.23 mmol/L.

Liver Function Tests: AST: 330 U/L, ALT: 392 U/L, GGT: 7 IU/L, LDH: 8735 IU/L, Total Bilirubin: 9.7 µmol/L, Direct Bilirubin: 4.22 µmol/L, Total Proteins: 43, Albumin: 27 g/L.

Coagulation Tests: PT (Prothrombin Time): 13.4 s; 75%, aPTT (Activated Partial Thromboplastin Time): 23.2%, TT (Thrombin Time): 20.5 s, Fibrinogen: 4.4 g/l, D-dimers: 4040 ng/mL, AT III (Antithrombin III): 73%.

Immunology Panel: IgA: 0.589 g/L**,** IgM: 1.02 g/L**,** IgG: 6.65 g/L**,** Haptoglobin: 0.177 g/L**,** ANA (Antinuclear Antibodies) screen: 0.2**,** IgM anti-dsDNA: 2.8 IU/mL**,** IgG: 4.5 IU/mL**,** Anti-MPO: 1.3 U/mL**,**Anti-PR3 (Proteinase 3) antibodies: 2.4 U/mL.

Imaging and Cultures:

• Abdominal ultrasound and chest X-ray showed normal findings.

• Hemoculture indicated a negative result for coagulase-negative Staphylococcus.

• Urine culture was sterile.

• Nasal swab revealed Streptococcus pneumoniae, while the throat swab was sterile.

• Immunochromatographic stool testing did not detect the presence of Shiga toxins type 1 (STX1) and type 2 (STX2) from enterohemorrhagic Escherichia coli.

• The activity of ADAMTS13 metalloprotease was measured at 20%, falling below the reference range of 67-150%.

Complement and Coagulation Factors:

• Total complement activity, classical pathway (Hemolytic test): 40 CH50/mL (reference range 48-103 CH50/mL)

• Total complement activity, alternative pathway (WIELISA Alt): 71% (reference range 70-125%)

• Complement C3: 0.8 g/L (reference range 0.9–1.8 g/L)

• Complement C4: 0.15 g/L (reference range 0.15-0.55 g/L)

• Factor H antigen: 194 mg/L (reference range 250-880 mg/L)

• Complement Factor I antigen: 95% (reference range 70-130%)

• Complement Factor B antigen: 184% (reference range 70-130%)

• Anti-Factor H IgG autoantibody: 26 AU/mL (reference range < 110 AU/mL)

• C1q antigen: 33 mg/L (reference range 60-180 mg/L)

• Anti-C1q IgG autoantibodies: 15 U/mL (reference range < 52 U/mL)

• SC5b-9 (terminal complement complex): 255 ng/mL (reference range 110-252 ng/mL)

Tables 1 and 2 show the values of urea, creatinine, LDH, blood pressure, urine output, Red Blood Cells, hemoglobin, haptoglobin, and platelets at different stages of the disease, including the onset, after the administration of hemodialysis and plasma exchange, and after the administration of eculizumab.

Based on the patient's history (marked by the absence of diarrhea), clinical manifestations (persistent hemolysis despite fresh frozen plasma administration, and absence of diuresis), and laboratory findings (lack of verotoxin, decreased levels of C3 complement component and CFH, reduced ADAMTS13 activity, and isolation of Streptococcus pneumoniae in nasal swab), a diagnosis of atypical hemolytic-uremic syndrome (aHUS) was established. Consequently, treatment with eculizumab, a terminal complement C5 component inhibitor, was initiated. Notably, diuresis was restored, and renal function improved by the fifth day of eculizumab administration.

The patient received two doses of eculizumab during hospitalization, spaced three weeks apart, and continued the regimen post-discharge. Presently, having received 50 doses, the patient exhibits normal laboratory parameters and maintains good overall health. Furthermore, immediate meningococcal immunization was administered post-eculizumab treatment due to the heightened risk of meningococcal infection.

We obtained verbal and signed consent of the patient´s parents to publish the case report.

All procedures performed were in accordance with the 1964 Helsinki declaration and its later amendments.

DISCUSSION

In examining the case of the afflicted young girl, we can discern that atypical Hemolytic Uremic Syndrome (aHUS) manifested as a result of pneumococcal infection, with the activation of both the classical complement pathway and the alternative complement pathway (4). This activation is linked to reduced activity of serum factor H regulatory protein and hepatic ADAMTS13 protease. The invasive pneumococcus, equipped with its neuraminidase enzyme, cleaves neuraminic acid from renal endothelium, hepatocytes, erythrocytes, and platelets, leading to the subsequent exposure of the Thomsen-Friedenreich (TF) antigen. IgM TF antigen antibodies trigger the classical complement pathway by activating the C1 component, leading to the cleavage of complement component C4 into C4a and C4b. The C4b fragment then cleaves the C2 component (yielding C2a, C2b), resulting in the formation of C3 convertase (C4b2a). The C3 convertase of the classical pathway facilitates the cleavage of the C3 complement component into C3a and C3b. The C3b fragment subsequently binds to C3 convertase (C4b2a), initiating the assembly of C5 convertase

Table 1. *The values of urea, creatinine, LDH, blood pressure, as well as urine output, at the onset of the disease, after the administration of hemodialysis and plasma exchange, and after the administration of eculizumab*

	Urea	Creatinine	LDH	Blood pressure	Urine output
Disease onset	21.8 mmol/L	261 umol/L	8735 IJ/L	130/80 mmHg	50 mL/24
After hemodialysis and plasma exchange	24 mmol/L	247 umol/L	6543 IJ/L	120/75 mmHg	70 mL/24
After eculizumab	8.6 mmol/L	43 umol/L	631 IJ/L	100/60 mmHg	500 mL/24

Table 2. *The values of Red Blood Cells (RBC), hemoglobin (HGB). haptoglobin and platelets at the onset of the disease, after the administration of hemodialysis and plasma exchange, and after the administration of eculizumab*

	RBC	HGB	Haptoglobin	Platelets
Disease onset	$3.06x10^{12}$/L	70 g/L	0.02 g/L	$20x10^{9}$/L
After hemodialysis and plasma exchange	$3x10^{12}$/L	80 g/L	0.05 g/L	$100x10^{9}$/L
After eculizumab	$3.6x10^{12}$/L	107 g/L	1.3 g/L	$385x10^{9}$/L

for the classical complement pathway (C4b2a3b). The C5 convertase facilitates the breakdown of the C5 complement component into C5a and C5b, ultimately enabling the creation of the C5b-9 complex, which detrimentally affects endothelial cell membranes. Consequently, a cascade of thrombocytopenia, hemolysis, and acute renal insufficiency unfolds, indicated by reduced haptoglobin levels, elevated total bilirubin, and increased lactate dehydrogenase (2, 5, 6).

The alternative pathway of the complement system activation is continually active due to the spontaneous hydrolysis of the complement component C3. The C3b fragment binds to Bb, with factor B having undergone protease-mediated breakdown into the Bb fragment. This resultant C3bBb complex serves as the "C3 convertase of the alternative complement pathway," catalyzing the breakdown of fresh C3 complement components (C3a, C3b). Binding of the C3b fragment to C3bBb gives rise to the generation of C5 convertase of the alternative complement pathway (C3bBb3b). The subsequent breakdown of the C5 complement component results in the formation of the C5b-9 complex, also known as the membrane attack complex, which leads to the disruption of glomerular cell membranes. The alternative complement pathway, which is constantly active at a low rate, is rigorously governed by regulatory proteins—C1 inhibitor, C4-binding protein, complement factor H (CFH), and complement factor I (CFI)—all of which effectively inhibit its unwarranted activation (7, 8).

CFH is the most significant protein for regulating the activity of the alternative pathway of the complement system. This plasma protein has two binding sites for the C3b fragment of complement component C3 and, under normal physiological conditions, acts as a guardian, protecting the host from harm triggered by the alternative pathway activation. A deficiency or impairment in CFH function leads to intensified C3b fragment activity, increased complement system activation (resulting in C3a, C5a, C5b-9 production), endothelial cell damage, and the formation of blood clots within microvasculature (9).

Finally, the diminished activity of the hepatic proteolytic enzyme ADAMTS13, crucial for breaking down von Willebrand factor on the endothelial surface, culminates in heightened microthrombosis in circulation. This occurs because von Willebrand factor, being a substantial molecular entity, circulates and acts as a nexus for platelet adherence, consequently fostering the formation of microthrombi (10).

In any scenario, plasmapheresis stands out as the frontline treatment for both typical and atypical HUS when initiated at the disease onset. This approach effectively eliminates dysregulated, non-functional proteins that regulate both the classical and alternative pathways of the complement system. If, even after five consecutive daily plasma exchanges, hemolysis persists or renal function does not show improvement, it signifies uncontrolled aHUS—this is the case even if the platelet count returns to normal levels (2, 11, 12).

The presence of uncontrolled aHUS signals the need for treatment with a complement C5 component blocker, such as eculizumab, recommended for lifelong therapy. It is important to note that platelet transfusion is contraindicated due to the potential exacerbation of blood clot formation in the microvasculature of various organs (5).

CONCLUSION

While pneumococcal immunization may offer a preventive avenue for aHUS, the scarcity of this condition directs our primary attention to the treatment and complication prevention in affected children, particularly chronic kidney issues. The lifelong administration of eculizumab in cases like the one presented poses both practical and financial challenges, where hospital visits require physical and psychological effort, and the treatment itself is costly and sometimes difficult to obtain. These cases emphasize the crucial role pediatricians have in ongoing complication prevention and management. Furthermore, the disease's etiology highlights the susceptibility of pediatric patients to acute infections, posing a significant risk due to complement system disruptions. Notably, the use of eculizumab increases the vulnerability to meningococcal infections, underscoring the need for vigilant monitoring and preventive measures in this patient population.

Abbreviations

ADAMTS13 - a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13
aHUS - Atypical Hemolytic Uremic Syndrome
CFH - complement regulatory factor H
CFI - complement regulatory factor I
HUS - Hemolytic Uremic Syndrome
TF antigen - Thomsen-Friedenreich antigen
vWF - von Willebrand factor

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Licensing

Sažetak

MULTIFAKTORSKA ETIOLOGIJA ATIPIČNOG HEMOLITIČKO UREMIJSKOG SINDROMA - PRIKAZ SLUČAJA

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Uvod: Hemolitičko uremijski sindromi karakterišu se istovremenom pojavom hemolitičke anemije-,mikroangiopatije, trombocitopenije i akutne bubrežne insuficijencije. U odnosu na klinički prodrom mogu biti: tipični, koji je češći i javlja se u 90% obolelih kada mu prethodi dijarealni sindrom (izazvan enterohemoragičnom Escherichia coli) i atipični ređi oblik vezan za pneumokoknu infekciju, poremećaj aktivacije komplementa alternativnim putem i kod upotrebe ciklosporina. U laboratorijskim analizama potvrđuje se hemolizna anemija (nalaz fragmentisanih eritrocita, sniženje hemoglobina, nemerljive vrednosti haptoglobina i povišene vrednosti LDH), trombocitopenija i porast azotnih materija (uree i kreatinina).

Prikaz slučaja: U radu je prikazan slučaj obolele devojčice uzrasta 18 meseci kod koje je nakon respiratorne infekcije došlo do razvoja akutne bubrežne insuficijencije. Deset dana pre toga devojčica je imala sekreciju iz nosa, a poslednjih sedam dana pre hospitalizacije imala je temperaturu. Takođe, dva dana pre prijema, počelo je povraćanje sa bolovima u stomaku koji nisu prestajali. Nakon konsultacije hirurga, a zbog sumnje na invaginaciju creva, isključeno je akutno hirurško oboljenje, a kako dete nije mokrilo, uz povišene vrednosti uree i kreatinina, posumnjalo se na hemolitičko uremijski sindrom koji je u daljem toku hospitalizacije i dokazan kao atipičan i to na osnovu kliničke slike u kojoj nije bilo dijarejalnog sindroma, ali je dete imalo sekreciju iz nosa unazad deset dana. Takođe, na primenu sveže smrznute plazme nije došlo do poboljšanja, a tu su i snižene vrednosti C3 komponente komplementa, H faktora i snižena aktivnost ADAMTS13, kao i odsustvo verotoksina enterohemoragične E. koli što sve govori u prilog postavljanja dijagnoze aHUS-a. Nakon prve doze ekulizumaba – terminalnog inhibitora komplementa C5 komponente, devojčica je oporavila bubrežnu funkciju i uspostavila diurezu.

Zaključak: Rano dijagnostikovanje aHUS-a je izuzetno teško jer kliničkom slikom dominiraju nespecifični simptomi kao što su sekrecija iz nosa, povraćanje, malaksalost i bolovi u stomaku. Takođe, ni u laboratorijskim analizama nema specifičnog kriterijuma koji bi nagovestio aHUS na samom početku bolesti. Kao meru prevencije možemo savetovati imunizaciju protiv pneumokoka koja se u našoj zemlji obavlja konjugovanom vakcinom u tri doze, počev od drugog meseca života. Takođe je neophodno precizno i brzo razlikovanje tipičnog od atipičnog HUS-a jer od toga zavisi lečenje i prognoza bolesti, jer se tipični HUS leči hemodijalizom i plazmaferezom, dok se atipični leči plazmaferezom, imunosupresivnom terapijom i ekulizumabom. Ne sme se zaboraviti na imunizaciju protiv meningokoka kada se primenjuje ekulizumab, zbog njegovog inhibitornog dejstva na C5 komponentu komplementa, što povećava rizik od meningokokne infekcije.

Ključne reči: atipični hemolitičko uremijski sindrom, pneumokok, bubrežna insuficijencija, sistem komplemenata, ekulizumab.

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Case report

RUPTURE OF A PANCREATIC PSEUDOANEURYSM AS A CONSEQUENCE OF CHRONIC PANCREATITIS: CASE REPORT OF A SURGICAL EMERGENCY

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Abstract: **Introduction:** Pseudoaneurysms of the pancreaticoduodenal arcade are rare, accounting for approximately 2% of all visceral artery aneurysms. They typically arise as complications of chronic pancreatitis, peptic ulcer disease, trauma, pancreatic and biliary surgery, or pancreas transplantation. Diagnosis often occurs only after rupture, leading to life-threatening internal bleeding. Bleeding may occur within a pseudocyst, with blood passing through the Vater's papilla into the digestive tract, or may result in the formation of a retroperitoneal hematoma that can rupture into the abdominal cavity, causing hemoperitoneum. The cell-saver is a tool that can be utilized for intraoperative blood cell salvage and autologous transfusions.

Case Report: Our patient, a 54-year-old male, an untreated alcoholic with no prior medical history or documented treatment, presented to the Clinic for Emergency Surgery at the University Clinical Center of Serbia with a sudden onset of upper abdominal pain. A quick ultrasound of the abdomen was performed, followed by an urgent CT scan of the chest and abdomen, revealing a hematoma extending from the right retroperitoneum and mesentery of the intestine, measuring 150x109x180mm in diameter, with signs of active bleeding in the region beneath the pancreas, indicative of hemoperitoneum. Due to hemodynamic instability, accompanied by a drop in arterial blood pressure and hemoglobin levels, an urgent laparotomy was performed. Active bleeding was identified from a ruptured pseudoaneurysm originating from the pancreaticoduodenal arcade. Hemostasis was achieved followed by tamponade, and the tampons were removed 30 hours post-surgery. The patient remained hemodynamically stable thereafter, recovered well from the surgery, and was discharged home in good general condition.

Intraoperatively, we utilized the Cell-saver to collect the patient's blood and subsequently administered autologous transfusion.

Conclusion: In patients with chronic pancreatitis presenting with sudden abdominal pain and hemodynamic instability accompanied by a drop in arterial pressure, hemoglobin, and hematocrit levels, the possibility of a ruptured pseudoaneurysm in the pancreatic or peripancreatic region should be considered. Timely diagnosis and prompt surgical intervention are crucial for a successful outcome. Effective collaboration among radiologists, anesthesiologists, and surgeons is essential. The utilization of the Cell-saver system significantly aids in maintaining cardiac output and hemodynamic stability in these patients.

Keywords: pseudoaneurysm, rupture, chronic pancreatitis, emergency surgery.

INTRODUCTION

Pseudoaneurysms of the pancreaticoduodenal arcade are rare occurrences, constituting approximately 2% of all visceral artery aneurysms (1). They typically manifest as complications of chronic pancreatitis, peptic ulcer disease, trauma, pancreatic and biliary surgeries, or pancreas transplantation (2). Often, these pseudoaneurysms remain undiagnosed until rupture, leading to life-threatening internal bleeding (3). Bleeding may occur within a pseudocyst, with blood passing through Vater's papilla into the digestive tract, or result in the for-

mation of a retroperitoneal hematoma that can rupture into the abdominal cavity, causing hemoperitoneum (3, 4).

Traditionally, blood transfusion has been a common therapeutic intervention for treating perioperative anemia and surgical blood loss. Anemia, whether acute or chronic, is associated with increased morbidity and mortality risk. To reduce the need for allogeneic blood transfusions, modern blood conservation principles have been developed, which include intraoperative blood cell salvage and autologous transfusion (5). This approach is particularly beneficial in cardiac and orthopedic surgeries, as well as operations anticipated to involve significant blood loss exceeding 1000 ml. The process of blood cell salvage involves three phases: collection, washing, and re-infusion. Blood collection from the operative field necessitates the use of a specialized suction device with dual lumens, known as a Cell-saver. One lumen draws blood from the operative site, while the other adds a predetermined volume of heparinized saline. Anticoagulated blood is then filtered and collected in a reservoir. Following centrifugation, red blood cells (RBCs) are washed and filtered to remove impurities, resulting in a hematocrit of 50-80%. Autologous transfusion can occur within six hours of RBC collection (6).

Potential complications associated with cell salvage include non-immune hemolysis, air embolism, febrile non-hemolytic transfusion reactions, coagulopathy, contamination with drugs or infectious agents, and incomplete washing leading to contamination with cytokines, leukocytes, and microaggregates. However, these risks have diminished with technological advancements, staff training, and increased experience in the method (6, 7). The primary benefit of this approach is the reduced need for allogeneic blood transfusions, which are associated with various complications, including increased mortality.

The 2009 AAGBI guidelines have identified indications for cell salvage use, including predicted blood loss exceeding 1000 ml or 20% of estimated blood volume. It is considered suitable for patients with low hemoglobin levels, increased bleeding risk, antibodies against RBC surface antigens, rare blood groups, or those who decline allogeneic transfusions (5-7). However, literature describing the use of Cell-saver in emergency surgeries of this nature is limited (8).

In this case report, we present the clinical and radiological features of an adult male patient who presented to our center as an emergency with hemoperitoneum secondary to a ruptured pancreatic pseudoaneurysm due to chronic pancreatitis. The patient underwent surgery within hours of admission, with perioperative Cell-saver utilization aimed at preventing additional blood loss and facilitating autologous transfusion.

CASE REPORT

Our patient is a 54-year-old male, an untreated alcoholic with no prior medical history or chronic therapy. He presented to the Clinic for Emergency Surgery at the University Clinical Center of Serbia in Belgrade in November 2023, complaining of sudden upper abdominal pain that had started three hours before admission. The patient denied nausea, vomiting, or changes in stool appearance, and he did not lose consciousness. On admission, he was conscious, oriented, but extremely agitated, with paler discoloration of the skin and visible mucous membranes. Auscultation of the chest revealed a normal respiratory murmur, while abdominal examination showed tenderness in the epigastrium without peritoneal signs or hernias. Predilection hernia sites were without manifest herniation. Initial hemoglobin level was 138 g/L.

Ultrasound examination revealed a suspicious break in the antropyloric part of the stomach wall and a septate, organized mass with a diameter of about 70 mm in the right hemiabdomen, suggestive of a pseudoaneurysm, septate dense collection, or other etiology. Given these findings, an urgent CT scan of the chest and abdomen was performed, which showed a hyperdense left lobe of normal-sized liver without focal changes. The trunk of the portal vein measured 10 mm in diameter, with extension of a hematoma from the right retroperitoneum and mesentery of the intestine into the infrapancreatic region, with signs of active bleeding. The CT findings suggested bleeding from the origin of a branch of the pancreaticoduodenal arcade, likely the lower one, with a differential diagnosis of arteriovenous fistula, suspected tumor, or inflammatory type, more likely a pseudoaneurysm (Figure 1-4).

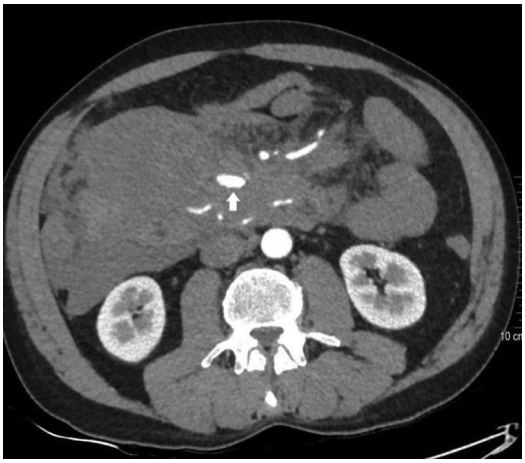

Figure 1. *Contrast-enhanced abdominopelvic CT, axial image, arterial phase: Huge retroperitoneal and mesenterial hematoma located on the right side with a pseudoaneurysm of the pancreaticoduodenal arcade (arrow)*

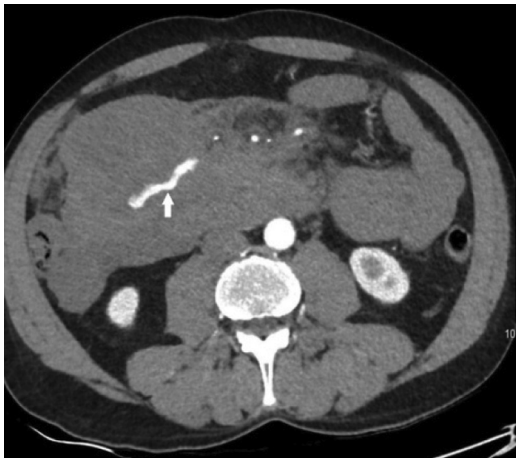

Figure 2. *Contrast-enhanced abdominopelvic CT, axial image, arterial phase: Huge retroperitoneal hematoma with contrast "blush" in the central region of the hematoma - a CT sign of active arterial bleeding (arrow)*

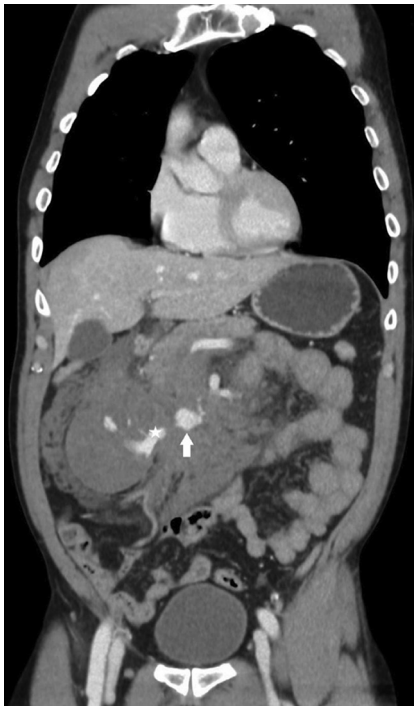

Figure 3. *Contrast-enhanced abdominopelvic CT, coronal reconstruction, venous phase: Huge retroperitoneal and mesenterial hematoma with pseudoaneurysm of pancreaticoduodenal arcade (arrow) and contrast "blush" in the central region of the hematoma (star)*

We decided to proceed with an urgent exploratory laparotomy. During the operation, we discovered blood and coagulum in all peritoneal recesses, along with a hematoma in the right peritoneal space extending towards the mesocolontransversum and the mesentery of the small intestine, with rupture towards the peritoneal cavity (Figure 5). To access the pancreas, we performed a

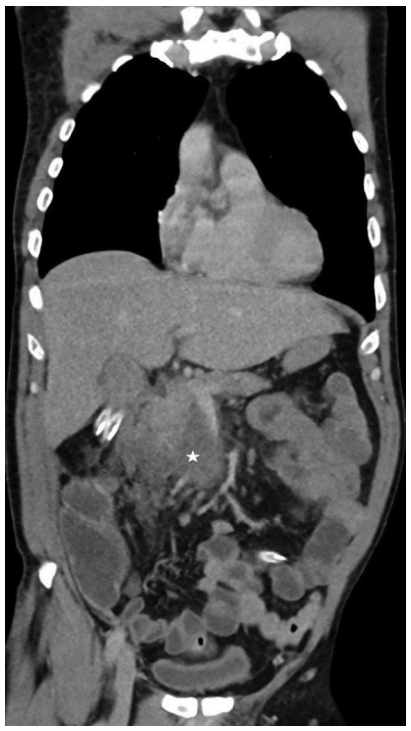

Figure 4. *Postoperative contrast-enhanced abdominopelvic CT, coronal reconstruction, venous phase: Minimal residue of mesenteric hematoma (star) without signs of active bleeding and pancreaticoduodenal pseudoaneurysm*

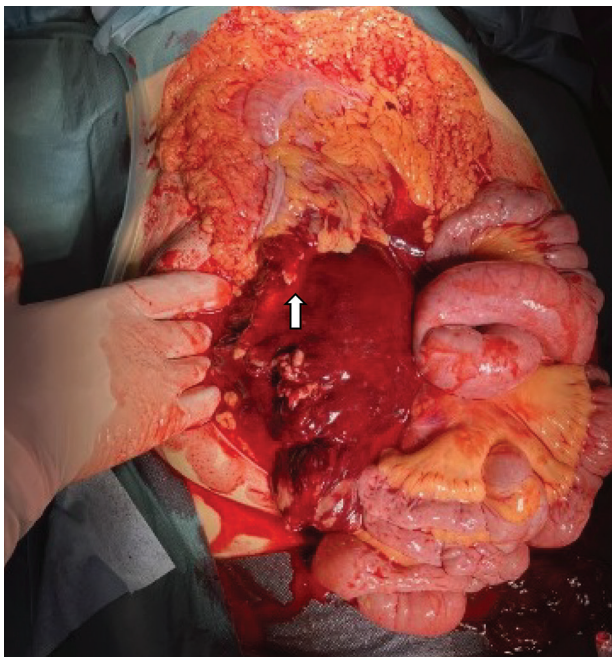

Figure 5. *Retroperitoneal hematoma with propagation in the mesocolon transversum and mesentery of the small intestine (arrow)*

Cattell-Braasch maneuver. We observed active bleeding in the area of the pancreaticoduodenal arcade due to the rupture of the pseudoaneurysm (Figure 6). We achieved permanent hemostasis and utilized the Cell-saver

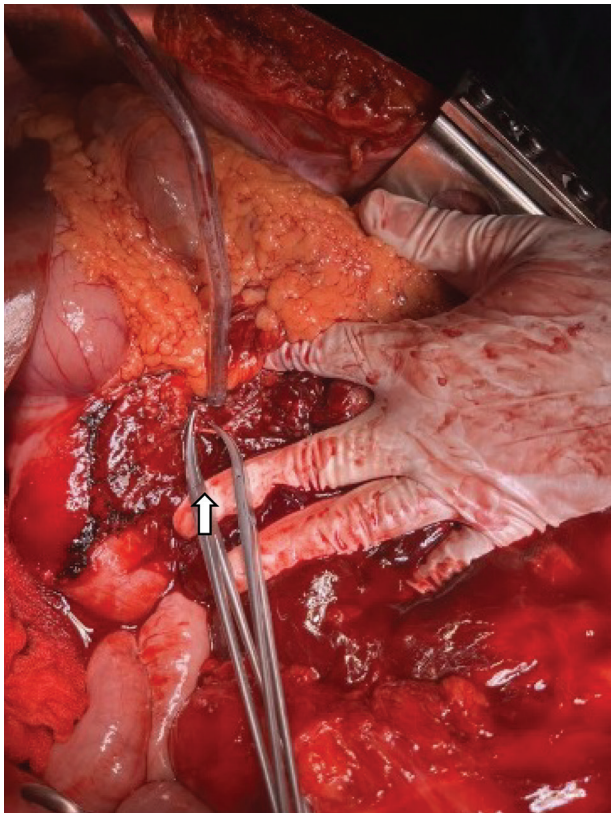

***Figure 6**. Site of active arterial bleeding (arrow)*

throughout the operation to preserve the minute volume. The operation concluded with tamponade of the retroperitoneal space on the right.

Postoperatively, the patient was managed in the ICU. After 30 hours, we performed a re-laparotomy to remove the tampons from the abdominal cavity. Hemostasis was satisfactory, and there were no signs of ischemia or necrosis in the colon and small intestine, which were both fully vital and normally colored. The pancreas exhibited a harder consistency consistent with chronic pancreatitis. Throughout the postoperative period, the patient remained hemodynamically stable and was discharged from the hospital in good general condition two weeks after the initial operation.

We obtained verbal and signed consent from the patient to publish this case report.

All procedures performed were in accordance with the 1964 Helsinki Declaration and its later amendments.

DISCUSSION

The pancreaticoduodenal arcade is an arterial network in the area of the pancreas head, connecting the coeliac artery and superior mesenteric artery. False or pseudoaneurysms of the pancreaticoduodenal arcade are more common than true aneurysms in the latest literature (where all layers of the wall, including the epithelium, are present) (9). Pseudoaneurysms typically develop due to chronic inflammatory and/or infective processes of the duodenum (such as penetrating duodenal ulcer) and pancreas (like chronic pancreatitis) (9, 10). Bleeding from this site represents a severe complication, occurring in approximately 4.6% of patients with chronic pancreatitis according to Bergert et al (11). Various endovascular strategies are constantly evolving for minimally invasive treatment solutions. While these solutions often lead to favorable outcomes, they require highly specialized facilities and a sufficient number of trained specialists, especially in emergency medical settings (12, 13). Criteria such as the patient's hemodynamic stability and correction of any pre-existing coagulopathy must be met to safely perform endovascular or minimally invasive procedures (10).

Our clinic is regarded as a reference center in the country for such cases and pathology, with a large number of skilled general and abdominal surgeons routinely performing a significant number of urgent laparotomies and explorative laparoscopies in patients with hemoperitoneum of any etiology. Based on our experience, in cases of patient hemodynamic instability, rapid drop in hemoglobin values during a short-term observation period, and any radiological signs of hemoperitoneum, we advocate for surgical intervention.

In conclusion, in any patient undergoing treatment for chronic pancreatitis who suddenly experiences hemodynamic instability with a drop in arterial pressure and hemoglobin and hematocrit values, a ruptured pseudoaneurysm of the pancreatic or peripancreatic region should be considered. Only timely diagnosis and prompt surgical treatment can lead to a successful outcome. Effective cooperation between radiologists, anesthesiologists, and surgeons is essential for success. The use of Cell-saver significantly aids in maintaining cardiac output and the patient's hemodynamic stability.

Abbreviations

NMR - Nuclear Magnetic Resonance
CT - Computed Tomography
RBC - Red Blood Cell

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Sažetak

RUPTURA PANKREASNE PSEUDOANEURIZME KAO POSLEDICE HRONIČNOG PANKREATITISA – PRIKAZ SLUČAJA

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Uvod: Pseudoaneurizme pankreatikoduodenalne arkade javljaju se veoma retko, čineći oko 2% svih aneurizmi visceralnih arterija. Nastaju kao komplikacija hroničnog pankreatitisa, ulkusne bolesti, traume, operacija pankreasa i žučnih puteva, kao i komplikacija nakon transplantacije pankreasa. Obično se dijagnostikuju tek kada dođe do njihove rupture i pacijenti budu životno ugroženi zbog krvarenja u trbušnoj duplji. Krvarenje može biti unutar pseudociste kada krv prođe kroz Vaterovu papilu u digestivnu cev, ali može doći i do stvaranja retroperitonealnog hematoma koji često rupturira prema trbušnoj duplji i dovodi do hemoperitoneuma. Cell-saver je sredstvo koje se može koristiti za obavljanje intraoperativnog skladištenja krvnih zrnaca (Cell-salvage), a zatim i autologne transfuzije krvi pacijentu koji je životno ugrožen.

Prikaz slučaja: Naš pacijent, muškarac starosti 54 godina, nelečeni alkoholičar, bez medicinskih podataka o prethodnom lečenju i primeni terapije, upućen je na Kliniku za urgentnu hirurgiju Univerzitetskog kliničkog centra Srbije zbog iznenadnog bola u gornjim partijama trbuha. Uradili smo orijentacioni ultrazvuk abdomena, nakon čega je usledio hitan CT grudnog koša i abdomena, koji je pokazao hematom koji se proteže iz desnog retroperitoneuma i mezoa creva prečnika oko 150 x 109 x 180 mm sa znacima aktivnog krvarenja u infrapankreatičnoj regiji - hemoperitoneum. Zbog hemodinamske nestabilnosti i pada arterijskog krvnog pritiska i vrednosti hemoglobina učinjena je hitna medijalna laparotomija. Pronašli smo aktivno krvarenje rupturirane pseudoaneurizme arterije koje potiče iz pankreetikoduodenalne arkade. Učinjena je hemostaza, odnosno tamponada i detamponada 30 sati nakon operacije. Pacijent je nakon toga bio hemodinamski stabilan, dobro se oporavio nakon operacije i otpušten je kući u dobrom opštem stanju. Koristili smo Cell-saver za prikupljanje krvi pacijenata intraoperativno i za davanje autologne transfuzije pacijentu nakon toga.

Zaključak: Kod svakog pacijenta koji se leči od hroničnog pankreatitisa i kod koga se iznenada razvije bol u trbuhu, hemodinamska nestabilnost sa padom arterijskog pritiska i padom vrednosti hemoglobina i hematokrita, treba razmotriti rupturu pseudoaneurizme pankreasnog ili peripankreasnog regiona. Samo pravovremena dijagnoza i pravovremeni hirurški tretman mogu dovesti do uspešnog ishoda. Dobra saradnja radiologa, anesteziologa i hirurga je ključ uspeha. Upotreba Cell-savera-a značajno olakšava održavanje minutnog volumena i hemodinamsku stabilnost pacijenta.

Ključne reči: pseudoaneurizma, ruptura, hronični pankreatitis, urgentna hirurgija.

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Review article

MALE INFLAMMATORY BREAST CANCER - AN ANALYSIS

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Abstract: Inflammatory breast cancer in males is an uncommon but extremely aggressive form of the disease. It is often misdiagnosed as a benign skin disease since it manifests as erythema along the chest wall. The management guidelines are not specific, and treatment is based on the experiences of female cancer patients. Since there is limited information available about this illness, this review aims to fill that gap by conducting a thorough analysis of case reports published in peer-reviewed journals since 2000.

Keywords*:* inflammatory breast cancer, erythema, metastasis, mastectomy, chemotherapy, hormone therapy, radiation therapy, prognosis.

INTRODUCTION

Inflammatory breast cancer (IBC) stands as a rare yet highly aggressive variant of breast cancer, characterized by its propensity for distant metastases and locoregional recurrence (1). Despite accounting for only 2% to 4% of all breast cancer cases in women, it contributes from 7% to 10% of breast cancer-related deaths (2, 3). IBC is distinguished by the presence of florid tumor emboli that obstruct the dermal lymphatics of the affected breast, leading to swelling and inflammation (1). According to the 8th edition of the American Joint Committee on Cancer's (AJCC) Tumor, Node, Metastasis (TNM) staging system (1, 2), IBC is defined as a distinct clinicopathologic entity with the designation T4d, and specific criteria outlined in Figure 1 must be met for an IBC diagnosis.

Male breast cancer is exceedingly rare, constituting approximately 0.5–1% of all breast cancers globally (4, 5), rendering male inflammatory breast cancer (MIBC) an even more uncommon entity. Mimicking benign skin pathologies, MIBC often leads to treatment delays. Given the scarcity of literature on this condition, this review article aims to analyze recent trends in MIBC.

MATERIALS AND METHODS

Methods

Electronic databases and scholarly platforms such as PubMed, ResearchGate, Google Scholar, and Scopus were extensively searched for relevant articles, using key terms "inflammatory breast cancer in men" and "male inflammatory breast cancer." Individual keywords were combined using Boolean logic (AND) to refine the search. Only articles published between 2000 and 2023 were included in the study.

Criteria for Article Inclusion:

1. Study design: Peer-reviewed literature providing clear information on selected variables.
2. Participants: Male patients diagnosed with inflammatory breast cancer.
3. Language: Preference for English; articles in other languages considered if accompanied by full text translation or detailed abstract.
4. Type of Article: Case series and case reports.

Participants and Outcome Measures: Only cases with a confirmed diagnosis of MIBC were analyzed.

Exclusion Criteria: Articles lacking sufficient information on variables of interest were excluded.

Risk of Bias/Limitations

Included articles were sourced from Open Access, personal requests to researchers via email, ResearchGate, or subscribed journals available through the Saudi Digital Library. The possibility of missing articles due to unavailability through these sources exists.

Methodological Quality Check

Checklist elements were compared to those used in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Version 2020

Table 1. *Patient characteristics in the included articles*

Serial No	Series	Year	Age (Years)	Location: Right(R) Left (L) Bilateral (B)	Clinical Presentation	Imaging modalities	Nodal Involvement	Distant Metastases	Histopathology	Immunochemistry	Treatment	Outcome
1	2	3	4	5	6	7	8	9	10	11	12	13
1.	Moayeri & Rezagholi (6)	2022	53	L	Chest lump with diffuse erythema over anterior chest wall extending to axilla	USG: 10 cm x 5.3 cm sub-areolar mass and multiple axillary nodes; MMG: Breast mass with cutaneous thickening; CT: Mass with necrotic areas, axillary lymph nodes	Multiple in left axilla	Solitary liver metastasis (12 mm)	Invasive ductal carcinoma	ER (-), PR (-), HER2/neu (-), Ki67 (-)	Neoadjuvant chemotherapy along with bisphosphonates, modified radical mastectomy, with axillary nodes (Levels I, II) clearance, postoperative radiation therapy to chest wall, axilla and supraclavicular area.	Alive at 6 months follow up
2.	Tanhueco & Youssef (7)	2021	78	L	Bilateral gynecomastia of three years with recent onset erythematous and tender lump on left side	USG: Left sub-areolar abscess; Repeat USG: Irregular vascularised hypoechoic mass (5.5 cm) seen to directly invade the thickened overlying skin; multiple axillary lymph nodes. MMG: well-marginated, round 60 mm mass with overlying skin thickening on the left breast and simple gynecomastia on the right side.	Left axilla	None	Invasive ductal carcinoma	ER (+), HER2/neu (-)	Neoadjuvant hormone therapy (Tamoxifen with no impact), mastectomy with left axillary clearance, adjuvant chemotherapy (5-Fluorouracil, Epirubicin, Cyclophosphamide and Docetaxel), radiation therapy to chest wall and axilla and hormone therapy (Gonadotropin Releasing hormone analogue and aromatase inhibitor).	Alive at the time of reporting

1	2	3	4	5	6	7	8	9	10	11	12	13
3.	Tashima et al. (8)	2019	67	L	Ignored breast lump of seven years with recent appearance of multiple small anterior chest wall lumps and erythema	CT : breast mass with multiple cutaneous masses; right iliac vein thrombosis, deep vein thrombosis of lower limbs	–	–	Invasive ductal carcinoma	Luminal Type A: ER (+), PR (+), HER2/neu (-)	Chemotherapy (5-FU, epirubicin, cyclophosphamide) and Intensity Modulated Radiation Therapy (IMRT) to chest wall.	Patient developed malignant hypercoagulable state (Trousseau syndrome) and died at 1 year 6 months.
4.	Hyakudomi et al. (9)	2013	85	R	Erythema and induration over anterior chest extending to axilla	MMG: 8 mm spiculated sub-areolar breast mass with cutaneous thickening; CT: a centrally located ill-defined breast mass with skin thickening and lymphatic oedema from anterior chest wall to axilla; bone scan-multiple areas of increased uptake.	Right axilla	Bones	Invasive ductal carcinoma	ER (-), PR (-), HER2/neu (-)	1st line (capecitabine) along with bisphosphonates, followed by 2nd line(TS-1) chemotherapy but both failed. With 3rd line (docetaxel + cyclophosphamide), cutaneous improvement was achieved but got complicated with febrile neutropenia and pneumonia.	Death at 2 years 3 months
5.	Loewen et al. (10)	2013	51	R	Breast mass with erythema, peau d'orange appearance, & nipple retraction.	PET scan: contralateral supraclavicular lymph node metastasis.	Right axilla and neck	Contralateral supraclavicular	Invasive ductal carcinoma	ER (+), PR (+), HER2/neu (-)	The patient refused chemotherapy and radiation and opted for hormone therapy (aromatase inhibitor).	Alive at 12 months with improvement in metastases seen on PET scan
6.	Morita et al. (11)	2005	72	R	Erythema over anterior chest wall and lump	USG: Hypoechoic breast mass (1.5 cm) CECT: Breast mass (2 cm)	Right axilla	No	Invasive ductal carcinoma	ER (-), PR (-)	Modified radical mastectomy, adjuvant chemotherapy (paclitaxel) and radiation therapy	Alive without recurrence at 15 months
7.	Choueiri (12)	2005	56	R	Erythema over anterior chest wall, breast lump	MMG: Marked cutaneous thickening over the chest wall.	No	No	Invasive ductal carcinoma	ER (-), PR (-), HER2/neu (-)	Systemic chemotherapy (5 fluorouracil, + Adriamycin, + Cyclophosphamide)	Death at 8 months

1	2	3	4	5	6	7	8	9	10	11	12	13
8.	Spigel et al. (13)	2001	48	R	Erythema and thickening over anterior chest wall and lump	MMG: Increased breast density and spiculated mass (1.7 cm) USG: ill-defined hypoechoic mass (2 cm)	No	No	Invasive ductal carcinoma with lobular features	–	Neoadjuvant chemotherapy (Adriamycin + Cyclophosphamide) and Mastectomy	Alive at the time of reporting
9.	Abner et al. (14)	2001	69	L	Erythematous rash over anterior chest wall and pain in back	MMG: Peri-areolar mass; Bone scan: - Multiple sites of increased uptake	No	Bones	Invasive ductal carcinoma	–	Hormonal therapy (tamoxifen); radiation therapy to spine.	Alive and significantly improved at 6 weeks

MMG: Mammogram; USG: Ultrasonogram

and previously published literature reviews on the subject for quality assessment.

Data Synthesis (Extraction and Analysis)

A manual examination of the reference lists of articles was conducted, and data pertaining to ten variables were extracted and organized in Table 1. The variables included the age of the patient, clinical features, location of the lesion, imaging modalities used for evaluation, presence or absence of nodal involvement or distant metastases, management, histopathology, immunohistochemistry, and outcome. Microsoft Excel (Office Version 2019) was then utilized to analyze the retrieved data. Descriptive statistical analyses were employed to characterize the features of the included cases, with information presented using measures of central tendency (mean), dispersion (range, standard deviation), and frequency. All discrepancies were resolved through consensus among the authors, and the review adhered to the principles outlined in the PRISMA statement.

RESULTS

Study Selection

The electronic database search yielded a total of 25 publications, as depicted in Figure 2. Twelve duplicate articles were eliminated, leaving 13 articles for further examination based on their titles and abstracts. Subsequently, 12 potentially relevant papers were identified as meeting the qualifying requirements. After excluding studies due to language and patient gender discrepancies, the review ultimately included nine publications.

Study Characteristics

Nine patients were included in the analysis, with a mean age of 64.3 years (SD 12.96), ranging from 48 to

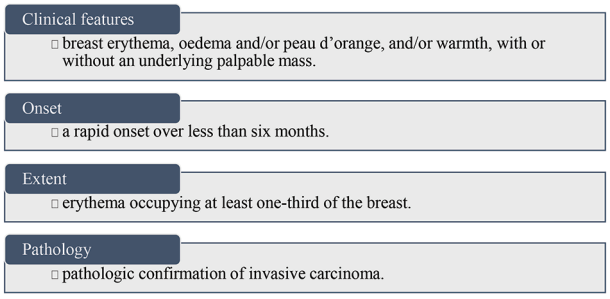

Figure 1. *Diagnostic criteria of inflammatory breast cancer*

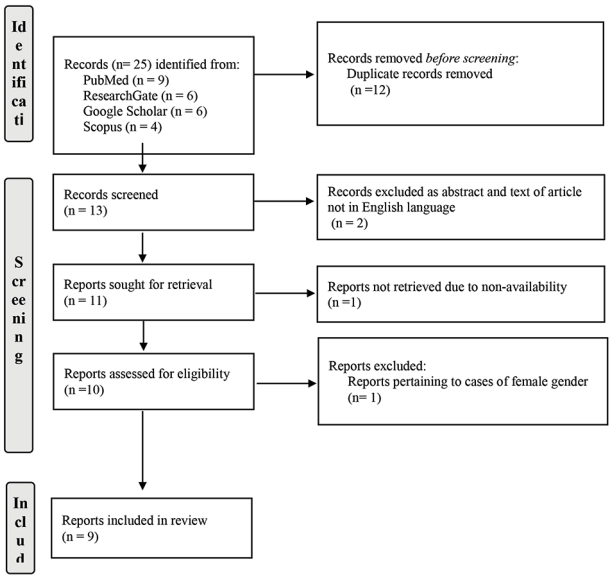

Figure 2. *PRISMA flow chart of the literature search strategies*

85 years. Only one patient (11.1%) was younger than 50 years old.

Clinical Presentation

Erythema over the anterior chest wall was the presenting complaint in all cases (n = 9; 100%). Additionally, four patients (44.4%) presented with a breast lump, and one (11.1%) had preexisting gynecomastia. The involvement of the right breast was observed in five cases (55.5%), while the left breast was involved in four cases (44.4%).

Imaging

Various imaging modalities, including mammograms (MMG), ultrasonograms (USG), computed tomography (CT) scans, positron emission tomography (PET) scans, and bone scans, were utilized to assess the type and extent of lesions. Breast masses (single or multiple) were identified in seven cases (77.7%), bony metastases in two cases (22.2%), marked cutaneous thickening in three cases (33.3%), ipsilateral axillary lymph node enlargement in five cases (55.5%), and supraclavicular lymphadenopathy in one case (11.1%).

Management

Modified radical mastectomy was the primary surgical treatment modality in four cases (44.4%), with two cases (22.2%) involving axillary lymph node clearance and two cases (22.2%) without lymph node dissection. Neoadjuvant chemotherapy was administered in two cases (22.2%), and neoadjuvant hormone therapy with Tamoxifen in one case (11.1%). Adjuvant chemotherapy was administered in two cases (22.2%), hormonal therapy in two cases (22.2%), and radiation therapy in four cases (44.4%). Systemic chemotherapy was received by three patients (33.3%), hormone therapy by two patients (22.2%), and radiation therapy to the chest wall or spine by two patients (22.2%).

Histopathology & Immunohistochemistry

All cases were diagnosed as invasive ductal cell carcinoma, with one case being the scirrhous type. Tumor embolization in dermal lymphatics was not confirmed in one case but, based on clinical features and a significant response to Tamoxifen, the patient was classified as MIBC. Immunohistochemistry analysis was available in seven cases, with five cases (71.4%) classified as triple-negative breast cancers (TNBC), one case (14.3%) as ER and PR negative, and one case (14.3%) as luminal Type A with ER and PR positive but HER2/neu negative.

Outcomes

Follow-up data were available for seven cases, with three patients (42.9%) documented to have died at 8 months, 1 1/2 years, and 2 1/4 years, respectively. Four cases (57.1%) were alive at follow-up, ranging from 6 weeks to 15 months (mean 8.6 months; SD: 6.05), but long-term outcomes and mortality were unknown.

DISCUSSION

Male inflammatory breast cancer (MIBC) is a rare condition; just nine cases that met the study's criteria were found in the extensive search of peer-reviewed literature published after 2000. The cases ranged in age from 48 to 85 years (mean 64.3 years; SD 12.96), and there was only 1 case (11.1%) below 50 years of age. In comparison, women typically experience onset within the fourth and fifth decades of life (15). The mean age of patients with MIBC in the review undertaken by Hyakudomi et al. (9) was 67.8 years.

Taylor and Meltzer in 1938 (16) classified IBC into two clinical groups: the primary form where the characteristics of IBC become evident in a previously normal breast, the secondary form, in which the clinical characteristics emerge after an initial noninflammatory breast cancer has received appropriate therapy. This classification is still in vogue, and all the cases in our review were primary in nature.

Immunochemistry analysis revealed that cancers in 5 (71.4%) cases were TNBC. In one (11.1%) case, ER and PR were negative, though HER2/neu status was not documented. Only one (11.1%) cancer was found to have ER and PR positive and negative HER2/neu (Luminal Type A). TNBC otherwise accounts for about 10–20% of invasive breast cancers and is characterized by a distinct molecular profile, a greater aggressive nature, a propensity for metastatic spread, and a lack of targeted therapies, thereby making it frustrating for researchers, physicians, and patients (17).

In our review, 7 cases had documented follow-up, and 3 (42.9%) patients had by 2 years, 3 months, whereas in 4 (57.1%) cases who were alive, the follow-up period was short, ranging from 6 weeks to 15 months (mean 8.6 months; SD: 6.05), and hence their long-term outcome and mortality were unknown. This dismal prognosis may be partly attributed to the cancer profile mentioned previously but may also be due to delays in diagnosis and treatment. The case of a 78-year-old man reported by Tanhueco and Youssef (7) had been diagnosed as a breast abscess and treated with a prolonged course of antibiotics when failure to achieve improvement led to imaging and diagnosis. Similarly, the 85-year-old patient presented by Hyakudomi et al. (9) had been following a dermatologist for six months

and being treated with antibiotics for a wrongly diagnosed chest wall infection. These cases point out the lack of awareness about MIBC even among certified healthcare providers and stress the need to promote educational activities related to this disease.

Due to the rarity of the disease, there are no specific treatment protocols for MIBC, and, like in female counterparts, the treatment is multidisciplinary, including neoadjuvant systemic chemotherapy, surgery, adjuvant chemotherapy, radiotherapy, and, in hormone receptor-positive disease, hormonal therapy (9, 18). Induction chemotherapy using anthracyclines followed by taxanes has been found to be effective in local disease control and improve overall survival. Similarly, for HER2/neu-positive cancers, targeted therapies like Trastuzumab and lapatinib have been found to be helpful (18). The patient described by Morita et al. (11) underwent radiation and paclitaxel (PTX) treatment after a mastectomy. The patient lived for fifteen months without experiencing any recurrence. In the case reported by Hyakudomi (9), 1st line (capecitabine) and 2nd line (TS-1) chemotherapy had failed but with 3rd line (docetaxel + cyclophosphamide), significant cutaneous improvement had been achieved, though the regimen caused febrile neutropenia as a serious adverse effect. A recent study by Johnson et al., however, found that there was no clear difference in pathologic complete response (pCR), but the survival outcomes in terms of overall survival (OS), relapse-free survival (RFS), and distant relapse-free survival (DRFS) are still dismal for IBC in comparison to the matched non-inflammatory controls (19). As a first-line adjuvant hormone therapy for estrogen receptor-positive male breast cancer, tamoxifen has been found to be effective, though deep vein thrombosis may warrant discontinuation of treatment (20). In the case reported by Tanhueco and Youssef (7), Tamoxifen was administered for three months as neoadjuvant therapy to downstage the cancer in anticipation of a surgical operation, but no real response was achieved. Due to insufficient suppression of oestradiol, men who get single-agent adjuvant treatment with an aromatase inhibitor have been shown to have worse results than those who receive only Tamoxifen (7). However, in this review, the patient reported by Loewen et al. (10), after refusing all forms of treatment, had been put on aromatase inhibitors and was alive at 12 months with improvement in metastases as documented by PET scan.

CONCLUSION

Male inflammatory breast cancer is a rare condition for which there is little published information in the literature. The illness has a dismal prognosis and a high mortality rate. As there are no distinct management procedures, the current course of treatment is consistent with that for female inflammatory breast cancer. Prognosis deterioration occurs with delayed diagnosis. Raising awareness through education can lead to early diagnosis and timely intervention, with potentially improved outcomes.

Abbreviation

IBC – Inflammatory Breast Cancer
MIBC – Male Inflammatory Breast Cancer
TNBC – Triple Negative Breast Cancers
MMG – Mammogram
USG – Ultrasonogram
CT Scan – Computed Tomography Scan
PET Scan – Positron Emission Tomography
ER – Estrogen Receptor
PR – Progesterone Receptor
Her2 – Human Epidermal Growth Factor Receptor-2
pCR – Pathologic Complete Response
RFS – Relapse-Free Survival
DRFS – Distant Relapse-Free Survival
PTX – Paclitaxel

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Sažetak

INFLAMATORNI KARCINOM DOJKE KOD MUŠKARACA - ANALIZA

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Inflamatorni karcinom dojke kod muškaraca predstavlja retku, ali izuzetno agresivnu formu bolesti. Često se greši u dijagnostikovanju, te se predstavlja kao benigno oboljenje kože, budući da se ma-

nifestuje kao eritem duž grudnog zida. Uputstva za terapiju nisu specifična, i tretman se zasniva na iskustvima ženskih pacijentkinja obolelih od karcinoma. S obzirom na ograničene informacije o ovoj bolesti, cilj ovog rada je da ispuni tu prazninu analizom slučajeva objavljenih u recenziranim časopisima od 2000. godine.

Ključne reči: inflamatorni karcinom dojke, eritem, metastaze, mastektomija, hemioterapija, hormonska terapija, radioterapija, prognoza.

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Review article

PREVENTION MEASURES OF HEPATITIS B IN HEALTHCARE INSTITUTIONS FROM THE PERSPECTIVE OF THE NURSING SCOPE OF WORK

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Abstract: Viral hepatitis B (hepatitis B) poses a significant public health challenge on a global scale, particularly affecting populations in middle- and low-income countries, including those in the developing world. It primarily impacts individuals engaging in risky behavior and healthcare workers directly or indirectly involved in providing services to these patients.

This paper will present information from pertinent professional and scientific sources on hepatitis B, preventive measures, and the role of nurses in their implementation. This review paper is a valuable contribution, providing recommendations and insights derived from the professional practice of nurses across all levels of healthcare.

Keywords: infection, preventive measures, healthcare, intrahospital hepatitis B infections.

INTRODUCTION

Viral hepatitis B (hepatitis B) remains a significant global public health concern, particularly in developing regions, impacting about one-third of the world's population. Approximately 350 million individuals are chronic carriers of the hepatitis B virus (HBV), with only 2% experiencing spontaneous recovery each year and developing seroconversion, indicated by anti-HBs antibodies (1). Primary HBV infection typically presents as asymptomatic, and complete recovery is anticipated in 90-95% of patients within three months (1). Various medical interventions, blood transfusions, or the use of contaminated needles, such as in cases of drug addiction or tattoos, can contribute to hepatitis B infections. Additionally, hepatitis B may manifest in individuals with other conditions, such as AIDS patients (2).

The term "Contagious Jaundice" traces back to the era of Hippocrates (460 - 370 BC), and evidence indicating the blood-borne nature of hepatitis dates back to 1885 (3, 4).

In Bremen, following the smallpox vaccination of 1,289 port workers in 1947, it was discovered that 15% of those vaccinated contracted hepatitis. Subsequently, Maccahun introduced the designations "hepatitis A" (formerly infectious hepatitis) and "hepatitis B" (previously serum hepatitis) (4). In 1964, Blumberg et al. identified a specific antigen in the serum of an Australian native, later named the "Australia antigen"(5). This antigen was subsequently linked to serum hepatitis. In 1970, Krugman et al. made a crucial discovery that cooking serum containing HBV destroyed the virus's infectivity after just one minute while preserving its immunogenicity. This pivotal knowledge laid the foundation for the development of vaccines against HBV (3, 4, 6).

The aim of this paper is to present information from relevant scientific/professional data sources related to epidemiology and prevention measures of hepatitis B in healthcare institutions, focusing on the nursing scope of work.

Etiology and Pathogenesis of Hepatitis B

Hepatitis B virus is a DNA virus that primarily targets hepatocytes and can lead to chronic infection. It is characterized by a spherical particle with a diameter of 47 nm, present in the blood in two forms: a round antigen with a size of 22 nm and a filamentous one of variable length, known as hepatitis B surface antigen (HBsAg).

The hepatitis B virus encompasses several crucial antigenic systems, including:HBsAg (Surface Antigen), HBcAg (Core Antigen), HbeAg (Core Protein Antigen).These antigenic systems collectively form the hepatitis markers (7).

Epidemiology

The Balkans and the Mediterranean region exhibit substantial genetic heterogeneity of Hepatitis B Virus (HBV) in Europe (8).

According to the World Health Organization (WHO), approximately 257 million people globally are chronically infected with hepatitis B, with 13 million cases in Europe, resulting in about 887 000 deaths annually. In Western Europe and North America, the prevalence is less than 1% of the population. Notably, Montenegro has seen a decline in hepatitis B incidence over the past two decades due to vaccination, although it remains a significant public health concern (9).

Worldwide, HBV infection occurs sporadically in certain regions. About 45% of the global population resides in areas with a high prevalence of chronic HBV infection, particularly in the Republic of China, Southeast Asia, tropical Africa, Central and Eastern Europe, Latin America, the Mediterranean, and the Middle East. The prevalence is most pronounced in poor and developing countries (9).

Data from WHO indicates that there are over 400 million chronic carriers of the virus, with 75% residing in Asia and the Western Pacific. Individuals acquiring chronic HBV infection in childhood face a 5% increased risk of developing hepatocellular carcinoma (HCC) per decade of life, which is significantly higher than the rate observed in uninfected individuals. Annually, 500 000 to 1.2 million people die due to liver failure, cirrhosis, or HCC, with at least 75% of these deaths attributed to HBV infection, ranking it as the tenth leading cause of death globally (10).

Routes of Transmission of HBV

Hepatitis B virus has been detected in all body fluids (11, 12) and is transmitted through sexual contact, percutaneous exposure, nosocomial transmission, blood and blood product transfusion, and perinatally (12, 13).

In underdeveloped and developing countries, vertical transmission is more common, whereas horizontal transmission is predominant in developed countries. In the USA, approximately 40% of new infections result from heterosexual transmission, and 25% from homosexual transmission, classifying hepatitis B as one of the most common sexually transmitted diseases. Healthcare workers, including doctors, nurses, and hospital staff, are particularly at risk. Prophylactic measures are mandatory for these professionals. In the event of injury with a sharp object/needle contaminated with the blood of an HBsAg and HBeAg positive patient, serological markers of HBV infection are detected in 37-62% of cases. Nosocomial infections are relatively rare and are usually associated with inadequate implementation of universal prevention measures or improper handling of medical instruments, needles, and medical waste (9).

Hepatitis B Prophylaxis

Understanding the various modes of hepatitis B transmission—such as sexual contact, blood inoculation, and vertical transmission—enables the implementation of several prophylactic measures to prevent the spread of hepatitis B. These measures encompass both general and specific protection strategies **(**12).

Individuals testing positive for HBV should receive education on appropriate home behavior, proper excrement disposal, the use of dedicated utensils, and the importance of protection during sexual intercourse. Specialized education is essential for intravenous drug users (14). General prevention measures within healthcare institutions mandate healthcare workers to utilize prescribed personal protective equipment (masks, gloves, glasses, aprons, caps) to prevent contact with infectious materials. Ensuring asepsis and antisepsis quality, proper infectious waste disposal, and comprehensive blood testing for all donors contribute significantly to infection control (12).

Special protection measures include pre-exposure and post-exposure immunoprophylaxis (12). Pre-exposure prophylaxis is carried out by vaccination. The use of vaccines against hepatitis B has three goals: prevention of virus transmission, prevention of clinically manifest disease, and prevention of the development of chronic hepatitis (15). Post-exposure prophylaxis is used in newborns of HBsAg-positive mothers in the first few hours after exposure, then after a single exposure to the HBV virus (a stabbing incident) and in persons who had sexual contact with infected persons (15).

Nurse/Technician Procedures in Primary Hepatitis B Prevention

Primary prevention of hepatitis B targets unvaccinated individuals, aiming to modify their attitudes and behaviors to avoid contracting the disease. This includes vaccination and health education (16).

Vaccination

Prior to the systematic implementation of vaccination, preventive measures were deployed to either

avert HBV infection or, if contracted, to control its impact. The advent of vaccination marked a significant stride in prevention efforts. The HBV vaccine received approval in 1982, with a recombinant DNA vaccine against hepatitis B introduced in 1986. This pioneering vaccine, derived through genetic engineering on yeast fungi, represents the world's first approved recombinant vaccine. Two recombinant vaccines, Engerix B and Recombivax HB, are currently in use. The vaccine must be stored between 2 to 8 degrees Celsius and should not be frozen or exposed to higher temperatures, as this diminishes its efficacy (10, 17).

The recombinant vaccine's high effectiveness and safety prompted the World Health Organization (WHO) to recommend its inclusion in the mandatory immunization schedule for infants in their first year of life in 1992 (18). Vaccination against hepatitis B infection is also advocated for individuals at increased risk due to risky behaviors and occupational hazards, particularly healthcare workers in contact with the hepatitis B virus (Table 1) (18).

Health workers (doctors, nurses, laboratory technicians, etc.), play a pivotal role in promoting and disseminating information about healthy lifestyles within the realm of primary health care. Their activities involve ensuring early treatment of diseases and advocating for preventive measures (18). Nurse technicians in primary health care are responsible for improving the health of patients through evidence-based recommendations, and they encourage individuals to receive preventive services such as examinations, counseling, and preventive medications. Nurses are important in promoting public health. Traditionally, the focus of health promotion by nurses has been on disease prevention and changing the behavior of individuals regarding their health. However, their importance as health promoters is more complex, as they have multidisciplinary knowledge and experience in health promotion in their nursing practice (19).

At the primary healthcare level, nurses engage in diverse activities, ranging from healthcare and medical-technical tasks to health education, educational work, and investigations. They actively participate in all stages of organizing and implementing vaccinations. The preparation phase, serving as the initial and crucial link in vaccination organization, significantly influences its success. Activities in this phase include program adoption, expert methodological instructions, planning, organizing immunization calls, ensuring vaccination conditions, supervising vaccine handling and storage, and conducting employee education and health awareness programs for the population. The implementation of vaccination is meticulously planned to meet the population's needs, aiming to provide immunization to all healthcare users. The evaluation phase, assessing the success of immunization, serves as a critical component in the vaccination process. It allows health workers to identify potential shortcomings in

Table 1. *Persons with increased and occupational risk of contact with the Hepatitis B virus*

Persons at Increased Risk
Newborns
Individuals living with hepatitis B patients or infected individuals
Residents of regions with a high prevalence of hepatitis B
Individuals in direct contact with blood and blood derivatives
Patients on a chronic hemodialysis program
Patients with hematological diseases, e.g., those suffering from hemophilia
Promiscuous individuals, i.e., those with more than one sexual partner
Individuals with a history of sexually transmitted diseases
Intravenous users of psychoactive substances
Individuals who are HCV and HIV positive
Men who have sex with men
Individuals at professional risk of contact with the hepatitis B virus
a. Health workers and hygienists employed in health institutions
b. Police and prison staff
c. Firefighters
d. Non-medical personnel of emergency medical assistance and emergency centers
e. Employees in utility companies (e.g., sewage, waste)
f. Travelers to areas with a high prevalence of HBV

their efforts and undertake corrective actions for improvement (20).

Vaccination Against Hepatitis B in Montenegro

In Montenegro, the vaccination against hepatitis B is meticulously regulated by the Rulebook on conditions and methods for the implementation of mandatory immunoprophylaxis and chemoprophylaxis against certain infectious diseases. The Rulebook was published in the "Official Gazette of Montenegro", no. 36/2020 and 35/2022.

As per the current rulebook, specifically Article 27, active immunization against hepatitis B is initiated in newborns and is intended to be completed by the time the child reaches 12 months of age (21). The vaccination program ensures comprehensive coverage to protect the population from the risks associated with hepatitis B.

Moreover, the rulebook, under Article 30, stipulates mandatory immunization for individuals based on epidemiological and clinical indications. This includes both active and passive immunization against hepatitis B. All persons who work in health institutions, encompassing pupils and students within the health field, are obligated to undergo immunization if they are unvaccinated or incompletely vaccinated. This requirement applies to those individuals whose academic responsibilities entail direct contact with infectious material (22).

The regulatory framework thus underscores the significance of protecting individuals within healthcare settings from the risks associated with hepatitis B through a robust vaccination strategy.

Health Education in Hepatitis B Prevention

Health education serves a vital role in preventing hepatitis B and its associated complications. It is a dynamic and individualized process that should be tailored to the specific needs and characteristics of each patient or target population. Here are key aspects of health education in the context of hepatitis B.

• **Individualized Approach**: Conducting health education requires recognizing that it is an individualized process. A one-size-fits-all approach is not effective, and the content of education should be adjusted based on factors such as cognitive abilities, social context, and economic situation relevant to the age group being targeted (22, 23).

• ***Continuous and Permanent Education:*** Health education is not a one-time event but a continuous process. It extends beyond the healthy population to encompass those who are sick, during illness, hospitalization, after discharge, and throughout the lifelong journey for virus carriers (24, 25).

• ***Adaptation to Age Groups:*** Different age groups have varying needs and capacities for understanding health information. Health education materials, both oral and written, should be adapted to suit the cognitive abilities and preferences of each age category.

• ***Oral and Written Instructions:*** Health education efforts include both oral and written instructions. In addition to verbal communication, producing informative and educational brochures, leaflets, and written materials ensures a comprehensive approach. The content of these materials should be accessible and relevant to individuals of all ages.

• **Lifelong Learning**: Health education is not confined to specific stages of life; it is a lifelong learning process. Even after initial education, individuals, including those with hepatitis B, need ongoing information and support. This is particularly important during illness, hospitalization, and the transition back to regular life after being discharged.

By adopting these principles, health education becomes a powerful tool in promoting awareness, prevention, and management of hepatitis B, contributing to better health outcomes for individuals and communities.

The importance of nurses/technicians in the secondary prevention of hepatitis B

Secondary prevention of hepatitis B refers to the timely recognition and detection of potential patients in the early stages of the disease, in order to stop its further progress. There are no jobs for healthcare workers that do not involve a certain degree of risk. In their daily work, the nurse/technician meets with potential patients and carriers of HBV. In doing so, he must pay great attention to preventing the spread of infection among patients, but also among healthcare workers (who should be vaccinated). Wards with an increased risk of transmission of HBV infection (intensive care units, operating rooms, hemodialysis centers, surgical wards, etc.) represent a risk of the emergence and spread of blood-borne infections. Infection transmission can be prevented by applying general (standard) prevention measures (24).

Measures to protect health workers from HBV infection

In many cases, the risk of nosocomial transmission of infections is highest before a definitive diagnosis is made and before precautions can be taken in accordance with that diagnosis. These measures are

designed to reduce the risk of transmission of microorganisms from recognized and hidden sources of infection in the hospital (25, 26).

The most important measure to reduce the risk of transferring microorganisms from one person to another, through direct or indirect contact, is hand hygiene. Hand hygiene involves washing hands with liquid soap with or without the addition of antiseptics and/or applying a disinfectant solution in the form of a solution or gel to dry hands, where the five moments of hand washing are respected. Hand hygiene must be performed before and after contact with each patient and after contact with blood, body fluids, secretions and excreta, as well as contaminated equipment and objects. Hand hygiene is mandatory even when the hands are protected by gloves during the listed actions (21).

Protective equipment consists of protective masks and eye protectors, protective aprons/coats, protective shoes, and slippers (21).

Proper handling of sharp objects - the use of sharp objects should be minimized. Immediately after use, dispose of sharp objects in designated containers, i.e. containers (with impenetrable and waterproof walls). Single-use objects and equipment used for patient care should be discarded in impermeable bags, subject to proper disposal as potentially infectious waste.

Procedure after professional exposure of healthcare workers to material potentially infected with the hepatitis virus

Bearing in mind the characteristics of HBV and the ways of its transmission, healthcare workers, that is, persons employed in healthcare institutions, represent a high-risk cohort for HBV infection compared to the general population. Occupational exposure is defined as risky contact of health workers with potentially infectious material (26).

The risk is related to the frequency of exposure to blood at the workplace and the number of contacts with patients who are HBeAg positive (a marker of high viral replication). The most common incident situations that carry the risk of HBV transmission are:

• injuries through the skin, i.e. needlesticks (stabbing incident)

• injuries by sharp objects.

• splashing of bodily fluids on the skin and mucous membranes (26).

Stab incidents occur every day in healthcare facilities. The procedure for a stabbing incident includes (26):

• immediate treatment of the wound,

• immediate reporting procedure to superiors within 24 hours,

• exposure risk assessment,

• testing the exposed person,

• testing the source of infection (if the source is known) with the signing of the consent i

• application of post-exposure prophylaxis.

Stab incidents most often occur during the use of sharps while working with a patient or after disposing of used sharps in the sharps waste section. If an incident occurs, the healthcare worker is obliged to report it to the department for hospital infections, which is necessary both for counseling the injured worker and for the application of timely post-exposure prophylaxis. Timely prophylaxis is applied within 24 to 48 hours together with HB immunoglobulin. HBIg provides passive immunity. The vaccine is given in four doses: day zero, after one month, after two and twelve months. The vaccine after exposure to the HBV virus does not provide completely safe protection but reduces the risk of infection (27).

Research has shown that most healthcare workers do not report a stabbing incident. The reasons are as follows: they do not know how to report, they consider the procedure too complicated, they are afraid of losing their job, they think that only removing blood and other body fluids from the skin is enough to prevent infection, or they think that the exposure is a consequence of their irresponsibility (27).

Counseling after occupational exposure to potentially infectious material

Healthcare professionals generally correctly estimate the risk of hepatitis B virus infection, while estimating the risk of HIV and hepatitis C to be higher than it is. These two infections were discovered later, so some healthcare workers probably know less about them. In addition, there is no adequate protection (vaccine) for any of them, and the perception of an extremely unfavorable outcome, fear of possible social consequences, i.e. the so-called “social contamination” (the possibility of projecting onto health workers the characteristics of the patients they care for, especially before there is sufficient evidence that more social stigma occurs against AIDS and hepatitis C sufferers than against those suffering from other communicable or non-communicable diseases), fear intensifies and risk is overestimated. That is why it is extremely important that a healthcare worker reports to the Counseling Center for HIV and Viral Hepatitis after an incident at the workplace, where they will have an interview with an epidemiologist and perform a risk assessment together with him, receive the neces-

sary information and be adequately advised and cared for. The advice, support, and encouragement of the healthcare worker are especially important both for post-exposure prophylaxis and for continuing to work. If it is an effort for a health worker, it is necessary to include psychosocial support and the help of a medical psychologist (27, 28, 29).

CONCLUSION

Healthcare workers can greatly contribute to the prevention of transmission of infections in healthcare facilities. Nurses are trained for active participation in the prevention of transmission of infections in health institutions, as well as blood-borne diseases among health workers, within their independent functions. The implementation of activities related to general and specific measures for preventing HBV infection can be achieved through well-designed programs tailored to the needs and challenges identified within healthcare institutions and among healthcare workers. They can be realized through several stages. By collecting data through supervision and from the institution's staff, and analyzing them, it is possible to identify current and potential problems related to knowledge, attitudes, and behavior at work, which may be related to the risk of infection with the hepatitis B virus. Identifying priorities, planning further activities, and setting goals is the basis for the successful implementation of the activities of nurses in the prevention of HBV infection in health institutions at all levels of health care.

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Licensing

Sažetak

MERE PREVENCIJE HEPATITISA B U ZDRAVSTVENIM USTANOVAMA IZ UGLA SESTRINSKOG DELOKRUGA RADA

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Virusni hepatitis B (hepatitis B) je značajan javno zdravstveni problem koji pogađa ljudsku populaciju na globalnom nivou, pretežno u zemljama sa srednjim i niskim dohotkom, kao i zemlje u razvoju. Najčešće pogađa osobe rizičnog ponašanja, a takođe su u riziku i zdravstveni radnici koji direktno ili indirektno učestvuju u pružanju zdravstvenih usluga ovim pacijentima. U ovom radu biće predstavljene informacije iz relevantnih stručnih/naučnih izvora podataka o Hepatitisu B, merama prevencije i procedurama medicinske sestre u sprovođenju istih. Ovaj revijalni rad predstavlja koristan prilog u kome se nude preporuke i iskustva iz područja struke, tj. profesionalne prakse medicinskih sestara na svim nivoima zdravstvene zaštite.

Ključne reči: infekcija, mere prevencije, zdravstvena zaštita, intrahospitalne hepatitis B infekcije.

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Review article

EPSTEIN-BARR VIRUS: CAUSES, CONSEQUENSES, DIAGNOSIS AND TREATMENT OF EPSTEIN-BARR VIRUS IN HUMAN

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Abstract: The Epstein-Barr virus (EBV) belongs to the family of herpesviruses, subfamily Gammaherpesvirinae, and genus Lymphocryptovirus. Despite this classification, there are two serotypes of the Epstein-Barr virus, namely type A and type B. Both types play significant roles in the development of viremia. Additionally, EBV infection can lead to lymphadenopathy, upper respiratory tract obstruction, spleen rupture, thrombocytopenia, and recently, there has been increased emphasis on the connection between this virus and certain malignant neoplasms. Diagnosing this virus can be challenging if clinicians rely solely on serological confirmation. In some cases, it is necessary to perform more specific methods, in addition to considering the clinical picture and history, to prove the presence of the virus in blood, nasopharyngeal swabs, and other tissue samples. The aim of this paper is to present the severity and consequences caused by the Epstein-Barr virus and to emphasize the importance of preventive measures in preventing the virus from coming into contact with susceptible individuals. Prevention plays a crucial role in reducing contact with the virus. Since the infection spreads via droplets, wearing masks in healthcare facilities and regular hand washing are hygiene priorities to prevent infection and further transmission.

Keywords: Epstein-Barr virus, carcinogenesis, transplantation, serological methods, autoimmune reactions.

INTRODUCTION

The Epstein-Barr virus (EBV) belongs to the herpesvirus family. Primarily, Epstein-Barr is a droplet virus, but it can also be transmitted through other bodily fluids (1). In addition to causing respiratory diseases, it is capable of latently infecting B lymphocytes by transcribing its own genes, leading to the genetic inversion of the immune response of B lymphocytes. This results in autoimmune reactions between B lymphocytes and other tissues, which supports the theory of the origin of multiple sclerosis (2). The primary disease caused by this virus is infectious mononucleosis, characterized by monocytosis in the blood count. This virus is linked to a wide range of diseases, including psychiatric, autoimmune, neurological, dermatological, and even malignant diseases (3). Over ninety-five percent of the population is affected by this virus, an important characteristic of which is its possession of double-stranded genetic material. The virus targets the epithelial cells of the upper respiratory tract, as well as the aforementioned lymphocytes (4). Every year, the number of patients with malignant tumors associated with EBV increases, leading to the death of over one hundred thousand individuals (5). It is estimated that over 200,000 cancer sufferers worldwide are linked to this virus (6). It has a latent presence in cells as well as strong oncogenic and epigenetic potential, and often goes unrecognized by immune factors due to its molecular mimicry, paving the way for the development of malignant tumor cells (6). The virus is also linked to epithelial and mesenchymal neoplasms (7,8). This virus possesses an envelope with a diameter ranging from 100 to 200 nm. It has DNA that is located within the nucleocapsid (9).

Symptoms, Carcinogenesis, and Epidemiological Parameters in Epstein-Barr Virus Infection

For those who manifest symptoms, they may include general weakness, enlargement of the spleen and lymph nodes, but also an increase in the number of lymphocytes in the blood. Viremia primarily occurs due to the rapid multiplication and infection of

B lymphocytes by the virus. A randomized controlled study has shown that patients suffering from chronic fatigue following infection with the virus remained in this state six months post-infection (10). Several randomized studies conducted in Chinese hospitals have shown that even after the use of sorafenib in patients undergoing tissue transplantation, the drug exhibited a protective property that prevented infection by the Epstein-Barr virus, even thirty-six months post-treatment (11). The WHO also links certain types of nasopharyngeal carcinoma (non-keratinized) to this virus (12). A meta-analysis that included 26 studies has shown a strong correlation between gingivitis and Epstein-Barr virus infection. What is particularly interesting in these studies is the fact that this correlation was not confirmed among African respondents (13). Some studies using genotyping methods revealed that over 90% of nasopharyngeal neoplasms contained high-risk Epstein-Barr virus BALF2 haplotypes. This is a clear indication of a very high correlation between the occurrence of a given cancer and the Epstein-Barr virus (14). The virus is also associated with stomach neoplasms (15). The designation "oncological virus" for the Epstein-Barr virus comes from its association with multiple malignancies, primarily those arising from B-lymphocytes (16). This virus exhibits two primary modes of infection: a latent state of infection and active viremia, the latter being attributed to the lytic potential of the virus (17). Infection with this oncogenic virus may remain asymptomatic in a certain number of individuals (18). Some studies that have been carried out so far have shown that the percentage of viruses in Reed-Sternberg cells that are pathognomonic for Hodgkin's lymphoma, and that possessed a given virus, ranges up to over 70%. More precisely, over 70% of Reed-Sternberg cells and Stennerberg's cells had Epstein-Barr virus in them (19).

Epstein-Barr Virus and Patients After Organ Transplantation

A particularly vulnerable population comprises those who have undergone tissue or organ transplantation. The Epstein-Barr virus is one of the primary concerns a few years after tissue transplantation due to its ability to remain latent in B lymphocytes and then reactivate after a few years, which confers special importance to this virus (20). In a multicenter study of individuals who were recipients of a transplanted kidney, about a quarter of the recipients developed activation of the latent Epstein-Barr virus. Such activation poses a severe problem that can lead to intense viremia and even serious consequences (21).

Diagnosing Viruses

The most commonly used methods in detecting this virus are serological tests, typically the ELISA test. However, a PCR (polymerase chain reaction) test can also be used to detect a given virus (22). PCR shows high sensitivity and specificity in detecting the viral genome, but its application requires a longer period of time than some other antigenic tests that are performed daily. Furthermore, the disadvantage of the PCR test is its considerably higher price compared to other tests (23). The PCR test detects certain types of genes within the genome of the virus, which are unique to that virus (24). The degree of probability that in the case of nasopharyngeal cancer the PCR test will detect the virus itself from the blood plasma is over 95 percent (25). Also, in the case of reactivation, more precisely reinfection of the virus from its many years of latent rest inside the cells, PCR proves to be a crucial test in proving the given, even if not an active virus. This is because PCR can multiply the virus gene up to several hundred thousand times (26).

In a case report of a 27-year-old patient with SLE (Systemic Lupus Erythematosus), who had positive serological tests for some viruses, the results were subsequently confirmed to be false positives by PCR test (27). Some studies show a very high correlation between SLE activation with the transition to latent Epstein Barr virus infection if the activation date of the chronic disease lasted more than half a year (28). Immunofluorescence assays (IFA) are considered the gold standard as a serological test for the detection of Epstein-Barr virus. However, since the performance and interpretation of IFA are complex and sometimes subjective, many laboratories use commercially available sensitivity and specific tests such as ELISA tests based on enzyme-linked immunosorbent assay or chemiluminescent methods. These tests are used as leading methods in virus detection and are simple to perform. Diagnostic approaches based on IFA, heterophile testing, immunoblot analysis, and PCR testing can be used to clarify some atypical serological results previously determined by immunoassay. This is because the PCR test can accurately detect the presence of the virus and thereby show whether ELISA and other tests were false positive or false negative (22).

The main advantage of the ELISA test compared to PCR testing is its ability to detect the virus without direct contact, relying instead on increased levels of specific antibodies. These antibodies can indicate whether the infection is acute or if the individual has developed immunity, providing protection against re-infection with the virus (29).

One method for confirming the presence of the virus is the immunofiltration method, which in a cer-

tain study showed approximately 13% false positive results (30). Additionally, exposure to and infection with multiple different viruses simultaneously can lead to a false positive finding (31). However, the Epstein-Barr virus can also trigger a strong allergic response in the body mediated by Th2-lymphocytes (32). Interestingly, over 90 percent of individuals infected with this virus do not exhibit any symptoms. There may be a latent-lytic switch in the Epstein-Barr virus. Laboratory analyses, such as the assessment of leukocyte count, procalcitonin, C-reactive protein, and interleukin levels, can be used to detect the presence of this virus (33, 34, 35). A retrospective analysis of hospitalized children in Shanghai revealed that almost 60 percent of cases were correlated with various immunological disorders (35).

Treatment of Individuals Infected with the Epstein-Barr Virus

In addition to pharmacological treatments, cellular treatments of T lymphocytes, which are specific for treating certain viruses like the Epstein-Barr virus, are possible (33). Achieving success in curing this infection has been challenging, but the drug Foscarnet has shown effectiveness in treating infections caused by the Epstein-Barr virus (34). Epstein-Barr virus infection in children, apart from sore throat, increased temperature, lymphadenopathy, and swollen eyelids, resulted in bacterial superinfection which required antibiotic application (36).

CONCLUSION

This apparently harmless virus is increasingly associated with serious chronic diseases. Serological tests, as well as the PCR test, are leading methods for the detection of this virus. An increasing number of current studies show that its role in neoplasm development is highly significant. The details are further elaborated on in the text, but the repercussions of this virus underscore the severity of Epstein-Barr infections as a public health issue.

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Sažetak

EPSTEIN-BARR VIRUS: UZROCI, POSLEDICE, DIJAGNOSTIKA I LEČENJE EPSTEIN-BARR VIRUSA KOD LJUDI

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Epstein-Barr virus (EBV) pripada porodici *Herpesviridae*, subfamiliji *Gammaherpesvirinae* i rodu *Lymphocryptovirus*. Bez obzira na to što postoje dva serotipa Epšten-bar virusa, a to su tip A i tip B, oba tipa imaju svoj značaj u nastanku viremije. Osim što može dovesti do limfadenopatije, opstrukcije gornjih respiratornih puteva, rupture slezine, trombocitopenije, poslednjih godina sve više se stavlja akcenat na povezanost ovog virusa i određenih malignih neoplazmi. Dijagnostika datog virusa može predstavljati problem ukoliko bi se kliničar oslonio samo na serološku potvrdu o ovom virusu, već pored kliničke slike i anamneze potrebno je u nekim slučajevima uraditi određene specifičnije metode da bi se dokazalo prisustvo virusa u krvi, u nazofaringejalnom brisu, ali i u uzorcima iz drugih tkiva. Cilj ovog rada je da predstavi ozbiljnost i posledice izazvane datim virusom i da naglasi preventivne mere koje zauzimaju prvo mesto u sprečavanju da virus inficira osobu, koja mu je izložena. Prevencija igra ključnu ulogu u sprečavanju kontankta sa datim virusom. Pošto se Epstein-Barr virusna infekcija prenosi kapljičnim putem, nošenje maske u zdravstvenim ustanovama, ali i redovno pranje ruku je higijenski primat da bi se sprečila zaraza i dalje širenje zaraze.

Ključne reči: Epstein-Barr virus, kancerogeneza, transplantacija, seroloske metode, autoimune reakcije.

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BUILDING LEADERSHIP IN NURSING PRACTICE

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Abstract: In the pursuit of a competent and competitive healthcare system, nurses and healthcare technicians, as key figures in the healthcare process and scientific discipline of nursing, should possess not only professional knowledge but also managerial abilities and skills. This includes the effective management of human and material resources within the healthcare system. Leadership in nursing practice can be understood as the influence of head nurses on the quality and effectiveness of all activities within their domain. By reviewing the literature on research concerning leadership in nursing and the factors influencing its development in nursing practice, which have not yet been definitively defined, we aim to provide an overview for the professional community in the fields of biomedicine and health, especially in healthcare where nurses operate at all levels. To achieve the goals necessary for developing leadership in nursing practice, the implementation of appropriate strategies, methods, and tools within the healthcare system is crucial for human resources, a key factor in improving healthcare delivery. The role of the head nurse, or nursing leader, is of paramount importance in enhancing the organization and quality of healthcare at all levels.

Keywords: Leader, nurse, manager, management, knowledge.

INTRODUCTION

Social and economic changes worldwide necessitate significant investments in research and innovation, particularly in healthcare and nursing (1). Leadership has been inherent in mankind since its inception as conscious and thinking beings, embodying strength, determination, courage, desires, ambitions, and the individual's will to effect change in themselves and others (2). The presence of efficient and effective leaders in nursing practice, who can successfully guide healthcare through the uncertainties brought about by changes, is of paramount importance for the continued advancement of healthcare and health perspectives. In the pursuit of a competent and competitive healthcare system, leadership ceases to be an option but becomes a necessity. To make meaningful contributions to healthcare and effectively manage change, the nursing profession needs to foster leadership at all levels: local, regional, national, and international (3). Nurses, as the bearers of the healthcare process, should not only possess professional knowledge but also managerial expertise and skills, enabling them to adeptly manage human and material resources within the healthcare system. Leadership is primarily about relationships and the willingness of others to follow, placing it within the realm of self and people management skills (4, 5). This profile plays a crucial role in the overall management structure, representing the intermediate tier of management within the healthcare hierarchy. It integrates the knowledge of the staff it oversees and serves as the main link in the chain of patient – nurses/technicians – head nurses/technicians – heads of departments/doctors (4, 6).

AIM

The aim of this study is to examine the most important factors and aspects that determine the development and construction of leadership in nursing practice.

METHOD

This review paper utilized a standard literature review strategy, involving searches of electronic databases and professional works related to leadership and management in healthcare, with a primary focus on nursing practice. A comprehensive search was conducted to gather relevant literature, incorporating both domestic and international sources available on official and pertinent websites.

Electronic databases searched included Pubmed, Scopus, Google Scholar, Serbian Citation Index, ResearchGate, and others. Keywords such as "nurses," "organization of nurses," "healthcare management," and "leadership in nursing" were employed to identify relevant publications. The search was limited to publications within the last ten years.

Human Resources Management in Healthcare

One of the key factors in the organization and implementation of changes in healthcare organizations and the system as a whole is the application of appropriate strategies, methods, and tools, with one of the most effective being the strategy of changing human resources. Without a thorough transformation of management practices in healthcare and without significant changes, both in the structure and in the work of all employees in health services, be it medical or non-medical personnel, there will be no improvement in healthcare as a whole. A mix of different skills and expertise will increasingly be required for the quality and efficient provision of healthcare services to healthcare workers. Transparency between operatives and supervisors, as well as among different departments providing services, teams of different experts on the same task, and faster and more efficient circulation of information, both internally and in relation to external factors, are the characteristics of the new, flexible health management. The transformation of health management should make the complex role of employees in health directed primarily towards the users of health services with constant work on their own education, as service providers, and on the education of users (4). For the successful implementation of changes, it is necessary to be motivated for changes. The motives of the members involved in the team can be different. From social motives aimed at securing personal existence and affirmation: the motive of combativeness, the motive of security, the motive for acquisition, the motive for personal affirmation, the motive of self-actualization, to the social motives aimed at connection with other people, the motive for obedience, etc. (5). The first group of motives refers to thinking, problem-solving, and decision-making skills, and the second group of motives is useful for teamwork by contributing to the effectiveness of communication among its members, through cooperation, providing support and help, and developing positive interpersonal relationships (5). Motivating employees for change is a task that the manager in the institution, in the role of agent, must perform. It is an extremely important task without which it is not possible to make changes. The very beginning of the organizational change process comes down to the maturing of managers' awareness that changes are necessary (5). Without the manager's conviction that changes are necessary, they will certainly not happen. Managers' motivation is a necessary but not sufficient condition for their success. Changes always imply a change in employee behavior to a greater or lesser extent. Almost every organizational change implies that employees change some of their routines, operations, the way they do their work, and their behavior (5,6). In order to accept and implement changes, employees must be truly convinced that they will bring something good, both to them personally and to the institution where they work (5). Organizations or institutions that operate in today's environment are in constant interaction with an environment that is changing and that affects the quality of business. This imposes the need to manage the organization towards achieving the ultimate business goal. This goal varies depending on the activity of the organization. In production organizations, it is visible and tangible, while in service organizations, the business goal is not tangible, but is reflected in the satisfaction of the end-users of the services. Management is viewed differently in professional literature, as a social phenomenon, skill, ability, scientific discipline, art, profession, etc. (7-9).

The essential features of management are (10):

• Working with and utilizing people to ensure that the organization's goals are achieved through the collective action of individual task bearers,

• Achieving the organization's goals, reflected in the fulfillment of its purpose and mission,

• Striving for a balance between efficiency and effectiveness,

• Managing relatively limited resources,

• Adapting to changing business conditions.

Management has evolved through the application of new technologies, especially information technologies, leading to the development of models of innovative organizations and institutions, characterized as follows (11):

• Strong focus on the goal: Successful organizations have interconnected activities, focused functions, and defined strategic priorities for development.

• Adaptability: A well-defined goal focus balanced with the ability and willingness to undertake fundamental and rapid changes, if necessary, requiring a high degree of organizational flexibility.

• Organizational cohesiveness: Integrativeness within the organization is a critical success factor achieved through effective communication, job rotation, role integration practices, long-term employment, and intensive training.

• Innovative organizational culture: Supports a climate that fosters change agents.

• Sense of integrity: Tendencies for long-term relationships and cooperation to maintain stable associations with other organizations, local and national bodies, etc.

• Engaged top management: More experienced managers are involved in all management processes based on knowledge and experience, rather than solely on their position within the organization.

• Shallower organizational hierarchies: Greater participation and the creation of multifunctional teams for planning, managing changes, and adapting with greater flexibility within and between teams.

In performing the tasks of an organization, managers should work together as a whole, so the term management encompasses all employees in a given organization who, in accordance with their powers and responsibilities, perform managerial tasks.

In management theory, healthcare institutions are recognized as the most complex organizations, requiring the most intricate management. Health institutions are organizations whose primary objective is to provide healthcare within national frameworks, emphasizing the crucial importance of their management. Management within healthcare institutions is executed by managers who serve as the principal executors of managerial functions.

Health management aims to satisfy and balance the interests of all participants in the health system, including patients (especially when they are sick), healthcare personnel within the organization, the institution itself, the community in which it operates, and the broader environment. This involves:

• Planning, organizing, implementing, and controlling health programs

• Coordinating resources such as personnel, finances, facilities, equipment, information, knowledge, technology, regulations, laws, and time

• Monitoring the development and implementation of health programs

• Providing support and encouraging community and individual participation.

• Influencing appropriate decision-making at all levels of the health system

• Working toward achieving set goals to improve the health status of the population (9-13).

LEADERSHIP IN NURSING

At the nursing level, head nurses/technicians assume managerial roles, thereby embracing their dual responsibilities. Building organizational knowledge, which comprises individual knowledge, necessitates managerial skills to effectively blend individual and team knowledge, identify essential knowledge, foster a culture of knowledge sharing, promote the generation of new knowledge, and retain top-performing employees as a competitive advantage (4).

With the emergence of a new profile of managers in healthcare, namely head nurses/technicians, it becomes imperative to concurrently address organizational and procedural issues. These form the foundation for cultivating leadership in nursing and overcoming barriers associated with educational profiles (4).

Nurses serve as the cornerstone of development in modern healthcare systems. Given the prevailing challenges such as healthcare worker shortages, leaders must adeptly assimilate various leadership styles and strategies for staff empowerment. This facilitates the creation of a conducive work environment that promotes the commitment of nursing staff, patients, and their respective organizations (14).

The correlation between leadership styles, staff perception of empowerment, and their level of commitment is crucial. Leaders must devise frameworks that encourage and facilitate a high level of commitment among nursing staff, particularly in light of the prevailing challenges related to healthcare worker shortages, particularly within the nursing profession (14). Motivation is the process of stimulating, directing, and sustaining activity to achieve a specific goal that satisfies a corresponding need. Motivating, on the other hand, is the managerial activity through which managers influence employees to actively engage, to the fullest extent possible, in realizing the organization's vision. The greater the number of motivated individuals within an institution, the more effectively they utilize their abilities and skills to achieve established objectives (9).

Despite appearing as a logical sequence based on the above definitions, motivation is actually a highly complex and intricate process. It cannot be regarded as a one-size-fits-all "recipe" applicable in every situation. Rather, it involves influencing employee behavior in a manner that aligns with the goals and needs of the organization (6). A leader in the healthcare sector is continually confronted with the necessity of ensuring a highly motivated staff on a daily basis. To meet this imperative, the leader must possess a deep understanding of motivation – its nature, significance, and ramifications – as well as the factors that both inspire and undermine motivation among their followers (7).

If a leader presents ambiguous goals to their followers, there is a high likelihood that work activities will proceed sluggishly, with insufficient enthusiasm, and at a significantly reduced volume compared to expectations (10). As a competent leader, the nurse

serves as the cornerstone of development in modern healthcare systems (5). By shaping the mission and vision, as well as the values and moral principles, nursing defines its identity, profession, and ethical framework. This underscores the role of the nurse, who possesses not only specific professional competencies but also holds a distinct ethical position and role within the healthcare system. Furthermore, there is a pressing need to involve the nursing profession in significant clinical decision-making processes (9).

Given the role of modern communication technologies and the imperative for all nursing staff to master them, there arises a necessity for continuous education in these domains. This is essential for enhancing patient care, improving work organization and record-keeping, as well as streamlining administration processes. Such proficiency significantly contributes to better time management, which holds particular significance in clinical settings where uninterrupted processes are essential (9). The law delineates the organization of activities, the execution of tasks, the necessary authorizations, and the conditions for performing said activities, encompassing education standards, specialization, and professional training (9).

Job satisfaction, a pivotal concept, is primarily characterized by the emotional responses of employees guiding their work performance and is fundamental to organizational success. It pertains to employees' positive or negative sentiments towards their job and the emotional reactions they exhibit in various work-related situations. Job satisfaction is influenced by both the individual employee's personality and the organizational environment they inhabit. An individual's personality plays a significant role in determining what brings them satisfaction (15).

Each individual possesses unique characteristics, yet for an employee to perform successfully in a specific role, a requisite level of knowledge is essential. Without it, the employee may experience dissatisfaction and struggle to fulfill assigned tasks. Organizations typically hire employees based on their existing knowledge levels for particular positions. However, given the dynamic nature of business environments, knowledge acquisition is an ongoing process. Once acquired, knowledge may become outdated relatively quickly due to constant change.

Employees can enhance their knowledge through various means, including internal knowledge exchange within the organization. Knowledge sharing is a discretionary behavior that holds significance for both individuals and organizations. It fosters continuous learning and contributes to several beneficial outcomes for the organization, such as enhancing innovation capacity, facilitating the transfer of best practices, and increasing productivity. However, measuring knowledge sharing can be challenging, necessitating the implementation of formal plans and incentives such as bonuses to encourage and reward this behavior (15).

The Nursing and Midwifery Council's updated Standards of Nursing Competence (NMC) underscore the significance of nurse leadership, complemented by the NHS's development of models to bolster leadership development. This article delineates the four elements of transformational leadership—idealized influence, inspirational motivation, intellectual stimulation, and individualized consideration—and explores their alignment with the NMC standards. Additionally, it deliberates on the advantages and drawbacks of nursing services' organizational structures (16).

Nursing education plays a pivotal role in nurturing students' capabilities, fostering a supportive culture, and augmenting their creativity, motivation, and ethical conduct. This preparation equips graduate nurses to emerge as future leaders within the healthcare system (17).

An integrative review identified ten scientific papers meeting the inclusion criteria. Analysis of these studies revealed that clinical leadership attributes primarily center on clinical aspects. The limited number of research-based studies underscores the imperative for further exploration in the realm of clinical leadership in nursing practice (18).

The role of nurse leaders is multifaceted and demanding within the broader context of healthcare across all sectors of a country's healthcare system. Its significance is increasingly garnering attention from both domestic and international organizations, with nurse leaders progressively assuming influential positions within healthcare structures. There is a pressing need to proactively and effectively enhance the preparedness of nurse leaders to undertake and sustain these challenging and dynamic roles (19).

This article endeavors to offer a comprehensive overview of nursing leadership by delving into the theoretical frameworks that underpin its manifestation, exploring various leadership styles in nursing within their respective contexts, and ultimately addressing strategies for nursing education aimed at cultivating leadership capacity and sustainability among nurses (20).

In international literature, there is a recurring emphasis on testing leadership models across various settings to better assist nurses. Further exploration of nursing leadership is imperative to enhance this pivotal competency in routine practice. Interdisciplinarity and management are among the numerous avenues to bolster this competence, potentially fostering team autonomy and self-actualization (21).

Nurse leaders continue to grapple with capacity issues both clinically and academically. In 2017, the American Nurses Association (ANA) conducted an extensive member needs assessment involving over 15,000 respondents. This assessment identified three distinct career categories: early career nurses, entry-level nurses, and nurse leaders. This article offers a broad overview of the program, encompassing evaluations and modifications, and examines the implications of utilizing ANA's career-level categories in virtual mentoring initiatives (22).

The 2019 coronavirus disease (COVID-19) pandemic has thrust nurses into a significant role in infection prevention and mitigation efforts for individuals with health issues across healthcare, medical, and social systems. This study sheds light on the importance of nurses in times of crisis, emphasizing undergraduate nursing education and postgraduate training. To realize this, it is imperative for state agencies to bolster collaboration with nursing schools and foster the development of human resources capable of constructing a sustainable, equitable, and resilient society (23).

The impact of leadership in nursing on the quality of healthcare

In the wake of nursing's evolution throughout the 20th century, endeavors to enhance nursing with insights from other scientific disciplines represent a natural progression aligned with the broader development of medicine and healthcare processes. Present-day nursing is marked by global interconnectedness among nurses and collaborative efforts to address key nursing issues. The challenges facing modern nursing, notably inadequate education and limited professional advancement opportunities, are particularly pronounced. In essence, the professional development of our nurses has largely been cultivated through their own experiences and enthusiasm in the workplace. However, there is a need for systematic reforms such as job systematization, formal recognition of higher education diplomas, clear delineation of new occupational titles in the occupational nomenclature, and adjustments to salary coefficients and wage levels. Additionally, greater support from governmental bodies and competent ministries in the healthcare sector is essential. Financial backing from both the state and healthcare institutions is crucial, including the provision of scholarships for nurses seeking further education, to the extent feasible.

Nurses have a key role in the implementation of health care, which caused major changes in the education and practice of nurses in the world and expanded the field of their professional work. The general trend is that recommendations and solutions related to nursing at the world level become valid and binding in all countries (24, 25). The proposal for measures to solve current problems related to education in the field of nursing is better coordination in connection with changes in the field of work of nurses; precise definition of the names of new occupations in the nomenclature of occupations; systematization of workplaces in healthcare institutions, which recognizes workplaces and job descriptions of senior nurses; review of all the changes that are the result of higher education of nurses in terms of defining jobs, increasing the coefficient and changing the salary; greater support from the state and competent ministries in the field of their work and financial support from the state, i.e. health institutions in providing scholarships for nurses who need to be educated to the extent that this is possible (25-27).

CONCLUSION

In conclusion, the attainment of leadership in nursing practice hinges upon the application of appropriate strategies, methods, and tools within the healthcare system. Human resources play a pivotal role in this endeavor, serving as a key factor in enhancing the healthcare system and its quality across all levels. The role of the head nurse, as a leader in nursing, holds exceptional importance in advancing healthcare organization and quality.

Nurses are fundamental to the development of modern healthcare systems, serving as pillars within the industry. Given the current challenges related to healthcare worker shortages, leaders must adeptly adopt various leadership styles and staff empowerment strategies to cultivate a work environment that fosters commitment among nursing staff, patients, and their organization.

The relationship between leadership styles and staff empowerment is integral, as it influences the level of commitment among nursing staff. Particularly critical are the ongoing challenges posed by healthcare worker shortages, especially within nursing professions. Nurses and healthcare technicians wield significant influence over the quality of healthcare delivery, both for individual patients and groups afflicted by the same ailment. Leveraging their competencies, nurse leaders collaborate with other healthcare professionals to mitigate overall healthcare costs.

SCHEDULE OF MEASURES

Building leadership in nursing practice can be ensured by introducing adequate systematization of workplaces, supplementing formal education through

appropriate seminars, workshops, and other informal and formal forms of human resources education, as well as by providing clear descriptions of workplaces, in which the head nurse is actively involved in implementation. The job description should contain all the components necessary for leadership, such as adequate knowledge, skills, and a clear description of work tasks for a specific job. Changes in nursing practice should encourage the creation of units for the improvement of nursing, i.e., centers dedicated to innovation, improvement, and evolution of practice so that nursing practice can determine its own path of change and transfer the results further to the wider healthcare system. Nurses are in a good position to be leaders, but in addition to additional knowledge and skills of leading teams and effective communication, educational assistance, and support programs, which will make them more effective in their role, they also need greater powers and participation in decision-making. There is a need to study, review, and reconsider the abandonment of the previous way of thinking, leadership style, and direction towards a new approach and organizational culture, by facing the need to introduce changes managed by a capable leader in nursing practice, who, above all, possesses professional knowledge and the ability to lead people.

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Sažetak

IZGRADNJA LIDERSTVA U SESTRINSKOJ PRAKSI

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U težnji ka kompetentnom i konkurentnom zdravstvenom sistemu, medicinske sestre i zdravstveni tehničari kao nosioci procesa zdravstvene nege kao naučne discipline delokruga mediciskih sestara, pored znanja iz struke treba da poseduju i menadžerske sposobnosti i veštine, odnosno da znaju upravljati ljudskim i materijalnim sredstvima unutar zdravstvenog sistema. Liderstvo u sestrinskoj praksi se može pojasniti kao uticaj glavnih sestara na kvalitet izvršenja svih aktivnosti iz te oblasti i njenu efikasnost. Pregledom literature o istraživanju liderstva u sestrinstvu i samim tim i aspekata koji utiču na njegovu izgradnju u sestrinskoj praksi, koje još uvek nije decidno definisano, pokušali smo da damo pregled stručnoj javnosti iz oblasti biomedicine i zdravstva, a posebno zdravstvene nege kao delokruga rada medicinskih sestara, na svim nivoima zdravstvene zaštite. Da bi se postigli svi ciljevi koji uslovljavaju izgradnju liderstva u sestrinskoj praksi, primena odgovarajućih strategija, metoda i alata u sistemu zdravstvene zaštite je najprimenjivija i najdelotvornija za deo ljudskih resursa, kao ključnog faktora za poboljšanje sistema zdravstvene zaštite u kome je uloga glavne sestre, tj. lidera u sestrinstvu od izuzetnog značaja za poboljšanje organizacije zdravstvene nege, kao i kvaliteta iste na svim nivoima zdravstvene zaštite.

Ključne reči: Lider, medicinska sestra, menadžer, upravljanje, znanje.

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Book review

ESSENTIALS OF SOCIAL MEDICINE AND MEDICAL ETHICS: A BOOK REVIEW

By **Maria Dencheva**

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BOOK DETAILS

First Book: Essentials of Social Medicine and Medical Ethics © First Edition, 2016
Editor: Lydia Katrova
Publisher: Lydia Katrova-Leading Technologies in Dentistry, Sofia, Bulgaria
ISBN Number: 978-954-90363-5-0

Second Book: Essentials of Public Health and Healthcare Management © Second Edition, 2017
Editor: Lydia Katrova
Publisher: Lydia Katrova-Leading Technologies in Dentistry, Sofia, Bulgaria
ISBN Number: 978-954-90363-7-4

Third Book: Essentials of Dental Health and Dental Practice Management © Second Edition, 2017
Editor: Lydia Katrova
Publisher: Lydia Katrova-Leading Technologies in Dentistry, Sofia, Bulgaria
ISBN Number: 978-954-90363-4-3

ABOUT THE BOOKS

This review of the trilogy written by Prof. Lydia Katrova illustrates the essential role of dentists' professionalization within the harmonized European Union framework of dental curriculum competences. As one of the founders of the Department of Dental Public Health at the Faculty of Dental Medicine of the Medical University of Sofia, the author leverages her experience as a practicing dentist, researcher, and educator to provide the program with appropriate instructional tools. The series of three books cover the disciplines of Social Medicine, Medical Ethics, Healthcare Management, and Dental Practice Management. The work reflects the dynamics of radical reforms in healthcare at national, European, and global levels, as well as the evolution of the dental profession within the context of Bulgaria's European integration and the challenges of the globalizing dental care market.

The selection of material included in these books and their structure align with the course program agreed upon by the Department of Public Dental Health, aiming to fulfill the overall curriculum objectives for the educational degree of "Doctor of Dental Medicine" in accordance with European and global trends in dental education. The textbooks are organized to succinctly present the most important elements of socio-professional identification and professional achievements of dentists, thereby equipping graduating dentists in Bulgaria (and beyond) to successfully establish independent dental practices in any European country.

The first book of the series, entitled "Essentials of Social Medicine and Medical Ethics," is divided into two parts, each comprising four and three chapters respectively. Part 1 (chapters 1 through 4), focused on Social Medicine, employs an interdisciplinary approach to enhance the individual professional development of dentists through the following key competences:

- Understanding social and public health phenomena and processes occurring at the individual, group, and community levels.
- Analyzing health status determinants and relevant health indicators for public health.
- Making decisions based on critical evaluation of facts and circumstances.
- Addressing technological, medical, legal, and ethical concerns that arise during professional activities (1).

Part 2 of the first book, dedicated to Ethics, consists of three chapters presenting the ethical framework for professional dentists, governing their relationships with patients, colleagues, and society in accordance with shared values in the social environment and a common understanding of morality.

The second book, titled "Essentials of Public Health and Healthcare Management," comprises nine chapters and aims to equip readers with knowledge, professional skills, and motivation in various areas, including:

- Understanding the development of healthcare within the broader societal context.
- Implementing effective management strategies within the health system.

- Preparing Doctor of Dental Medicine professionals to function effectively within a regulated profession.

- Managing dental practices within real social and market environments.

- Engaging in partnerships for the implementation of community measures aimed at achieving individual and public oral health goals.

I concur with the sentiments expressed by Prof. Nairn Wilson in the Foreword of this book: "...Professor Katrova is to be congratulated in bringing together a wealth of information in a succinct, carefully crafted text. As such, this book is an important source of reference for dentists in Bulgaria and beyond seeking knowledge and understanding of public health and healthcare management. Dentists with this knowledge and understanding will, hopefully play an important role in ensuring that the importance of dentistry and oral health is not overlooked in the further development of existing healthcare systems". Nairn H F Wilson CBE DSc (*h.c.*) PhD MSc BDS FDS *Edin & Eng* FFD FFGDP FCDSHK DRD FHEA FACD FADM FKC. Professor of Dentistry, King's College London, London" (2).

The third book, titled "Essentials of Dental Health and Dental Practice Management," aims to assist dental students and practitioners in finding their optimal practice patterns and establishing suitable working environments to achieve professional prosperity while maintaining their health and longevity. Additionally, it aims to sensitize them to the population's needs for appropriate services, prevention, and improved quality of life. The textbook comprises three parts:

- The first part, including chapters 1 through 4, addresses the assessment of dental health, the promotion of a healthy environment and behaviors, and the prevention of dental diseases.

- Part two, comprising chapters 5 through 9, delves into the principles of ergonomics, organizing the workplace, conducting procedures, timing, and recommendations for teamwork.

- Part three, featuring chapters 10 and 11, focuses on establishing and managing dental practices (3).

Upon reading the words of appreciation on page 5 of the book, it becomes evident that this robust work is the result of a long and successful collaboration with world-renowned specialists and institutions in the fields of public health and dental education, including: The Association for Dental Education in Europe (ADEE), The Council of the Chiefs Dental Officers in Europe (CECDO), The School of Public Health at Harvard University (SPH HU), The University "René Descartes," Laboratoire d'Ethique Medicale, Paris and MEDIS Institute, Munich, Germany.

While there are numerous publications containing statistical information, health strategies, and investigations into various aspects of public health, there are few focused specifically on the needs of dental school graduates to become competent in the framework issues (political, social, epidemiological, professional, legislative) necessary to succeed as independent dental practitioners. The content and structure of this work align with the general educational objectives of the undergraduate dental curriculum harmonized with EU competences.

The particular advantages of these books compared to competing publications lie in their focused, balanced, and concise structure, allowing for adaptation and customization to national particularities while retaining appropriate global and enduring professional concepts. This work presents an original concept and references the newest facts and findings relevant to the dental profession. It represents a genuine effort to "translate" complex social and professional issues into terms understandable and implementable by dental practitioners in their work, motivating them to collaborate in the realization of health strategies while preserving their professional autonomy and integrity. These books serve as suitable tools for this purpose and are unlikely to become outdated, as the pursuit of professionalism never does.

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Časopis izlazi u elektronskom i štampanom formatu, tri puta godišnje. Odmah nakon objavljivanja, svi radovi su besplatno dostupni online, na web stranici časopisa i drugim bazama podataka.

Molimo autore da dostave, potpisane od svih autora, formulare Author statement, Patient consent, and Conflict of interests prilikom prilaganja članka (https://new.sanamed.rs/).

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Ako je rad deo magistarske ili doktorske teze, ili istraživačkog projekta, to treba navesti u posebnoj napomeni na kraju teksta. Takođe, ako je članak prethodno predstavljen na nekom naučnom skupu, potrebno je navesti naziv, mesto i vreme održavanja skupa, kao i način na koji je rad objavljen (npr. promenjen naslov ili sažetak).

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Svaki deo rukopisa (naslovna strana, itd.) mora početi na posebnoj strani. Sve strane moraju biti numerisane po redosledu, počev od naslovne strane. Podaci o korišćenoj literaturi u tekstu označavaju se arapskim brojevima u zagradama, i to onim redosledom kojim se pojavljuju u tekstu.

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Provera broja reči u dokumentu može se izvršiti u programu *Word* kroz podmeni *Tools-Word Count* ili *File-Properties-Statistics*.

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Naslov rada treba da bude sažet, ali informativan.

Ako je potrebno, može se dodati i podnaslov.

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Ako je bilo materijalne ili neke druge pomoći u izradi rada, onda se može sažeto izreći zahvalnost osobama ili institucijama koje su tu pomoć pružile.

Treba otkucati listu svih skraćenica upotrebljenih u tekstu. Lista mora biti uređena po abecednom redu pri čemu svaku skraćenicu sledi objašnjenje. Uopšte, skraćenice treba izbegavati, ako nisu neophodne.

U donjem desnom uglu naslovne strane treba otkucati ime i prezime, telefonski broj, broj faksa i tačnu adresu autora sa kojim ce se obavljati korespodencija.

Stranica sa sažetkom. Sažetak mora imati do 400 reči. Treba koncizno da iskaže cilj, rezultate i zaključak rada koji je opisan u rukopisu. Sažetak ne može sadržati skraćenice, fusnote i reference.

Ključne reči. Ispod sažetka treba navesti 3 do 8 ključnih reči koje su potrebne za indeksiranje rada. U izboru ključnih reči koristiti Medical Subject Headings — MeSH.

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Originalni rad treba da ima sledeće podnaslove: uvod, cilj rada, metod rada, rezultati, diskusija, zaključak, literatura.

Prikaz bolesnika čine: uvod, prikaz bolesnika, diskusija, literatura.

Pregled iz literature čine: uvod, odgovarajući podnaslovi, zaključak, literatura.

Bolesnici i metode/materijal i metode. Treba opisati izbor bolesnika ili eksperimentalnih životinja, uključujući kontrolu. Imena bolesnika i brojeve istorija ne treba koristiti.

Metode rada treba opisati sa dovoljno detalja kako bi drugi istraživači mogli proceniti i ponoviti rad.

Kada se piše o eksperimentima na ljudima, treba priložiti pismenu izjavu u kojoj se tvrdi da su eksperimenti obavljeni u skladu sa moralnim standardima Komiteta za eksperimente na ljudima institucije u kojoj su autori radili, kao i prema uslovima Helsinške deklaracije. Rizične procedure ili hemikalije koje su upotrebljene se moraju opisati do detalja, uključujući sve mere predostrožnosti. Takođe, ako je rađeno na životinjama, treba priložiti izjavu da se sa njima postupalo u skladu sa prihvaćenim standardima.

Treba navesti statističke metode koje su korišćene u obradi rezultata.

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Diskusija. Ne treba činiti obiman pregled literature. Treba diskutovati glavne rezultate u vezi sa rezultatima objavljenim u drugim radovima. Pokušati da se objasne razlike između dobijenih rezultata i rezultata drugih autora. Hipoteze i spekulativne zaključke treba jasno izdvojiti. Diskusija ne treba da bude ponovo iznošenje zaključaka.

Literatura. Reference numerisati rednim arapskim brojevima prema redosledu navođenja u tekstu. Broj referenci ne bi trebalo da bude veći od 30, osim u pregledu literature, u kojem je dozvoljeno da ih bude do 50.

Izbegavati korišćenje apstrakta kao reference, a apstrakte starije od dve godine ne citirati.

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Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Knjiga:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Poglavlje ili članak u knjizi:**

Latković Z. Tumori očnih kapaka. U: Litričin O i sar. Tumori oka. 1. izd. Beograd: Zavod za udžbenike i nastavna sredstva, 1998: 18–23.

Tabele. Tabele se označavaju arapskim brojevima po redosledu navođenja u tekstu, sa nazivom tabele iznad.

Slike. Sve ilustracije (fotografije, grafici, crteži) se smatraju slikama i označavaju se arapskim brojevima u tekstu i na legendama, prema redosledu pojavljivanja. Treba koristiti minimalni broj slika koje su zaista neophodne za razumevanje rada. Slova, brojevi i simboli moraju biti jasni, proporcionalni, i dovoljno veliki da se mogu reprodukovati. Pri izboru veličine grafika treba voditi računa da prilikom njihovog smanjivanja na širinu jednog stupca teksta neće doći do gubitka čitljivosti. Legende za slike se moraju dati na posebnim listovima, nikako na samoj slici.

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If a paper is a part of a master's or doctoral thesis, or a research project, that should be designated in a separate note at the end of the text. Also, if the article was previously presented at any scientific meeting, the name, venue and time of the meeting should be stated, as well as the manner in which the paper had been published (e.g. changed title or abstract).

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Each manuscript component (title page, etc.) begins on a separate page. All pages are numbered consecutively beginning with the title page.

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title page and abstract in English, can have the length up to 5000 words for original paper, report, paper on the history of medicine and literature overview, while for patient presentation, practice paper, educative article it can be up to 3000 words, and other papers can be up to 1500 words.

The word count check in a document can be done in *Word* processor program in submenu *Tools Word Count* or *File Properties Statistics*.

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A short title of less than 50 spaces, for use as a running head, is included.

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Statistical methods used, are outlined.

Results. Results are clear and concise, and include a minimum number of tables and figures necessary for proper presentation.

Discussion. An exhaustive review of literature is not necessary. The major findings should be discussed in relation to other published works. Attempts should be made to explain differences between results of the present study and those of the others. The hypothesis and speculative statements should be clearly identified. The discussion section should not be a restatement of results, and new results should not be introduced in the discussion.

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1. **Article:** (all authors are listed if there are six or fewer, otherwise only the first six are listed followed by *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Book:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Chapter or article in a book:**

Trier JJ. Celiac sprue. In: Sleisenger MH, Fordtran J5, eds. Gastro-intestinal disease. 4 th ed. Philadelphia: WB Saunders Co, 1989: 1134–52.

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