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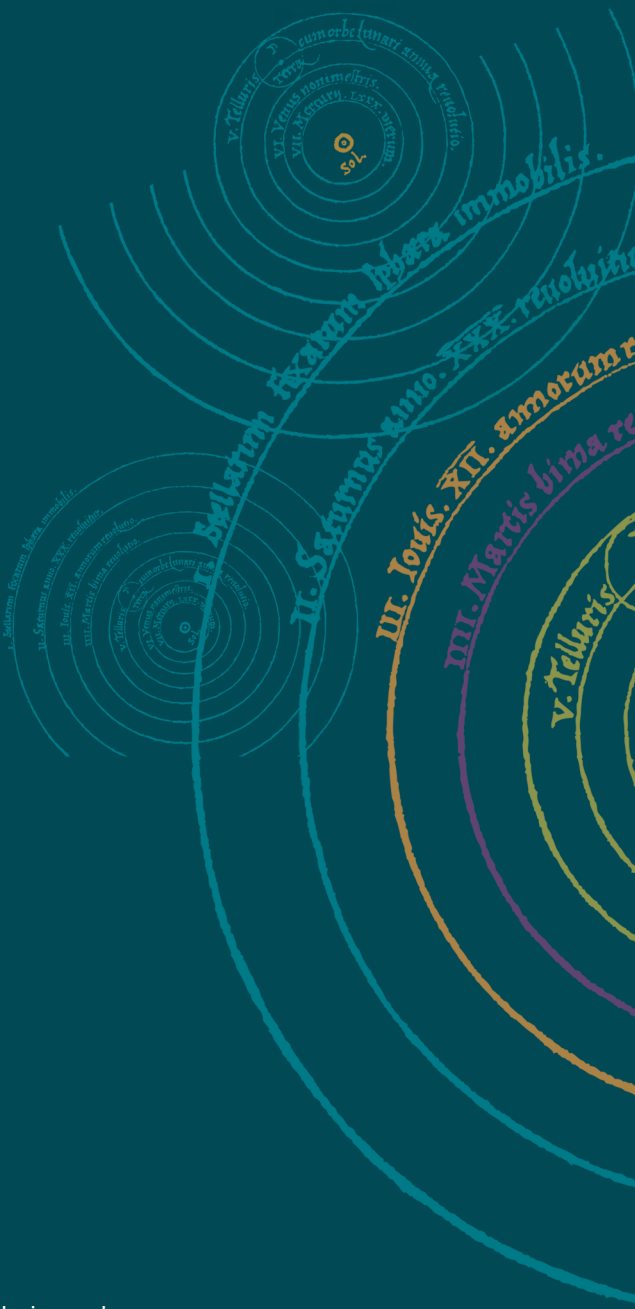

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EDITORIAL

Aldona Kubica, Łukasz Pietrzykowski

Department of Health Promotion, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland

The therapeutic plan implementation in patients discharged from the hospital after myocardial infarction

Key words: adherence, myocardial infarction; ACEI, $P2Y_{12}$ receptor inhibitors, statins

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According to the European Society of Cardiology guidelines dual antiplatelet therapy (DAPT) for 12 months, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), beta-blocker and statin [1] are recommended in patients after myocardial infarction (MI). Adherence to this treatment determines the achievement of therapeutic targets [2–8]. Previous studies have shown that patients after MI often do not adhere to the treatment plan. Discontinuation of the recommended post-MI therapy predisposes to serious thrombotic events, particularly MI, in-stent thrombosis, stroke and death [9–14]. The knowledge regarding the level and determinants of adherence to treatment recommendations in post-MI patients enables proper care and education planning for this population.

The series of recent publications reporting results of a single centre, observational, cohort clinical trial with 1-year follow-up, was intended to reflect 'real world' practice [15–18]. All study participants received in-hospital educational and motivational verbal interventions on ischemic heart disease, focusing on its symptoms and management supported by an educational brochure entitled "Myocardial infarction" that was handed out at the beginning of hospitalization. The first educational visit was carried out within the first two days after admission to the hospital. The visit included an assessment of patient knowledge of the disease, its symptoms, and prevention (20 standardized questions). Throughout the entire hospital stay, patients had an opportunity to ask questions and obtain comprehensive answers. The educational and motivational visits were conducted by trained educational nurses.

The readiness for discharge from the hospital was assessed using a validated questionnaire Readiness for Hospital Discharge after Myocardial Infarction Scale (RHD-MIS) [19, 20]. The RHDS-MIS consists of 23 questions included in three subscales assessing subjective (assessed by the patient) and objective (assessed by medical personnel) knowledge about the disease and patient expectations. Additionally, the questionnaire contains non-scored questions regarding the patient's opinion on the readiness for discharge.

The analysis of medication discontinuation was performed based on prescription filling data provided by the National Health Fund (NHF) for reimbursed drugs: ACEI (ramipril, perindopril) $P2Y_{12}$ receptor inhibitor (clopidogrel) and statin (atorvastatin, simvastatin, rosuvastatin). The NHF is the only institution in Poland that covers the costs of hospitalization, outpatient treatment and prescribed medications. Drugs non-reimbursed by the NHF were not included in the analysis. All study participants patients received appropriate prescriptions (including ACEI, $P2Y_{12}$ receptor inhibitor and statin) at discharge from the hospital. Two hundred fifty-two patients were enrolled on the study. The final analysis was conducted for 225 participants (73.3% men, 26.7% women) aged 30–91 years (mean age 62.9 ± 11.9 years), for whom data were obtained from the National Health Fund.

According to the authors' best knowledge, this research [15–18] is the first one to comprehensively

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analyse the level of adherence to medication and its determinants as well as the variability of these determinants during the follow-up after hospital discharge.

The mean adherence level during 1-year of follow-up for all three groups of medications (ACEIs, $P2Y_{12}$ receptor inhibitors and statins) was 64.1 ± 24.5%, with a value of 67.2 ± 31.8% for ACEI, 61.6 ± 34.2% for P2Y12 receptor inhibitors, and 64.4 ± 32.1% for statins. Over time, a gradual decline in adherence was observed for all groups of medications. Sufficient adherence for all medication groups was found only in 29.4% of patients throughout the whole follow-up period [15–18]. These findings are in line with those obtained by Naderi et al. [2] in a meta-analysis of 20 studies evaluating 7 groups of drugs showing a mean adherence level of 57.0% and its decline over consecutive quarters of follow-up. Similar findings were reported also in other publications [11–14].

The multivariate analysis defined determinants of medication adherence: age under 65 years in the first quarter of follow-up for ACEI, P2Y12 receptor inhibitor and statin; prior CABG in the 1st quarter of follow up for ACEI and P2Y12 receptor inhibitor; level of education and place of residence for P2Y12 receptor inhibitor in the 1st quarter of follow-up; economic status for all assessed drugs in the 2nd quarter; marital status for ACEI in the 1st quarter of follow-up; arterial hypertension for ACEI in the 1st quarter of follow-up [15–18]. Identifying the factors responsible for the decline in adherence in the sequential quarters helps better understand the mechanisms governing this phenomenon and apply targeted corrective interventions. Additional educational and motivational efforts should be directed to elderly, less educated, living alone patients and those after CABG in order to increase the likelihood of implementation of prescribed medication after discharge from the hospital. Maintenance of medication during long term treatment requires special support in rural residents and patients with lower economic status [15–18].

The therapy discontinuation remains a challenge for therapeutic teams. Elimination of this phenomenon might largely improve the clinical and economical outcomes of treatment [3, 8, 16].

The highest likelihood of therapy discontinuation, including long-term discontinuation (> 30 days) and permanent therapy cessation was found for statins and the lowest for ACEIs. It was found that patients are most prone to discontinue therapy between the 2nd and 3rd quarter of follow-up. In contrast to the permanent cessation of therapy, a significant increase in the incidence of temporary therapy discontinuation was already seen in the 1st quarter of follow-up [15–18].

Multivariate logistic regression analysis identified occupational activity and a prior MI as independent predictors of lack of post-discharge therapy initiation with P2Y12 receptor inhibitors. The research found no predictors of lack of post-discharge therapy initiation with other medications either when analysed individually or together. Multivariate analysis indicated age above 65 years and prior revascularization as independent predictors of therapy discontinuation but failed to identify independent predictors of the permanent cessation of therapy with any of the medications as well as the temporary discontinuation and permanent cessation of treatment with all three medications together [15–18].

Preparation for discharge, including education in the field of secondary prevention after a MI, is a current standard of care, however, not always meeting the patient's expectations [21–27].

The assessment of readiness for discharge was based on the RHD-MIS. The analysis of adherence to treatment in relation to the results achieved in RHD MIS did not provide unequivocal results both in terms of the overall result and the results in individual subscales. This applies to individual drug groups tested separately and to all groups together. Significant differences noted in individual quarters for individual drugs may, contrary to expectations, suggest worse adherence in patients who were better prepared for discharge from the hospital [15–18]. These surprising results require further in-depth research to explain this phenomenon. According to the previously published studies, better adherence to treatment should be expected in patients with a higher level of readiness for discharge. The study confirms that patient education should continue after discharge from the hospital [26–36].

The patients with a high expectation score had longer treatment interruptions only for the P2Y12 receptor inhibitor. No relations between medication adherence and the level of expectations were found in the first two quarters, while for the last two-quarters of follow-up, however, an inverse relationship between the level of expectations and adherence was shown. When related to the levels of expectations (high vs medium vs low), adherence for ACEI in the 4^{th} quarter of follow-up was 39 ± 31% *vs*. 58 ± 43% *vs*. 57 ± 43% ($p = 0.0099$; $R = -0,16$; $p = 0.0187$). Similarly, for P2Y12 inhibitor the numbers were 37 ± 41% *vs*. 53 ± 43% *vs*. 55 ± 41% ($p = 0.0282$; $R = -0,15$; $p = 0.0438$). No differences, however, were found for statins [15–18].

The observed relation of expectations and adherence might indicate a mismatch between the educational contents and patient expectations. The study protocol, however, did not include additional educational initiatives to be delivered to fulfil patient individual expectations after the provision of the standard education intervention. The identification of patient expectations might allow further personalization of educational and motivational programmes [15–18].

Several limitations of the research reported in the series of publications should be considered. Medications non-reimbursed by the National Health Fund

were excluded from the analysis. The authors analysed a limited number of factors as potential determinants of therapy discontinuation. Moreover, the authors do not have patients' reports concerning the reasons for therapy discontinuation. On the other hand, the strengths of this research are comprehensiveness and the homogeneity of the study population.

The reported research enabled making several important observations.

The vast majority of post-MI patients discontinue, either temporarily or permanently, one of the essential medications within one year following MI. Adherence to pharmacotherapy decreases over time after MI. Several socioeconomic and clinical factors have been identified to affect medication adherence over time. The readiness for discharge from the hospital assessed with the RHD-MIS does not clearly affect the implementation of the therapeutic plan in the long-term follow-up in patients after MI. Data suggesting a negative impact of some aspects of readiness for discharge on adherence to treatment require further, in-depth research.

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EDITORIAL

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Out-of-hospital cardiac arrest and COVID-19 pandemic

Key words: OHCA, COVID-19

The COVID-19 pandemic has caused profound changes in the functioning and effectiveness of healthcare worldwide. In particular, access to pre-hospital care has deteriorated, which was of particular importance for the effectiveness of treatment in patients with out-of-hospital cardiac arrest (OHCA). Regardless of this, infection with SARS-CoV-2 virus is a factor contributing to the occurrence of acute cardiovascular events, including OHCA.

Recently numerous reports regarding the impact of COVID-19 on the incidence of OHCA have been published. During the first wave of the COVID-19 pandemic in London, a dramatic rise in the incidence of OHCA, accompanied by a significant reduction in survival was observed. Moreover, the pattern of increased incidence and mortality closely reflected the rise in confirmed COVID-19 infections [1]. These observations were in line with the data collected from European, Australian, New Zealand and U.S. largest cities reviling showing significant OHCA escalations generally parallel to the local prevalence of COVID-19. Importantly, most of these patients died without COVID-19 testing [2]. Data from the North East England Ambulance Service revealed that despite reduced incidence of emergency calls during the pandemic compared with 2019, there was a rise in the incidence of OHCA and OHCA deaths during the same period [3]. Also, Glober et al. [4] observed increased OHCA incidence during the COVID-19 pandemic when compared with the prior year. Although patient characteristics were similar, initial shockable rhythm and proportion of patients who died in the hospital decreased during the pandemic. Rollman et al. [5] compared emergency medical services responses to out-of-hospital cardiac arrest (OHCA) and ST-segment–elevation myocardial infarction (STEMI) during the 2020 COVID-19 pandemic to 2018 to 2019 and evaluated the impact of California's March 19, 2020, stay-at-home order. Increase of weekly OHCA counts (173 *vs.* 135; incidence rate ratios, 1.28; 95% CI, 1.19–1.37; $p < 0.001$) and decrease of STEMI (57 *vs.* 65; incidence rate ratios, 0.87; 95% CI, 0.78–0.97; $p = 0.02$) was found [5]. Wienbergen et al. [6] reported a significantly higher rate of patients admitted with cardiogenic shock (21.9% *vs.* 14.2%, $p < 0.01$) and out-of-hospital cardiac arrest (OHCA) (14.3% *vs.* 11.1%, $p < 0.01$) comparing the presentation of STEMI patients in the year 2020 with the years 2006 to 2019 in a German registry. In England, a significant increase in the incidence of OHCA in patients with acute myocardial infarction during the COVID-19 period paralleled with reduced access to guideline-recommended care and increased in-hospital mortality was observed [7]. The increased OHCA incidence and worse outcomes were also observed in Singapore and Poland during the COVID-19 pandemic [8, 9]. An increased in OHCA incidence by 62% during COVID-19 was observed in Detroit, without, however, a significant change in prehospital return of spontaneous circulation (ROSC) [10]. On the other hand, early during the pandemic, rates of sustained ROSC for OHCA were lower throughout the

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US, even in communities with low COVID-19 mortality rates [11]. Overall survival was also lower, primarily in communities with moderate or high COVID-19 mortality [11]. Contrary to most of the publications in the Netherlands during the first COVID-19 lockdown, the incidence of OHCA remained on the sable level, while there was a significant reduction in the number of patients with chest pain or STEMI [12]. A Spanish Nationwide Prospective Cohort Study showed that during the COVID-19 period, the incidence of resuscitation attempts declined and survival to hospital admission (OR = 1.72; 95%CI = 1.46–2.04; p < 0.001) and discharge (OR = 1.38; 95%CI = 1.07–1.78; p = 0.013) fell compared to the non-COVID period. This pattern was also observed when comparing non-pandemic weeks and pandemic weeks. COVID-19 incidence impinged significantly upon outcomes regardless of regional variation, with low, medium, and high incidence regions equally affected [13]. According to the report from the Swedish Registry for Cardiopulmonary Resuscitation during the pandemic phase, COVID-19 was involved in at least 10% of all OHCA cases. In this subset of patients, the 30-day mortality was 3.4-fold increased as compared to non-COVID patients [14]. Assessment of cardiopulmonary resuscitation practices during the COVID-19 period revealed a decrease in the initiation of these procedures regardless of whether patients were suspected of SARS-CoV-2 infection or not [15]. Therefore, it is extremely important to communicate good CPR practices to avoid a drastic and lasting reduction in survival after OHCA [15–17]. Two meta-analyzes agreed that the incidence and mortality following OHCA were higher during the COVID-19 pandemic [18, 19]. Moreover, Borkowska et al. [19] showed that suspected or diagnosed COVID-19 resulted in a reduced survival rate after OHCA, probably due to the lower rate of shockable rhythms in COVID-19 patients, but not due to reluctance to bystander CPR.

COVID-19 has significantly impacted outcomes in OHCA patient through decreased access to medical care, and the reshaping of emergency medical response and hospital-based healthcare systems and policies. Moreover, changes in patient behaviour towards seeking help during the pandemic and the long-term consequences of not doing so should be taken into account [20–22]. Recently results of the OSCAR-POL registry have been published in Cardiology Journal [21]. This long-term observation from 2006 to 2018 showed circadian, monthly and seasonal variability of OHCA occurrence with no differences between particular days of the week. Significant circadian variability was observed within days of the week, seasons of the year, and particular years. Further in-depth studies on the impact of COVID-19 on the variability patterns of OHCA occurrence are necessary [23–26]. The research mainly based on registries should consider previously demonstrated risk factors and treatments [27–31]. This approach will allow to a full assessment of the impact of COVID-19 on OHCA.

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ORIGINAL ARTICLE

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COVID-19 infection in cancer patients: the effect of Hepatitis B immunization

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ABSTRACT

Introduction: To investigate the clinical characteristics and outcomes of cancer patients with COVID-19 infections and evaluate the effect of hepatitis B immunization status on susceptibility to COVID-19 infection and mortality risk.

Materials and methods: The records of 1,515 patients who presented to the Medical Oncology clinic between March 2020 and December 2020 were analysed retrospectively. The demographic and clinical characteristics and laboratory findings of cancer patients with (case group) and without (control group) COVID-19 infection were compared.

Results: Of the 1,515 patients, 153 (10.1%) had been diagnosed with COVID-19, and the median age of cancer patients with COVID-19 infection was 53.9 (range; 18–82) years. The most common types of cancer were breast cancer (26.2%), gastrointestinal system cancers (22.3%), genitourinary-system cancers (16.5%) and lung cancer (15.5%). The presence of metastatic disease [hazard ratio (HR): 0.09, 95% CI (0.01–0.83), ($p = 0.03$)] and receipt of palliative chemotherapy in the cancer patients with COVID-19 infections [HR: 0.1, 95% CI (0.01–0.69), ($p = 0.02$)] were identified as prognostic factors in multivariate analysis as univariate analysis did not indicate palliative treatment as a prognostic factor. When the case group and control groups were compared in terms of hepatitis B immunization status ($p = 0.24$), no statistically significant difference was identified between the two groups. Furthermore, hepatitis B immunization status ($p = 0.37$) were not found to be associated with COVID-19-related mortality risk.

Conclusion: Hepatitis B immunization status were not associated with the risk of COVID-19 transmission and mortality. The present study identified the presence of metastatic disease and palliative chemotherapy as negative and positive prognostic factors, respectively.

Key words: COVID-19 infection, hepatitis B, mortality, immunization

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Introduction

Cancer patients have been identified as a high-risk patient group during the COVID-19 pandemic [1–3]. SARS-CoV2 (severe acute respiratory syndrome-coronavirus-2) infection is associated with poorer outcomes in cancer patients than in those without cancer, due to associated advanced age, frailty, comorbidities (hypertension, diabetes, cardiac and pulmonary diseases, etc.), malnutrition and treatment-related immunosuppression [3], and there is a further risk of COVID-19 infection due to the associated therapeutic applications and frequent hospital visits [4].

There is a difference in COVID-19 infection and mortality rates between age groups. COVID-19 infection and mortality rates are very low in the population between the ages of 0 and 20 years, in contrast to the adult population, and symptoms are milder among infected children and adolescents [5]. Several hypotheses have been put forward to explain this finding, the first of which claims that the immune system of adolescents and children is not as mature as in adults, and so the immune response against the virus is not exaggerated. The second is that childhood vaccines, such as those for mumps, rubella, poliomyelitis, hepatitis A, hepatitis B and varicella, protect SARS-CoV-2 through cross-reactive antibodies [6, 7]. For example, it has been shown

that in developing countries where the BCG vaccine is included in the routine vaccination program, there is a lower incidence and better clinical outcomes of COVID-19 than in developed countries without routine BCG vaccination [8, 9]. That said, the role of childhood vaccines in COVID-19 is uncertain and requires further research.

Do the presence of HBV (hepatitis B virus) infection and HBV antibody seropositivity affect clinical outcomes in cancer patients with COVID-19 infections? The answer to this question is not yet known. To the best of the authors' knowledge, there has been no study to date investigating the relationship between COVID-19 and hepatitis B immunization status among cancer patients nor non-cancer patients.

To address the abovementioned hypothesis, the present study investigates the clinical characteristics and outcomes of cancer patients with COVID-19 infections in the authors' oncology centre and examine the relationship between hepatitis B immunization status and the risk of COVID-19 transmission and mortality.

Materials and methods

The files of all cancer patients who presented to the Dicle University Faculty of Medicine Medical Oncology between March and December 2020 were analysed retrospectively. Information on the demographic and clinical characteristics, treatments, and laboratory findings of the patients (history of COVID-19; COVID-19 PCR test results; HbsAg, Anti-HBs, and Anti-Hbc IgG levels) were obtained from the hospital's file registry system.

Patients with a laboratory-confirmed SARS-CoV-2 infection upon presentation to the pandemic hospital, i.e., patients with a positive PCR test, were accepted as COVID-19 cases. Those who were clinically diagnosed with COVID-19 but who had a negative PCR test were excluded from the study. Cancer patients diagnosed with COVID-19 (positive PCR test) were defined as the case group, while cancer patients not diagnosed with COVID-19 were defined as the control group. The clinical and laboratory findings and survival outcomes of both groups were evaluated.

Of the 1,515 patients who presented to the oncology clinic, 153 were diagnosed with COVID-19 infection during the pandemic. 1,454 of the 1,515 patients had hepatitis B panel tests. But the clinical data of 103 patients with COVID-19 infection were accessed from the archive system, among which the hepatitis B panel tests of 92 were available. 1362 patients, except 92 patients who were diagnosed with COVID-19 infection were defined as the control group. All statistical analyses were made based on these numbers of patients. The patients were categorized according to age, gender, presence of comorbidities, type of cancer diagnosis, disease stage (metastatic/non-metastatic), therapeutic applications (adjuvant/neoadjuvant therapy, palliative therapy and non-receipt of therapy), therapeutic agents (chemotherapy, immunotherapy, tyrosine kinase inhibitors, anti-hormonal therapies), and hepatitis B immunization status (vaccinated, resolved infection, isolated anti-HBc Ab (+), non-immunized and HBsAg-positive), and the case and control groups were compared based on these parameters. The case groups were further categorized into survivors and non-survivors.

Statistics

A statistical assessment of the data was made using PASW Statistics (Version 18.0. Chicago: SPSS Inc.). Descriptive statistics were used to evaluate patient characteristics and the frequency of parameters, a Student-t-test was applied to normally distributed numerical variables; Chi-square, Fisher's exact and Mann-Whitney U tests were applied for the analysis of non-normally distributed or non-parametric variables, and a logistic regression analysis was made. A multivariate analysis was carried out using the Cox model. The confidence interval of 95% and p-value of the significance of < 0.05 were accepted.

Results

Of the 1,515 patients who presented to the oncology clinic, 1,454 patients had hepatitis B panel tests. The study included a total of 1,454 patients, comprising 763 (52.5%) men and 691 (47.5%) women whose data could be accessed. During the pandemic, 153 (10.1%) patients were diagnosed with COVID-19 infection. Of the 153 patients diagnosed with COVID-19, 18 (11.7%) died. The general characteristics of 103 (6.8%) patients with fully accessible data and a diagnosis of COVID-19 infection are presented in Table 1. The median age of the cancer patients with COVID-19 infection in the present study was 53.9 (range; 18–82) years. Of the patients, 51% (n: 52) were women, and there was a history of comorbidities in 42.7% of the patients. The most common types of cancer among the COVID-19-positive patients were breast cancer (26.2%), gastrointestinal system cancers (22.3%), genitourinary system cancers (16.5%) and lung cancer (15.5%). There was no statistically significant difference in mortality risk by age, gender, and comorbidities among patients with COVID-19 infection. Regarding the type of primary diagnosis, there was also no statistically significant difference in mortality risk ($p = 0.76$).

Metastatic disease was recorded in 60.2% (n: 62) of the patients, and the rate of metastatic disease was

Table 1. Mortality risk in patients diagnosed with Covid 19 according to disease and treatment characteristics

	N (%)	Non-survivor (N%)	Survivor (N%)	HR (95% CI)	P-value
All patients	103	18 (17.5%)	85 (82.5%)		
Age (median, yrs.)	53.9 (18–82)	51 (18–80)	54 (18–82)	0.98 (0.95–1.02)	0.51
Gender				0.55 (0.19–1.56)	0.26
Male	51 (49%)	11 (61.1%)	40 (47.1%)		
Female	52 (51%)	7 (38.9%)	45 (52.9%)		
Comorbidities				1.45 (0.52–4.03)	0.46
Yes	44 (42.7%)	9 (50%)	35 (41.2%)		
No	59 (57.3%)	9 (50%)	50 (58.8%)		
Diagnosis					0.76
Brain	4 (3.9%)	1 (5.6%)	3 (3.5%)	1.66 (0.07–37.72)	0.74
GUS	17 (16.5%)	1 (5.6%)	16 (18.8%)	0.31 (0.16–5.95)	0.43
GiS	23 (22.3%)	6 (33.3%)	17 (20%)	1.76 (0.17–18.32)	0.63
Soft tissue	7 (6.8%)	1 (5.6%)	6 (7.1%)	0.83 (0.04–16.99)	0.90
Breast	27 (26.2%)	3 (16.7%)	24 (28.2%)	0.62 (0.05–7.31)	0.70
Lung/pleura	16 (15.5%)	4 (22.2%)	12 (14.1%)	1.66 (0.14–18.87)	0.68
Head and Neck	4 (3.8%)	1 (5.6%)	3 (3.5%)	1.66 (0.07–37.72)	0.74
Others	5 (4.9%)	1 (5.6%)	4 (4.7%)	Reference	
Stage				4.04 (1.09–15.1)	**0.04**
Metastatic	62 (60.2%)	15 (83.3%)	47 (55.3%)		
Non-metastatic	41 (39.8%)	3 (16.7%)	38 (44.7%)		
Treatment options					0.10
No treatment	15 (14.6%)	5 (27.8%)	10 (11.8%)	Reference	
Adjuvant/neoadjuvant	36 (35%)	3 (16.6%)	33 (38.8%)	**0.17 (0.03–0.87)**	**0.03**
Palliative	52 (50.4%)	10 (55.6%)	42 (49.4%)	0.47 (0.13–1.70)	0.25
Anti-Tumoral agents (n: 88)					0.77
Chemotherapy	54 (62.1%)	7 (58.3%)	47 (62.7%)	Reference	
TKi	10 (11.5%)	1 (8.3%)	9 (12%)	0.67 (0.07–6.08)	0.72
Immunotherapy	3 (3.4%)	1 (8.3%)	2 (2.7%)	3.35 (0.26–42.07)	0.34
Hormonal therapy	20 (23%)	3 (25%)	17 (22.6%)	1.18 (0.27–5.11)	0.82

* independent samples T-test.

higher in the non-survivors than in the survivors. In an evaluation of the association between mortality risk and the presence of metastatic disease, the mortality rate was found to be higher in patients with metastatic disease [24.2% in metastatic patients, 7.3% in non-metastatic patients (HR: 4.04, 95% CI (1.09–15.1), (p = 0.04)]. Of the patients, 52% (n: 52) were undergoing palliative chemotherapy and 36% (n: 37) adjuvant/neoadjuvant therapy, while 14.6% (n: 15) were receiving no treatment. When the sample was evaluated based on treatment modalities, survival was better for COVID-19 positive patients receiving adjuvant/neoadjuvant therapy than for the group receiving no treatment [HR: 0.17, 95% CI (0.03–0.87), (p = 0.03)]. There was no statistically significant difference in the mortality rates of those receiving palliative chemotherapy and those undergoing no treatment [HR: 0.47, 95% CI (0.13–1.70), (p = 0.25)]. Of the 87 patients receiving treatment, 62.1% (n: 54) were receiving chemotherapy, 23% (n: 20) hormonal therapies, 11.5% (n: 10) tyrosine kinase inhibitors and 3.4% (n: 3) immunotherapy agents. When the treatments of the patients were compared, no statistically significant difference was found in the mortality rates associated with the different therapeutic agents (p = 0.77).

When the total 1,454 patients were evaluated in terms of hepatitis B immunization, data was available for 92 patients with a COVID-19 diagnosis and 1,362 pa-

Table 2. COVID-19 transmission and mortality risk according to hepatitis B immunization

	All patients						Covid-19 +					
	N (%)	Covid (+)	Control	X^2	HR (95% CI)	P	N	Non-survivor	Survivor	X^2	HR (95% CI)	P
All Patients (n)	1454	92(6.3%)	1362 (93.7%)				92	16 (17.4%)	76 (82.6%)			
Age (median, range)	57(18–103)	54	57	0.32*	0.99 (0.98–1.00)	0.32	54.5 (18–82)	51	55	0.50*	0.98 (0.95–1.02)	0.50
Gender				0.87	0.96 (0.63–1.47)	0.87				0.17	0.45 (0.14–1.43)	0.17
Male	763 (52.5%)	49 (53.3%)	714 (52.4%)				49 (53.3%)	11 (68.8%)	38 (50%)			
Female	691 (47.5%)	43 (46.7%)	648 (47.6%)				43 (46.7%)	5 (31.2%)	38 (50%)			
Anti-HBs				0.90	0.97 (0.63–1.49)	0.90				0.12	0.42 (0.14–1.27)	0.12
Positive	894 (61.5%)	56 (60.9%)	838 (61.5%)				56 (60.9%)	7 (43.8%)	49 (64.5%)			
Negative	560 (38.5%)	36 (39.1%)	524 (38.5%)				36 (39.1%)	9 (56.2%)	27 (35.5%)			
Anti-HBC IgG (n = 895)				0.73	1.10 (0.61–2.00)	0.73				0.33	2.11 (0.45–9.73)	0.33
Positive	445 (49.7%)	24 (52.2%)	421 (49.6%)				24 (52.2%)	6 (66.7%)	18 (48.6%)			
Negative	450 (50.3%)	22 (47.8%)	428 (50.4%)				22 (47.8%)	3 (33.3%)	19 (51.4%)			
Hepatitis B immune status				0.22		0.24				0.22		0.37
Vaccinated	664 (45.7%)	41 (44.6%)	623 (45.7%)		reference		41 (44.6%)	4 (25%)	37 (48.7%)		reference	
Resolved infection	206 (14.2%)	14 (15.2%)	192 (14.1%)		1.18 (0.59–2.07)	0.74	14 (15.2%)	3 (18.8%)	11 (14.5%)		2.52 (0.48–13.02)	0.26
İsolated Anti-HBc Ab +	211 (14.5%)	8 (8.7%)	203 (14.9%)		0.59 (0.27–1.29)	0.19	8(8.7%)	3 (18.8%)	5 (6.6%)		5.55 (0.95–32.40)	0.06
Non-immunised	286 (19.6%)	25 (27.2%)	261 (19.2%)		1.45 (0.86–2.44)	0.15	25 (27.2%)	6 (37.5%)	19 (25%)		2.9 (0.73–11.62)	0.12
HBsAg-positive	87 (6%)	4 (4.3%)	83 (6.1%)		0.73 (0.25–2.09)	0.56	4 (4.3%)	0 (0%)	4 (4.3%)		0.00	0.99
Anti-HBs level				0.43		0.44				0.58		0.60
< 2 IU/L	560 (38.5%)	36 (39.1%)	524 (38.4%)		reference		36 (39.1%)	9 (56.3%)	27 (35.5%)		reference	
2–9 IU/L	104 (7.2%)	10 (10.8%)	94 (6.9%)		1.54 (0.74–3.22)	0.24	10 (10.9%)	1 (6.2%)	9 (11.8%)		0.33 (0.03–3.00)	0.32
10–99 IU/L	303 (20.8%)	17 (18.5%)	286 (21%)		0.86 (0.47–1.56)	0.63	17 (18.5%)	3 (18.8%)	14 (18.4%)		0.64 (0.15–2.76)	0.55
100–999 IU/L	352 (24.2%)	18 (19.6%)	334 (24.5%)		0.78 (0.43–1.40)	0.41	18 (19.6%)	2 (12.5%)	16 (21.1%)		0.37 (0.07–1.95)	0.24
> 1000 IU/L	135 (9.3%)	11 (12%)	124 (9.1%)		1.29 (0.63–2.60)	0.47	11 (12%)	1 (6.2%)	10 (13.2%)		0.30 (0.03–2.68)	0.28

Status

Table 3. Multivariate analysis for mortality risk in patients with COVID-19

	Multivariate analysis	
	HR (95% CI)	P-value
Age	0.96 (0.91–1.01)	0.20
Gender (male/female)	0.43 (0.11–1.71)	0.23
Comorbidities (no/yes)	2.00 (0.41–9.73)	0.39
Stage (metastatic/ non-metastatic)	11.16 (1.19–104.6)	0.03
Treatment options		0.06
No treatment	reference	
Adjuvant/neoadjuvant	0.43 (0.05–3.79)	0.45
Palliative	0.10 (0.01–0.69)	0.02
Hepatitis B immunization (no/yes)	0.43 (0.11–1.62)	0.21

tients in the control group. The detailed clinical and laboratory findings of the patients related to hepatitis B are presented in Table 2. The seroprevalence of hepatitis B (HbsAg +) was 6% (87/1454) among the study patients. In the case group, 4.3% (n: 4) of patients had HbsAg positivity, 60.9% (n: 56) had anti-Hbs positivity and 52.2% (n: 24) had anti-HBc IgG positivity. In the control group, 6.1% (n: 83) of the patients had HbsAg positivity, 61.5% (n: 838) had anti-Hbs positivity and 49.6% (n: 421) had anti-Hbc IgG positivity. The mean anti-Hbs level was 10 IU/L in the case group compared with 18.2 IU/L in the control group ($p = 0.66$). When the immunization status of the patients was analysed, 44.6% (n: 41) of the patients were found to be vaccinated, 15.2% (n: 14) had resolved infection, 8.7% (n: 8) had isolated anti-Hbc IgG antibody positivity, 27.2% (n: 25) were non-immunized and 4.3% (n: 4) were HbsAg positive in the case group. In the control group, in turn, 45.7% (n: 623) were vaccinated, 14.1% (n: 192) had resolved infection, 14.9% (n: 203) had isolated anti-Hbc IgG antibody positivity, 19.2% (n: 261) were non-immunized, and 6.1% (n: 83) were HbsAg positive. When the case and control groups were compared according to these five categories, there was no statistically significant difference in the risk of COVID-19 transmission ($p = 0.22$) or the risk of mortality ($p = 0.22$) between the groups. When the patients' anti-Hbs antibody levels (< 2 IU/L, 2–9 IU/L, 10–99 IU/L, 100–999 IU/L and > 1000 IU/L) were categorized, no statistically significant difference was found between the two groups in the risk of COVID-19 transmission ($p = 0.43$) and the risk of mortality ($p = 0.53$) based on antibody levels.

Age, gender, presence of comorbidities, stage of the disease, treatment options, hepatitis B immunization status were examined with univariate and multivariate analyses. The results of the analyses are presented in Table 3. The multivariate analysis identified palliative chemotherapy [HR: 0.1, 95% CI (0.01–0.69), ($p = 0.02$)] and stage [HR: 0.09, 95% CI (0.01–0.83), ($p = 0.03$)] as independent prognostic factors for mortality risk in patients with COVID-19 infection as univariate analysis did not indicate palliative treatment as a prognostic factor.

Discussion

Among the different patient groups, cancer patients are at one of the greatest risks from the COVID-19 pandemic [1–3]. The present study investigates the effect of the characteristic and clinical outcomes of cancer patients who presented to the authors' clinic during the COVID-19 pandemic related to COVID-19 transmission risk and mortality, intending to identify the associated risk factors.

Among the 1,515 patients who presented to the clinic during the pandemic, 10.1% (n: 153) were diagnosed with COVID-19, which is a rate considerably higher than reported in COVID-19 incidence studies conducted with cancer patients (10.1% *vs*. 0.79–1.3%) [10, 11]. This may be attributed to the fact that the reported studies were carried out during the early stages of the pandemic, and that cases increased afterwards, and that a COVID-19 test was administered routinely to the patients before treatment following the recommended guidelines later in the pandemic, leading to the detection also of asymptomatic cases.

The Southeastern Anatolia Region of Turkey, where the oncology centre is located, is an endemic area for hepatitis B infection (7%, with a high prevalence of HBsAg) [12], and so all patients referring to the oncology centre are routinely checked for hepatitis B serology with Elisa before treatment planning. Chemotherapy-induced immunosuppression may cause HBV reactivation in active or inactive HBV carriers, and HBV reactivation during anti-tumour therapy can lead to life-threatening clinical manifestations (fulminant

hepatitis, hepatic failure, and mortality) in addition to discontinuation of anti-tumour therapies [13]. Guidelines recommend HBV screening for treatments with severe immunosuppressive activity or patients at high risk of HBV infection, and prophylactic antiviral therapy in cancer patients at high risk of HBV reactivation [12, 13]. In the present study, 34.7% of cases had encountered hepatitis B at some point in their lives, and 6% had HbsAg positivity. The seroprevalence of hepatitis B among patients was consistent with the prevalence of hepatitis B in the study region (6% *vs.* 7%), and there was no significant difference in HbsAg positivity between the patients with COVID-19 and the control group [4.3% *vs.* 6.1% ($p = 0.56$)].

Whether or not hepatitis B seropositivity and immunization status affect the course and outcomes of COVID-19 infection are yet to be confirmed. Chronic HBV infection may affect the likelihood of developing clinically important infectious manifestation with COVID-19 [13–15]. A review article suggested that chronic HBV infection may contribute to a decrease in virus-specific T-cell activity, and indirectly to the intensity of the cytokine storm [16]. It is also hypothesized that immunization with hepatitis A, hepatitis B and BCG vaccines can provide a protective effect against COVID-19 through immune maturation [6]. That said, in an animal study investigating whether childhood vaccines, including hepatitis B and BCG, produced cross-reactive neutralizing antibodies against SARS-CoV-2, none were found to produce antibodies against SARS-CoV-2 after vaccination [17]. In the present study, when the immunization profiles (vaccinated, resolved infection, isolated anti-HBc Ab (+), non-immunized and HBsAg-positive) developed against hepatitis B were compared between the case and control groups, no significant difference was noted in the risk of COVID-19 transmission between the groups ($p = 0.22$), and no significant difference was noted either in mortality risk between the different immunization profiles of COVID-19-positive patients ($p = 0.37$). It was further observed that anti-Hbs serum levels had no effect on COVID-19 transmission ($p = 0.44$) or mortality ($p = 0.60$).

COVID-19 infections can lead to impaired liver function and severe liver injury [18]. A meta-analysis of studies evaluating the hepatic findings of COVID-19 reported an HBV prevalence of 0.9% [19]. The prevalence of HBV infection was found to be 6.1% and 4.3% in the study control group patients with a cancer diagnosis and cancer patients with COVID-19, respectively. Although these rates seem higher than those reported in the literature, they were close to the prevalence (7%) of the endemic region in the general population. In a previous study evaluating the clinical characteristics of patients with hepatitis B and COVID-19 coinfection, 20 (6.1%) of 326 COVID-19 positive patients had concurrent HBV infection. The study found no significant difference in discharge rates, length of hospital stays, exacerbation of liver injury, and mortality between the patients with and without hepatitis B infection [20].

Among cancer patients, those with thoracic malignancies such as lung cancer are considered at high risk of COVID-19 mortality due to associated age, comorbidities, history of smoking and existing pulmonary damage, in addition to the treatments administered for the disease [21]. In the present study, lung cancer was the fourth most common form of cancer after breast, gastrointestinal system (GIS) and genitourinary system (GUS) cancers, among the study patients with COVID-19 infection. However, lung cancers did not differ from the other cancer types in terms of COVID-19-related mortality risk ($p = 0.68$).

In the present study, multivariate analysis showed that the presence of metastatic disease and the receipt of palliative chemotherapy were statistically different between the survivors and non-survivors among the cancer patients with COVID-19 infection as univariate analysis did not indicate palliative treatment as a prognostic factor. Survival among the COVID-19 positive patients receiving palliative therapy was better than in those receiving no treatment [HR: 0.1, 95% CI (0.01–0.69), ($p = 0.02$)]. Most patients in the group receiving no treatment were in remission. Although this would appear to be contradictory, it actually recalls the idea that chemotherapy can suppress possible excessive immune reactions (cytokine storm) due to COVID-19 and can provide a survival benefit to the patients. In this regard, a previous study comparing the immune response to SARS-CoV-2 in cancer patients undergoing active antitumor therapy with the immune response in healthy individuals reported differences in immune cell profiles, indicating different inflammatory responses in the two groups. The study suggested that cancer treatments such as chemotherapy, biological agents and immunotherapies may affect the body's immune response against COVID-19, leading to a milder manifestation of the infection in cancer patients with COVID-19 infection [22]. Also, fewer myelosuppressive therapeutic agents were preferred for palliative chemotherapies, and dose reductions and delays were applied more frequently during the pandemic, following the recommended guidelines [23]. In contrast, granulocyte colony-stimulating factor (GCSF) support was more often preferred for the minimization of the risk of myelosuppression. Likely, these adaptive practices may also influence the study findings.

The present study was unable to identify any statistical differences in the treatments of the survivors and non-survivors diagnosed with COVID-19. The potential

interaction between oncological therapeutic agents and COVID-19 infection is not fully known [24], although the TERAVOLT study, which investigated the risk factors associated with mortality in patients with thoracic malignancies and COVID-19 infections and presented at ASCO 2020's meeting (American society of clinical oncology 2020), reported the treatment of cancer patients with chemotherapy to be a risk factor for mortality associated with COVID-19 infection, while treatment with tyrosine kinase inhibitors and immunotherapy was not a risk factor. The same study further reported advanced age (> 65 years), comorbidities, performance status > 1, and receiving steroid or anticoagulant therapy to be risk factors associated with mortality [21]. In a comparison of the patients in the present study in terms of the applied anti-tumour therapies (chemotherapy, immunotherapy, tyrosine kinase inhibitor and hormonal therapies), it was observed that types of anti-tumour therapy did not affect mortality in patients with COVID-19 infection. In a study conducted in the early stages of the pandemic that evaluated cancer patients with COVID-19 infection, the receipt of chemotherapy within four weeks of the emergence of COVID-19 infection symptoms and male gender were reported to be poor prognostic factors. In addition, hepatitis B virus infection was detected in 6% of the 205 patients in the study, although the same study observed that the presence of hepatitis B virus infection was not among the risk factors for mortality [25]. A study by Lee et al., in turn, reported the receipt of chemotherapy within the last four weeks to have no significant effect on COVID-19 mortality, while advanced age and the presence of cardiovascular comorbidities were high-risk factors [26]. Cancer patients undergoing active treatment have been referred to as high-risk patients since the beginning of the pandemic. After viewing the findings of different studies, it is expected that the potential roles of cancer and cancer treatments during COVID-19 will be clarified through further studies.

The limitations of this study include its single-centre and retrospective design, the heterogeneous patient population in terms of diagnosis, stage and treatments, and the lack of information about COVID-19 treatments (such as steroids, etc.) that might have an impact on mortality risk. Moreover, the fact that the study was carried out in one particular region in the country, and that the patient group had other diseases, may have influenced the study findings. Finally, some of the control group patients may contract COVID-19 in the future, which is another study limitation.

Conclusions

In conclusion, this study is the first to evaluate the relationship between COVID-19 and hepatitis B immunization in cancer patients. The present study identified the presence of metastatic disease and the receipt of palliative chemotherapy as negative and positive prognostic factors, respectively, but no statistically significant relationship between the risk of COVID-19 transmission and mortality, and hepatitis B immunization status. Factors other than hepatitis B immunization status are likely to be more effective in the risk of COVID-19 transmission and mortality among cancer patients.

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VIA MEDICA

ORIGINAL ARTICLE

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MC4R polymorphism in rs17782313 influences on insulin resistance

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ABSTRACT

Introduction: There are many factors responsible for the development of metabolic syndrome – mainly associated with lifestyle, but also genetic ones. MC4R (melanocortin 4 receptor) genes variants have been associated with the risk of developing obesity, type 2 diabetes mellitus and coronary artery disease.

Aim of the study: To investigate the association between MC4R rs17782313 polymorphism and concentrations of glucose, insulin, HOMA-IR and QUICKI values in the whole study group.

Materials and methods: Study group consisted of 294 patients (136 men and 158 women). Collected venous blood samples were stored at -70^{0}C until the study group was completed. In the laboratory of Clinical Hospital 1 in Zabrze, the DNA materials were isolated, proper concentration of the DNA (15 ng/μL) were prepared and quality and quantity were checked by spectrophotometry. Allelic discrimination was performed with the use of fluorescent-labelled TaqMan Pre-designed SNP Genotyping Assay probes.

Results: No statistically significant differences in concentrations of cholesterol, HDL, LDL, TG between genotypes in women and men were observed. In the whole group of patients, glucose and insulin levels did not differ significantly between TT, CT and CC carriers. Significant differences in values of HOMA-IR and QUICKI between TT, CT and CC carriers as well as between TT carriers and CT+CC carriers were found. CC+TT carriers have a significantly lower value of HOMA-IR and higher QUICKI value than TT carriers.

Conclusions: MC4R polymorphism in rs17782313 may be associated with insulin resistance. Further studies are necessary to completely assess the association between investigated polymorphism, insulin resistance and risk of diabetes mellitus development.

Key words: melanocortin 4 receptor, insulin resistance, diabetes mellitus, single nucleotide polymorphism, QUICKI, HOMA-IR

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Introduction

Abdominal obesity, insulin resistance, raised blood pressure, reduced serum concentration of high-density lipoprotein and elevated serum concentration of triglycerides are gathered as metabolic syndrome, which is closely linked to a high risk of developing cardiovascular diseases and diabetes mellitus. The development of metabolic syndrome is associated both with environmental and genetic factors which influence obesity, glucose and insulin metabolism[1]. Prevalence depends on gender, age socioeconomic status, and ethnic group. Many studies reported that one of the most important factors necessary for metabolic syndrome development is abdominal obesity [1]. Due to the rising prevalence of obesity, the prevalence of metabolic syndrome also increases dramatically; it is estimated that 34% of women and 50% of men have MS in Poland [2]. The main cause of insulin resistance, which leads to hyperglycaemia, is an increased level of plasma fatty acids released from adipose tissue [1]. Thus, new markers involved in metabolic syndrome development are still being sought. MC4R (melanocortin 4 receptor) is the G-protein coupled receptor that binds Pro-opiomelanocortin (POMC)-derived melanocortin peptides and transmits satiety signal in the paraventricular nucleus [3]. Its gene is located on the long arm of chromosome 18. MC4R is considered an important regulator of food intake and metabolism which dysfunction may be associated with the develop-

ment of obesity, insulin resistance, type 2 diabetes and coronary artery disease [4]. Many SNP near the MC4R gene are reported to be associated with an increased risk of obesity [5, 6].

Insulin resistance (IR) is described as a disorder in the regulation of glucose homeostasis which is manifested by decreased insulin ability to reduce serum glucose level despite its normal or increased level in serum [7]. This pathological condition is caused by decreased sensitivity of muscles, adipose tissue, liver, and other body tissues to insulin [7]. The insulin sensitivity resistance is often assessed using Homeostasis Model Assessment — Insulin Resistance (HOMA-IR). To assess insulin sensitivity which is the inverse of insulin resistance the quantitative insulin sensitivity check index (QUICKI) is used [7].

The study aimed to investigate the association between different variants of the MC4R gene in rs17782313 and serum concentrations of glucose, insulin, HDL, LDL, TG, HOMA-IR and QUICKI values in a group of Polish patients (the industrial region of Silesia, Poland).

Materials and methods

Study sample

294 study samples of whole blood were collected. Inclusion criteria contained: age > 18 years, no tumour, no dialysis at the time of sampling and informed consent. Patients were included in the study by a random selection.

Evaluation of DNA levels

Whole blood samples were collected for the examination, then isolated by column method. Afterwards, they were stored until the study group was collected. The concentration of genetic material 15 ng/μL was obtained by mixing DNA with water according to the dilution protocol and checked with a denoviX spectrophotometer.

Preparation of samples

Preparation for PCR included: preparation of the mixture by vortexing on a short spin probe, mixing with water, buffer and mix (reaction mix to Roche device), re-vortexing, centrifugation. The solution was mixed with the DNA and transported to the PCR plate. PCR reaction was performed by Roche Lightcycler 96. Alleles were marked as A in VIC and G in FAM (Tab. 1).

Statistical analysis

The Shapiro-Wilk test was used to assess the data distribution. Variables data are presented as mean ± SD. The significance between distributions of genotypes and alleles, gender, the occurrence of hypertension, coronary artery disease (MIC), diabetes mellitus, cigarettes smoking was tested using Pearson's $\chi 2$ test. To compare valuable data between the three groups (genotypes TT, CT and CC), the Kruskal-Wallis test with multiple comparisons was performed. To compare valuable data between two groups (groups TT, CT+CC) Mann-Whitney U test was performed. Concentrations of cholesterol, HDL, LDL, TG were analysed separately for women and men. Levels of glucose, insulin, values of HOMA-IR and QUICKI were analysed for the whole study group.

Results

No statistically significant differences were found in concentrations of cholesterol, HDL, LDL, TG between genotypes in groups of women and men (Tab. 2, 3).

In the whole group of patients, glucose and insulin levels did not differ significantly between TT, CT and CC carriers (Tab. 4). Significant differences in values of HOMA-IR and QUICKI between TT, CT and CC carriers as well as between TT carriers and CT+CC carriers were found. CC+CT carriers have a significantly lower value of HOMA-IR and higher QUICKI value than TT carriers (Fig. 1, 2).

Discussion

Many studies reported a significant association between MC4R SNP in rs17782313 and parameters of metabolic syndrome, however, the results were often inconclusive. Research conducted by Brodowski et al. revealed that the probability of MS development in a group of postmenopausal women is higher in individuals with the CT or CC genotype in rs17782313. Women with CT or CC genotype had higher levels of TG, total cholesterol, LDL-C and Apolipoprotein B than those with TT genotype[8]. On the contrary, the study carried out by Szkup et al. reported that MC4R SNP in rs17782313 is not linked to a higher risk of metabolic syndrome development in a group of 45–60-year-old women [9]. H. Yarizadeh et al. showed that in the population of overweighted or obese Iranian women the presence of allele C in rs17782313 is associated with higher HOMA-IR value and elevated insulin level [10]. Contrary to these results, the presented study found significantly higher HOMA-IR value in patients with TT genotype compared to TC and CC individuals. The differences in HOMA-IR and QUICKI value between genotypes were insignificant in the study conducted by Brodowski [8] and not assessed in research conducted by Szkup [9]. The authors assume that the presence of allele T is associated with increased HOMA-IR value

Table 1. Characteristic of study group (n = 294)

	Genotype						p
	TT		CT		CC		
	n	%	n	%	n	%	
Gender							0.253
Women	103	63.58%	53	32.72%	2	1.23%	
Men	85	61.59%	45	32.61%	6	4.35%	
Hypertension							0.46039
Yes	96	65.75%	44	30.14%	5	3.42%	
No	92	59.74%	54	35.06%	3	1.95%	
MIC							0.34531
Yes	31	63.27%	15	30.61%	3	6.12%	
No	157	62.55%	83	33.07%	5	199.20%	
Diabetes mellitus							0.36361
Yes	21	70.00%	9	30.00%	0	0.00%	
No	167	61.85%	89	32.96%	8	2.96%	
Nicotinism							0.66682
Yes	41	57.75%	26	36.62%	2	2.82%	
No	147	64.19%	72	31.44%	6	2.62%	
	mean	SD	mean	SD	mean	SD	p
Age	53,66	16.84	51.26	16.92	58.88	18.01	0.1929
BMI	26,80	3.70	26.49	4.03	25.18	1.77	0.2554

BMI — body mass index, MIC — coronary artery disease

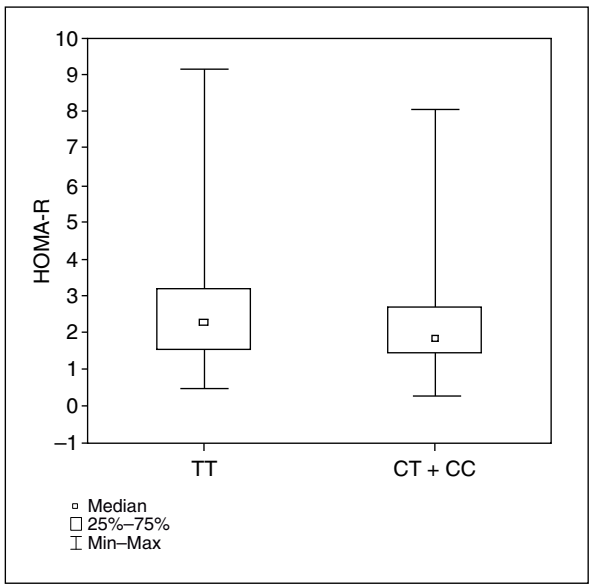

Figure 1. Comparison of HOMA-IR value between TT carriers (wild genotype) and CC or CT carriers (p = 0,036, n = 294) HOMA-IR — homeostasis model assessment-insulin

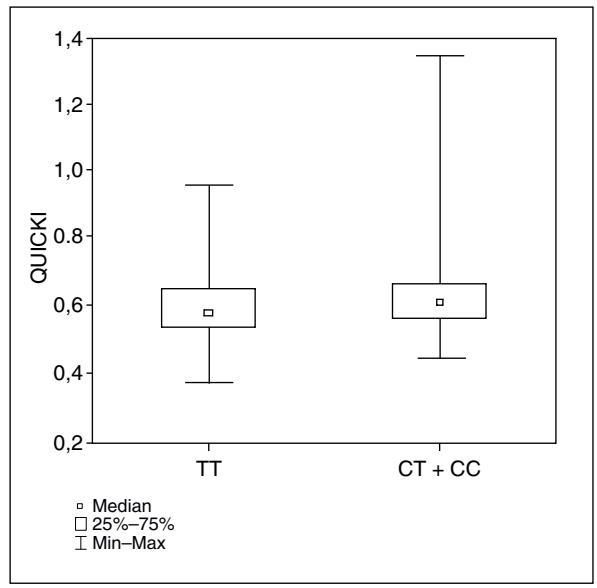

Figure 2. Comparison of QUICKI value between TT carriers (wild genotype) and CC or CT carriers (p = 0,018, n = 294) QUICKI — quantitative insulin sensitivity check index

Table 2. MC4R rs17782313 polymorphism and cholesterol, HDL, LDL, TG levels in women (n = 167)

	Women						p
	TT		CT		CC		
	mean	SD	mean	SD	mean	SD	
Cholesterol	6.05	1.16	6.46	1.21	6.58	0.57	0.1747
HDL	1.34	0.35	1.44	0.30	1.23	0.86	0.1946
LDL	4.09	1.04	4.45	1.13	4.90	0.21	0.1179
TG	1.37	0.80	1.24	0.54	1.00	0.18	0.461

HDL — high-density lipoprotein, LDL — low-density lipoprotein, MC4R — melanocortin 4 receptor, TG — triacylglycerols

Table 3. MC4R rs17782313 polymorphism and cholesterol, HDL, LDL, TG levels in men (n = 142)

	Men						p
	TT		CT		CC		
	mean	SD	mean	SD	mean	SD	
Cholesterol	5.88	1.31	6.14	1.51	6.83	1.84	0.3323
HDL	1.15	0.33	1.29	0.43	1.22	0.21	0.2822
LDL	4.11	1.17	4.27	1.23	4.82	1.31	0.3405
TG	1.41	0.96	1.67	1.89	1.54	1.14	0.9505

HDL — high-density lipoprotein, LDL — low-density lipoprotein, MC4R — melanocortin 4 receptor, TG — triacylglycerols

Table 4. MC4R rs17782313 polymorphism and concentrations of glucose, insulin, HOMA-IR and QUICKI values in the whole study group (n = 294)

	TT		CT		CC		p
	mean	SD	mean	SD	mean	SD	
Glucose	84.81	24.16	80.42	16.05	73.25	10.94	0.0891
Insulin	13.06	9.74	11.39	5.72	7.98	3.49	0.0364
HOMA-IR	2.51	1.39	2.31	1.43	1.42	0.62	0.0135
QUICKI	0.60	0.10	0.62	0.12	0.69	0.09	0.0079

HOMA-IR — homeostasis model assessment-insulin, MC4R — melanocortin 4 receptor, QUICKI — quantitative insulin sensitivity check index

and insulin resistance, however, the differences in genotype distributions between diabetes and nondiabetic patients were insignificant. One must bear in mind that other studies tested different models of inheritance, thus contradictory results can depend on the used model. This study used the dominant model of the MC4R rs17782313 inheritance (TT, CT+CC).

In the presented work no significant association between MC4R SNP in rs17782313 and obesity was found. This observation is in line with two similar studies conducted in Poland [9, 11] and one carried out in the Czech Republic [12]. On the contrary, other population studies conducted in Pakistan [13] and Greece [14] showed that homozygotes CC have a higher risk of obesity; similarly, in the Romania population heterozygotes CT are more predisposed to obesity [15]. It can be supposed that the presence of allele C is associated with an increased risk of obesity. However, due to differences in research findings, further studies are necessary to thoroughly investigate the influence of SNP MC4R on the prevalence of overweight and obesity. One should also take into account the role of population characteristics which can be responsible for the lack of association between SNP of MC4R and obesity in the Polish population.

Lipid profile disturbances as a component of metabolic syndrome were also analysed in the conducted research. Similar to this study, other studies conducted in Poland [9, 11] and Greece [14] did not find a statistically significant association between MC4R SNP in rs17782313 and the lipid profile of patients. There is only one study reporting a reduced risk of lipid disturbances among individuals with T allele in a group of Polish postmenopausal women [8].

Some studies demonstrated a relationship between MC4R SNP in rs17782313 and glycaemic profile – fasting blood glucose and insulin level. Yarizadeh et al. showed significantly higher insulin level in CT or CC carriers in comparison to TT carriers [10]. However, a similar study conducted by Lazopoulou et al. in the Greek population did not reveal the association between MC4R SNP in rs17782313 and insulin or glucose level [14]. This research has found no association between investigated SNP and glucose or insulin concentration.

The most significant results of this study concern the statistical association between the parameters measuring insulin resistance (HOMA-IR and QUICKI) and the studied SNP. In the studied population of women aged 45–60, no correlation was found between this parameter and metabolic syndrome [9]. Further studies in both genders are necessary to confirm or rule out the association between insulin resistance and MC4R SNP.

Conclusion

The obtained results showed that SNP in rs17782313 of MC4R gene is not significantly associated with lipid profile disturbances which are characteristic of metabolic syndrome. However, statistically significant differences in HOMA-IR and QUICKI value may suggest an influence of investigated SNP on insulin resistance. TT genotype was present more often in patients with increased insulin resistance while CT and CC genotypes were associated with decreased insulin resistance and higher insulin sensitivity. No statistically significant association between studied SNP and occurrence of hypertension, coronary artery disease and diabetes mellitus was observed. Further studies with a larger number of patients are needed to clarify the role of SNP in rs17782313 of MC4R gene in the pathogenesis of metabolic syndrome and insulin resistance which is closely related to this disorder.

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VIA MEDICA

ORIGINAL ARTICLE

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Subjective evaluation of skin toxicity and quality of life in patients undergoing anti-cancer treatment at the Department of Cancer Chemotherapy

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ABSTRACT

Introduction: Skin complications are a frequent side effect of oncological treatment, which may impair patients' quality of life. The aim of this study is a subjective assessment of skin toxicity and life quality during anticancer treatment.

Material and methods: We analysed patients with malignant cancer, receiving conventional chemotherapy, molecularly targeted drugs, or both, between January 2019 and February 2020, for at least six weeks. The researchers' questionnaire assessed the type and intensity of skin toxicity, its impact on the emotional state and life quality. Subjective needs concerning education about the potential toxicity of treatment and dermatological care were analysed. Global quality of life was assessed using the EORTC QLQ-C30 scale.

Results: We analysed 78 patients, aged 27–78 years (41 men; 37 women). Twelve patients received anti-EGFR antibody. Skin toxicity influence on emotional state and life quality was assessed by age, gender, duration and type of therapy. Skin complications were reported by 95% of patients, 53% confirmed the influence of skin toxicity on emotional state and 32% on everyday functioning. The inverse correlation between life quality and skin lesions' severity was found (correlation coefficient = 0,33, $p < 0,0001$). 31% of patients were willing to have a dermatologist in the team of leading doctors. 28% reported a total lack of possible skin side effects information. 82% declared total skin toxicity acceptance in case of the good effect of anti-cancer therapy.

Conclusions: Dermal toxicity negatively affects various areas of patient functioning. Improvement can be made by proper education of patients, effective prevention and treatment.

Key words: skin toxicity, quality of life, systemic treatment, monoclonal antibodies, epidermal growth factor receptor

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Introduction

Systemic anticancer treatment may cause skin side effects in 40–90% of patients [1–3]. This mainly concerns molecularly targeted drugs. Monoclonal antibodies and tyrosine kinase inhibitors directed against the epidermal growth factor receptor (EGFR) cause skin toxicity in almost all treated patients [4, 5]. Immunotherapy in more than a third [6].

Skin toxicity may impair the quality of life, and if severe, lead to discontinuation of anticancer therapy. Patients should be properly prepared for potential adverse effects which allow to effectively minimize the level of anxiety in the situation of their occurrence as well as improve compliance with medical recommendations.

This study aims to subjectively evaluate skin toxicity in patients undergoing systemic treatment, its impact on their emotional state and quality of life. Moreover, the study assesses the extent to which patients are informed about potential complications as well as their needs for the prevention and treatment of these side effects.

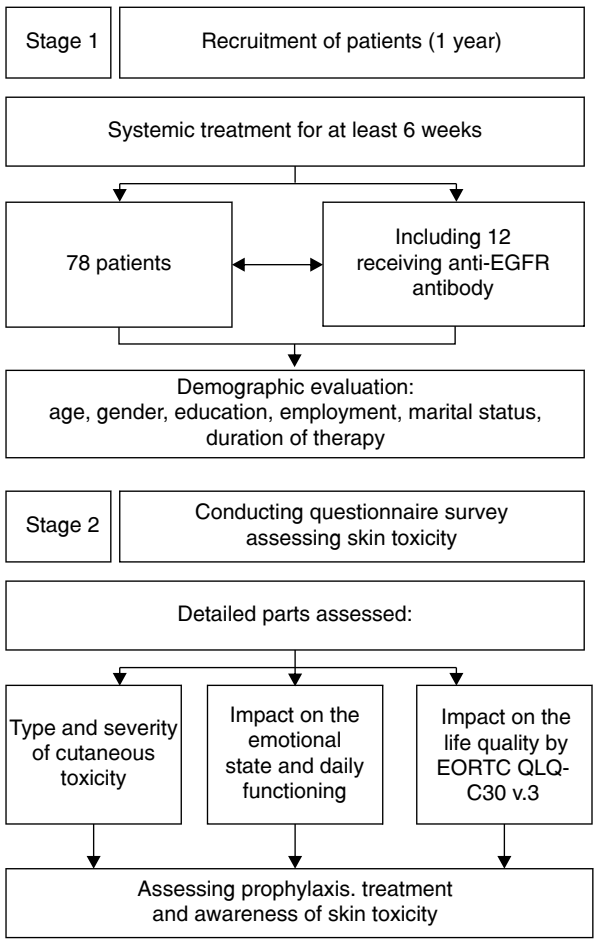

Figure 1. The scheme of the course of the study

Material and methods

This questionnaire survey was conducted between January 2019 and February 2020 in a group of cancer patients who received either palliative or adjuvant systemic treatment for at least 6 weeks at the Department of Chemotherapy, Nicholas Copernicus Hospital, Lodz, Poland. Each patient gave informed consent for the survey. Bioethics committee approval for the study was obtained.

An original questionnaire, consisting of three parts, was used to assess the type and severity of cutaneous toxicity and its impact on the emotional state and quality of life. In the first part — demographic: age, gender, education, employment, marital status and duration of therapy were analysed. In the second part patients' global quality of life was assessed according to the standardized EORTC (European Organization for Research and Treatment of Cancer) QLQ-C30 (Quality of Life Questionnaire Core 30) version 3. In the third part of the study adverse effects of skin and its appendages, occurring in the last month were analysed (in the initial version of the questionnaire 18 patients were asked about complaints occurring during the last week, but such a time interval was considered not representative of skin complications and was changed in subsequent questionnaires). Moreover, the influence of skin toxicity on emotional state and daily functioning was analysed. Prophylaxis and treatment of dermatological complications were assessed. The patients were asked about their knowledge of the possibility of dermal side effects and the possible need for dermatological consultation. The scheme of the course of the study is shown in Figure 1.

Statistical significance of selected parameters was determined by chi-square test, Mann-Whitney U test and Kendall correlation, all tests were two-sided, no correction for multiple testing was applied.

Results

78 patients (41 men, 37 women) were included in the study. Demographic data of the patients, information about the types of cancer and systemic treatment are presented in Table 1. 78% of the patients claimed that their feelings during cancer treatment should have the least negative impact on their daily life. 90% agreed that quality of life during chemotherapy was very important to them. The specific results of the quality of life using the EORTC QLQ-C30 questionnaire (version 3) are presented in Table 2.

93% of patients reported the occurrence of side effects affecting the skin, its appendages and mucous membranes during systemic treatment. The results of the severity of these lesions are shown in Table 3.

There was a positive correlation between the total quality of life scores and skin lesion severity (Kendall's tau b = 0.33; $p < 0.0001$), indicating an association between worsening quality of life and greater severity of skin side effects. The relationship was confirmed by the chi-square test (analysis of subgroups separated by a median of total points), which showed that lower skin lesion severity was more likely to coexist with better quality of life (chi-square test $p = 0.0003$). The negative impact of skin toxicity on the emotional state was reported by 53% of patients, while 32% reported its impact on daily functioning. The results of examining the severity of this impact according to gender are shown in Table 4. The male group reported a statistically significant greater negative impact of skin side effects on emotional state compared to females (chi-square test $p = 0.0007$; Mann-Whitney test $p = 0.0034$). In the group of women, it is noteworthy that the adverse effect of skin lesions on daily functioning was numerically greater compared to men, but this difference was not statistically significant.

Table 1. Patient demographic data, information on types of cancer and applied systemic treatment

Age	**Median: 66 y.o. Range: 27–78 y.**	**Number of patients (n)%**
Sex	male	n = 41 (≈53%)
	female	n = 37 (≈47%)
Education	primary/ vocational	n = 34 (≈44%)
	secondary	n = 30 (≈39%)
	higher	n = 14 (≈18%)
Marital status	Living alone	n = 15 (≈19%)
	Living with partner/ children/grandchildren/ parents	n = 63 (≈81%)
Length of oncological therapy	Less than 12 months	n = 34 (≈44%)
	More than 12 months	n = 44 (≈56%)
Duration of current treatment	Less than 3 months	n = 34 (≈44%)
	3–12 months	n = 31 (≈40%)
	1–3 years	n = 10 (≈13%)
	More than 3 years	n = 3 (≈4%)
Type of malignant neoplasm	colorectal cancer	n = 38 (≈49%)
	breast cancer	n = 11 (≈14%)
	ovarian cancer	n = 5 (≈6%)
	pancreatic cancer	n = 5 (≈6%)
	lung cancer	n = 4 (≈5%)
	stomach cancer	n = 4 (≈5%)
	testicular cancer*	n = 2 (≈3%)
Scheme of systemic treatment	chemotherapy	n = 57 (≈73%)
	chemotherapy with anti-EGFR antibody**	n = 11 (≈14%)
	olaparyb	n = 2 (≈3%)
	abiraterone	n = 1 (≈1%)
	anti-HER2 antibodies	n = 5 (≈6%)
	pembrolizumab	n = 1 (≈1%)
	panitumumab	n = 1 (≈1%)

* In addition, single patients with diagnosed cancer of: prostate, cervix, fallopian tube, oesophagus, nasopharynx, anus and pleural mesothelioma, uterine sarcoma, melanoma.
**chemotherapy + cetuximab: n = 10; chemotherapy + panitumumab: n = 1)

Table 2. The results of the quality of life study according to the EORTC QLQ-C30 (version 3) questionnaire

Quality of life of patients according to the EORTC QLQ-C30 questionnaire (version 3)	
Questions number 1–28, regarding the severity of factors impairing quality of life	
Possible worsening of the quality of life with scores:	Possible range of point totals: 28–112
1 — Slightly 2 — Moderately 3 — Considerably 4 — Extremely	Achieved range of total points: 29–80 Median: 53 Mean: 52.5
Question 29: How would you rate your general health over the past month?	
Badly — 2.6% of patients (n = 2) Rather bad — 3.8% (n = 3) Average — 52.6% (n = 41) Fairly well — 23.1% (n = 18) Good — 17.9% (n = 14)	
Question 30: How would you rate your overall quality of life over the past month?	
Badly — 1.3% of patients (n = 1) Rather bad — 7.7% (n = 6) Average — 53.8% (n = 42) Fairly well —16.7% (n = 13) Good — 20.5% (n = 16)	

Table 3. The results of the severity of adverse effects on the skin, its appendages and mucous membranes

The severity of adverse effects on the skin, its appendages and mucous membranes — 17 questions	
Possible severity of side effects with scores:	Possible range of severity sum scores for side effects: 0–68
No change — 0 A little — 2 Moderately — 3 Very much — 4	Achieved range of total points: 0–37 Median: 11 Mean: 13.29 No skin side effects: 7.7% of patients (n = 6)

As many as 28% of respondents reported being completely uninformed about possible skin-related side effects of anticancer treatment. Figure 2 shows data on the sources from which patients drew information about possible skin complications, for all respondents and according to the type of systemic treatment received. Only 44% of patients felt completely informed about possible skin toxicity. Among patients treated with EGFR inhibitors, the level of awareness was higher, with all of them reporting that they were completely (9/12) or moderately (3/12) informed about potential cutaneous side effects of anticancer treatment. In comparison, 58% of patients felt completely informed about the life-threatening side effects of anticancer treatment.

As many as 82% of the respondents admitted that they were able to completely accept cutaneous side effects of treatment in case of a favourable result of the therapy and 18% of the patients would be able to accept them partially. As many as 55% declared that they did not receive recommendations from their doctor on how to prevent cutaneous side effects. In addition, 40% of patients who experienced skin toxicity said that their physician did not recommend them any treatment for skin lesions or did not inform them of the need to avoid factors that exacerbate symptoms. Figure 3 shows data on the frequency and type of recommendations given by the oncologist for prevention (3A) and treatment

Table 4. The influence of skin toxicity on the emotional state and functioning of patients

	Females (n = 37)	**Males (n = 41)**	
6 questions regarding the negative impact on patients' emotional state:			
Possible negative impact scoring: 0 — No impact 1 — Slightly 2 — Moderately 3 — Considerably 4 — Extremely	Possible range of point totals: 0–24 • Achieved range of total points: 0–16 • Average point totals: 2.08 • No negative impact in 67.6% of women (n = 25)	Possible range of point totals: 0–24 • Achieved range of total points: 0–19 • Average point totals: 4.76 • No negative impact in 29.3% of men (n = 12)	chi-square test p = 0.0007; Mann-Whitney test p = 0.0034
5 questions regarding the negative impact on patient functioning			
Possible negative impact scoring: 0 — No impact 1 — Slightly 2 — Moderately 3 — Considerably 4 — Extremely	Possible range of point totals: 0–20 • Achieved range of total points: 0–12 • Average point totals: 2.78 • No negative impact in 59.5% of women (n = 22)	Possible range of point totals: 0–20 • Achieved range of total points: 0–18 • Average point totals: 2.20 • No negative impact in 75.6% of men (n = 31)	chi-square test p = 0.127; Mann-Whitney test p = 0.1939

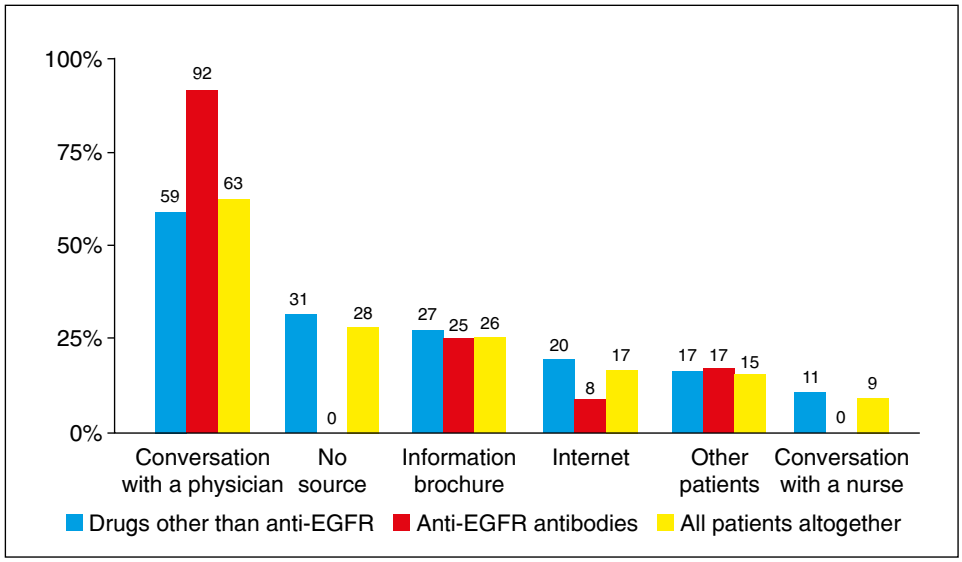

Figure 2. Patients' information sources about potential skin toxicity of the treatment, among patients with different types of treatment

(3B) of cutaneous side effects, according to the type of systemic therapy as well as data about the frequency of using preventive measures, if applied (3C).

58% of respondents agreed that they could use an antibiotic long-term if it reduced the severity of skin lesions, and 83% expressed acceptance of long-term use of skin care creams or medicated ointments. Among those who experienced skin side effects, 6% considered intermittent interruption or termination of anticancer treatment because of high lesion severity. Dermatological consultation was ordered only once. Four patients (5%) saw a dermatologist regardless of the oncologist's recommendation. 31% of respondents expressed the need for a dermatologist in the oncological treatment team.

Discussion

The nature of cutaneous toxicity of systemic treatment depends on the type of drugs and differs in pathomechanism.

Baldness is most commonly caused by paclitaxel (> 80%), doxorubicin (60–100%), cyclophosphamide (> 60%) and fluorouracil (10–50%) [7].

Nail damage during the systemic treatment most commonly includes onycholysis, leukonychia and paronychia. These complications affect almost half of patients treated with taxoids and 1/3 of patients receiving anti-EGFR antibodies [8]. In our study, brittleness, ingrown nails, inflammation and cracking of the skin

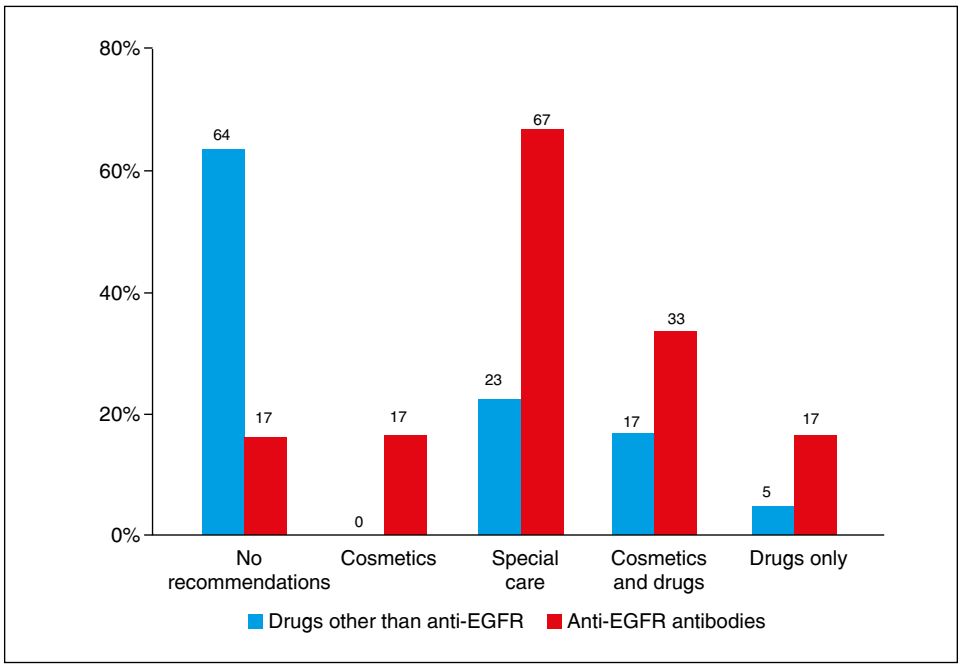

Figure 3A. Frequency of various recommendations for prophylaxis against skin toxicity depending on the type of systemic treatment

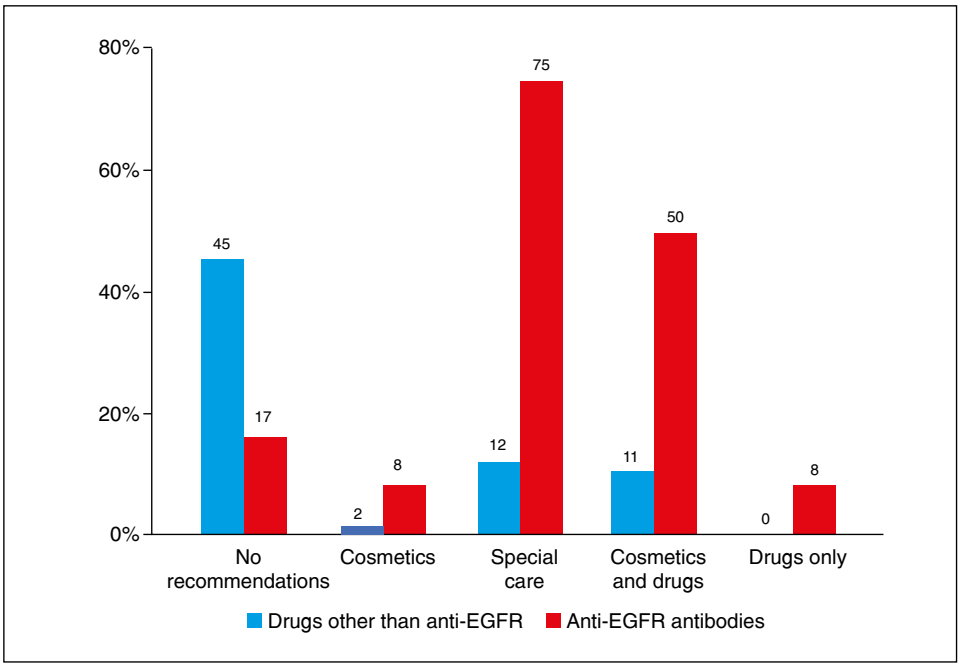

Figure 3B. Types and frequency of recommendations for prophylaxis against skin toxicity, depending on the type of systemic treatment

around the nails were observed in 31% of all patients and 83% of patients treated with anti-EGFR antibodies.

Hand-foot syndrome is observed in approximately 10–60% of patients undergoing anticancer treatment and is most commonly a complication of treatment with capecitabine, liposomal doxorubicin, docetaxel and fluorouracil [9]. Grade G1-2 hand-foot syndrome presents with erythema, hyperkeratosis and swelling of the palmar surface of the hands and soles of the feet. Grade G3 is associated with skin exfoliation,

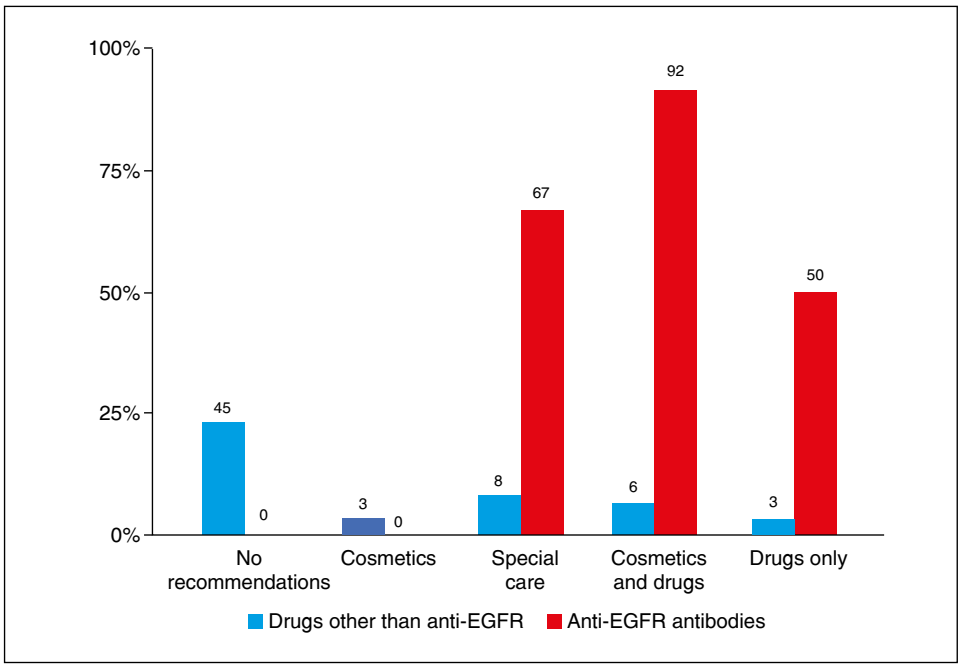

Figure 3C. Types and frequency of prophylaxis used against skin toxicity among patients on different systemic treatments

blistering, ulceration and pain which make self-care difficult [10].

Taxoids, in addition to affecting hair and nails, can also cause erythema and skin rash [11]. Anti-EGFR antibodies, panitumumab and cetuximab, interfere with keratinocyte function and stimulate a non-specific immune response in the skin [12, 13]. Skin toxicity affects up to 97% of patients receiving these drugs together with chemotherapy and most commonly manifests as acne-like rash, dry and pruritic skin, periungual dermatitis and erythematous lesions. A G3/4 grade rash is observed in approximately 20–40% of patients receiving chemotherapy and anti-EGFR antibody, and G3/4 grade nail toxicity in approximately 15% [12, 14]. All patients included in the present study who underwent combination chemotherapy with anti-EGFR antibody reported an acne-like rash of varying severity (G ≥ 3 in 27% of subjects), consistent with the expected frequency of this complication.

Dry skin was the most common skin complication reported by the patients, occurring in 63% of them. In the group treated with anti-EGFR antibodies, dry skin affected all patients (G ≥ 3 in 27%). In addition, 82% of patients receiving anti-EGFR antibody reported damage of nails and nail area, and 55% reported features of hand-foot syndrome. This high incidence of these side effects may have been because patients were receiving fluorouracil infusions at the same time.

Trastuzumab and pertuzumab antibodies are directed against the HER2 receptor (human epidermal growth factor receptor, type 2) which is also expressed in keratinocytes. They may cause skin toxicity in the form of rash, dry skin and nail plate changes [15, 16].

Skin toxicity had a negative impact on the emotional state of more than half of the surveyed patients and daily functioning in more than one-third of them. The negative impact of skin lesions on the emotional state was twice higher in men compared to women (4.76 *vs.* 2.08). These findings suggest that male patients may need more support with education, prevention and treatment of skin toxicity compared to women.

However, in a study of 379 patients by Gandhi et al, it was women who were 5 times more likely (15% *vs.* 3%) than men to report negative effects of skin toxicity on their professional and private lives. This study also found that interpersonal relationships were mostly affected in patients receiving targeted treatment (26%) compared to chemotherapy (4%) and radiotherapy (5%). Similar results were obtained by Rosen et al. [5, 17].

According to Nikolaou et al. and Barrios et al. skin toxicity caused by targeted drugs is a more frequent reason for dose modification compared to standard chemotherapy. This poses a risk of premature termination of anticancer therapy [18, 19]. The increasing availability of targeted therapy causes the proper management of skin toxicity to become an important issue.

In our study, patients with poorer quality of life were more likely to report increased skin complaints. The analysis of data from American and European centers concerning skin toxicity during systemic treatment confirms that skin complications may worsen the quality of life of patients [2, 5, 17]. Hackbarth et al.

evaluated 91 patients, 70% of whom declared that the occurrence of skin toxicity in the course of systemic treatment significantly limited their daily activity [2]. In a study conducted on 283 patients in 2007–2008, Rosen et al. showed that skin side effects related to targeted therapy have a negative impact on patients' quality of life, especially on their emotions and daily functioning [5]. In a study by Gandhi et al. dry skin, nail changes and burning sensations had the greatest impact on the quality of life of patients undergoing systemic treatment [17]. Many studies that aimed to evaluate the relationship between skin toxicity or its severity and quality of life have yielded inconclusive results [20–22]. Unger et al. demonstrated worsening of quality of life in patients receiving anti-EGFR antibody together with chemotherapy when G ≥ 3 versus G1-2 complications occurred [23]. On the other hand, in a study by Peeters et al. paradoxically, patients with more severe skin toxicity during treatment with anti-EGFR antibody reported better quality of life [24]. In the case of anti-EGFR therapy, this paradoxical relationship between reported quality of life and severity of skin symptoms may be related to patients' awareness that the occurrence of skin toxicity is an expected effect of the drug proving its efficacy, which may be a supportive factor in the acceptance of side effects [25].

An important aspect is to properly inform patients about possible skin complications. In our center, only 44% of the patients felt completely informed about the expected cutaneous toxicity of the treatment. Patients who received anti-EGFR antibodies appear to be better informed about potential skin toxicity compared to the rest. All of these subgroups declared that they were completely or moderately informed about potential cutaneous side effects of anticancer treatment. This may be related to physicians' less awareness of the cutaneous toxicity of drugs other than anti-EGFR.

In a study by Gandhi et al., 67% reported that cutaneous side effects of therapy were more severe than they expected. They found that before treatment, 47% of patients expressed significant concern about possible hair loss, 14% about skin irritation and 13% about dry skin. These results differed from those obtained during treatment, where only 29% of patients were concerned about hair loss, while skin irritation and dryness were feared by 23% and 24% of patients, respectively [17]. The discrepancy may have resulted from the fact that patients did not receive sufficient information before treatment regarding possible cutaneous side effects.

Adequate education that reinforces a sense of control during developing complications may help maintain the quality of life of patients experiencing cutaneous toxicity. Frith et al. developed a 4-step strategy to improve patients' acceptance of cutaneous side effects. This consists of anticipating, coming to terms with the inevitable, becoming ready and taking control. A patient who is prepared for the side effects of systemic treatment may have lower levels of anxiety and psychological distress when complications occur [26]. Having specific information about possible cutaneous toxicity is additionally associated with more accurate adherence to recommendations for prevention and treatment of complications and with better-reported quality of life [11].

The effectiveness of the treatment of cutaneous side effects, and thus the tolerance of anticancer treatment as well as the patients' quality of life, can be improved by the collaboration between oncologists and dermatologists.

As many as 40% of the patients who reported skin side effects in this study stated that the oncologist neither initiated treatment of the lesions nor provided information on lifestyle modifications that could improve the skin condition. This is probably due to the high proportion of adverse reactions, such as dry skin, which patients may not have reported during a routine medical examination.

The occurrence of G ≥ 3 skin toxicity is an indication for dermatological consultation, especially if no improvement is obtained after 1–2 weeks of treatment [27]. Only one patient of the 78 included in this study was referred to a dermatologist. At the same time, more than one-third of the respondents expressed the need for the presence of a physician of this specialty in the therapeutic team.

In a study by Gandhi et al., 16% of all patients who experienced skin complications were referred to a dermatologist and 54% of patients admitted that they would feel better if they had this option [17]. A study by Guerrero et al. involving 127 patients with cutaneous complications of therapy, showed that 51% of them had a change in the diagnosis of skin symptoms after consultation with a dermatologist, and 64% were recommended with further dermatological interventions [28].

Dermatological consultation can be particularly helpful in cases of increased skin toxicity when the oncologist is inclined to discontinue systemic treatment for this reason. Barrios et al. analysed the medical data of 44 patients in whom discontinuation of anticancer treatment due to skin toxicity was considered. In the dermatological assessment, interruption of anticancer treatment was considered justified in only 6 of the 44 cases [18].

Another study showed that the assessment of cutaneous toxicity made by oncologists and dermatologists was consistent in only 62% of cases. Oncologists had the greatest difficulty in naming and assessing the severity of skin lesions, dermatologists in classifying skin toxicity according to the NCI CTCAE criteria [29].

Therefore, the presence of a dermatologist in the therapeutic team to diagnose and treat skin complications during anticancer therapy is justified. Moreover, the use of a consistent nomenclature and a scale for assessing the severity of skin lesions will further improve the management of cutaneous toxicity.

It has also been shown that skin toxicity, in addition to its impact on quality of life, is also associated with increased costs of patient hospitalization [27]. In a study by Phillips et al. at a US center, the median length of hospital stay for patients requiring dermatological consultation was 6 days greater compared with patients not requiring medical intervention in this regard [30].

In the USA we can observe the development of a branch of medicine called "supportive oncodermatology" which is an answer to the escalation of skin toxicity as a complication of systemic treatment. Similar actions in Polish conditions could positively influence the quality of life and effective therapy of patients.

Conclusions

This study shows that cutaneous toxicity is an important but underestimated side effect of systemic treatment, which is associated with a poorer quality of life and an adverse effect on a patient's emotional state.

We have demonstrated the need for greater involvement of medical (including nursing) staff in educating patients about possible skin toxicity, its prevention and treatment.

Patients' access to professional sources of information, such as information brochures and websites, should also be increased.

Although these goals seem to be satisfactorily achieved among patients treated with anti-EGFR antibodies, prevention and treatment of skin toxicity caused by chemotherapy and other targeted drugs remain a challenge.

Education reinforces patients' sense of control during the appearance of side effects and increases the chances of effective compliance, thus giving greater chances of successful treatment of skin toxicity.

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VIA MEDICA

ORIGINAL ARTICLE

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Ki-67 proliferative index correlation to the immunohistochemistry profile in early female breast cancer: a review of 515 cases

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ABSTRACT

Introduction: Many biological markers are used as prognostic and predictive indicators in invasive breast cancers management. Among them, tumour size, grade, patho-morphological subtype, hormone receptors status and HER2 receptor expression in addition to Ki-67 proliferative index. Also, they play a key role in adjuvant treatment decision making. Our aim was to evaluate the association between Ki-67 proliferative index and breast cancer immunological subtype.

Material and methods: A total of 515 early invasive patients were enrolled, tumour biological characteristics as histopathological subtype, immune-histo-chemistry (ER,PR,HER2) status and Ki-67 proliferation index values have been collected. The Ki-67 index level of 20%, was used as the cut-off point to differentiate between low and high Ki-67 expression levels. Statistical analysis has been performed using the Chi square test online tool.

Results: In this cohort, about 42%, 33%, 7%, and 18% of the cases were grouped as luminal A-like, luminal B-like, HER2 enriched subtype, and triple-negative, respectively. All luminal A-like patients had Ki-67 level less than 20%. About 3% of the cohort, are luminal B-like tumours with Ki-67 level less than 20%, where 30.3% of the patients were luminal B-like tumours with Ki-67 level ≥ 20%. In HER2 enriched subtype, Ki-67 of < 20% level seen in 1.9% of cases, and Ki-67 levels ≥ 20% was observed in 5.2% of the cases. In the triple-negative group, Ki-67 was 20% or higher in 16% of cases, and only 1.7% of patients had Ki-67 level less than 20%.

Conclusion: Luminal A-like tumours were the most frequently encountered subtype, they have low Ki-67 levels and are known to be of a low histological grade tumour, and usually associated with a good prognosis. Also, data indicates that high Ki-67 levels are seen more often in Luminal B-Like breast cancers as well as in triple-negative breast cancers and HER2 enriched tumours.

Key words: breast neoplasms, Ki-67 proliferation index, eestrogen receptor, Progesterone receptor, HER2

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Introduction

According to 2018 WHO reports, breast malignancy is the most common cancer among the female gender with the lifetime risk of 12%. It is followed by colorectal, lung, cervical and thyroid cancer as the most common cancers in women [1, 2]. The previous reports showed that breast cancer immuno-histochemical subtypes have a real impact on the disease prognosis and to the response to hormonal blockade treatment and chemotherapy. In 1983, Gerdes et al., described the Ki-67 protein, which is a nonhistone protein, works as a surfactant and helps the chromosomes to preserve discrete confirmations in a condensed state. If the Ki-67 coating layer is missing, during the metaphase of the cell cycle, the chromosomes remodelled into an unshaped or amorphous mass, where the cell division and replication will be compromised [3]. Ki-67 proliferation index significance has been widely studied, it is used as a diagnostic, prognostic and predictive marker in the

management of cancers originated in breast, pancreas, colon and prostate in addition to endometriosis [4–8]. Tumours that express a higher levels of Ki-67 proliferation index have a worse prognosis than tumors that express lower levels [9].

Material and methods

A total of 515 patients were included in this study. All the patients had an early/loco-regional breast cancer diagnosis in the period between 2014–2020. Informed consent from the patients was not necessary, however, the study results were a secondary outcome of a regional audit which was approved by the Institutional Review Board under the number GSART336. After the diagnosis, they underwent the recommended management. Patients with metastatic disease at presentation or not fit for curative management has been excluded. The medical records have been retrieved, the data related to the patients' demographics, tumour biological characteristics as histopathological subtype, immune-histo-chemistry (ER, PR, HER2) status and Ki-67 proliferation index values have been collected and analysed. The Ki-67 index level of 20%, was used as the cut-off point to differentiate between low and high Ki-67 expression. The statistical analysis has been performed using Chi-square test on excel, the calculated p-values of less than 0.05 were considered statistically significant.

Results

Our retrospective study was carried out on 515 patients with operable early invasive breast carcinomas. The age span of the cohort, ranges between 27–97 years, with a mean of 63 years. The different clinico-histo-pathological parameters of breast cancer varieties are shown in (Tab. 1). Among the 515 cases, 297 patients aged less than 70 years (57.6%) and 218 (42.3%) aged more than 70 years. In terms of the histopathological features, 436 cases (84.6%) were IDC, NST (invasive ductal carcinoma, of no special type), 48 tumours showed invasive lobular carcinoma (ILC) (9.3%), 12 (2.3%) cases were papillary carcinoma and 9 (1.7%) patients had mucinous carcinoma. About 49% (254) of the cases were grade II, 32% (166) grade III and about 18.4% (95) were grade I tumours (Tab. 1). With regard to the female sex hormone expression, the ER (Oestrogen receptor) positive expression tumours were 72.6% and PR (progesterone receptors) positive expression detected in 58% of the cases. Approximately 17% of tumours were HER2+ (score 3+ or amplified FISH test), where 18% of cases were triple-negative phenotype. We have used 20% as the cutting point for Ki-67 proliferation expression. Ki-67 nuclear positivity of ≥ 20 % was detected in 52% (262) of the cases (Tab. 1). We have classified the 515 cases according to the available immune-phenotyping results into four groups: 1) luminal-A like (ER-positive or PR-positive and HER2-negative), 2) luminal-B like (ER-positive and/or

Table 1. Tumour characteristics and its relation to different immuno-histochemical subtypes, % (n)

Criteria	All	Luminal A-Like	Luminal B-like	HER2 Enriched	Triple-negative	P value
Age (years)						
< 70	57.6% (297)	23% (117)	18% (93)	4.85% (25)	12% (62)	0*
≥ 70	42.3% (218)	19.2% (99)	15.1% (78)	2.3% (12)	5.6% (29)	
Tumour grade						
G I	18.4% (95)	15% (78)	02.9% (15)	0	0.38% (2)	< 0.00001
G II	49% (254)	25% (128)	18% (95)	02.3% (12)	03.7% (19)	
G III	32% (166)	2% (10)	12% (61)	4.85% (25)	13.4% (70)	
Ki-67						
< 20%	48% (249)	42% (216)	2.9% (15)	1.9% (10)	1.7% (9)	0.0003
≥ 20%	52% (266)	–	30% (156)	5.2% (27)	16% (82)	
Histological subtype						
IDC, NST	84.6% (436)	33% (172)	29% (151)	06.6% (34)	15% (79)	< 0.0001
ILC	09.3% (48)	06.6% (34)	2% (10)	0	0.77% (4)	
Papillary	02.3% (12)	0.77% (4)	1.1% (6)	0.2% (1)	0.2% (1)	
Mucinous	1.7% (9)	1.1% (6)	0.6% (3)	0	0	
Others	2% (10)	0	0	0.2% (1)	1.7% (9)	

PR-negative and HER2-positive or HER2 negative with high Ki-67 levels), 3) HER2 enriched (ER-negative, PR-negative and HER2-positive), and (4) triple-negative (ER-negative, PR-negative, HER2-negative), the cases distribution in the cohort was 42%, 33%, 8%, and 17.6% of the cases, respectively (Tab. 2).

As showed in (Fig.1), luminal B-Like breast cancers showed the highest proportion of high Ki6-7 index value, 30.3 % (156) of the cohort, followed by triple-negative breast cancer, 15.9% (82), and the least was Her2 enriched subtype, 05.2% (27). Nonetheless, luminal A-Like cancers showed the highest proportion of low Ki6-7 index value, 42% (216), followed by luminal B-Like cancers with 02.9% (15), triple-negative breast cancers were 01.7% (n = 9) and HER2 enriched tumours were 1.9% (n = 10). Our data discloses a statistically significant correlation between tumour grade and Ki-67 proliferative index levels among the different histopathological tumour subtypes (P values of 0 < 0.00001).

Table 2. Ki-67 proliferation index and breast cancer phenotypes

Breast cancer IHC subtype	Low Ki-67 % (n)	High Ki-67 % (n)
Luminal A Like	42 (216)	–
ER+VE, PR+VE, HER2-VE		
ER+VE, PR-VE, HER2-VE		
Luminal B Like	02.9 (15)	30.3 (156)
ER+VE, PR+VE, HER2+VE		
ER+VE, PR-VE, HER2+VE		
ER+VE,PR+VE,HER2-VE		
Triple-negative		
ER-VE, PR -VE, HER2-VE	01.7 (9)	15.9 (82)
Her2 Enriched		
ER–VE, PR–VE, HER2+VE	01.9 (10)	05.2 (27)

Discussion

Breast cancer is regarded as a heterogeneous disorder, tumour detailed assessment and categorization into certain immuno-histochemical subtype based on molecular studies is recommended to predict disease prognosis and facilitate management decisions and planning. In addition to the Ki-67 proliferation index, many other biomarkers and online tools have been utilised to assess the prognosis and disease recurrence prediction. These biological criteria include ER (Oestrogen Receptor) expression, PR (Progesterone Receptor) expression, HER2 (*Human Epidermal Growth Factor Receptor — type 2*) expression, and Oncotype DX recurrence score, where the online tools include; NPI (Nottingham Prognostic Index) and PREDICT (Tab. 3). This is required to identify cases associated with a sufficiently high risk of disease relapse to warrant them adjuvant chemotherapy and prolonged hormonal manipulation treatment if appropriate. Assessment of the Ki-67 proliferation index is based on IHC (immune-histochemical) staining of the tumour cells for the Ki67 protein, it is detected in the active course of the cell cycle (Late G1, S, G2, and M), and not detected during

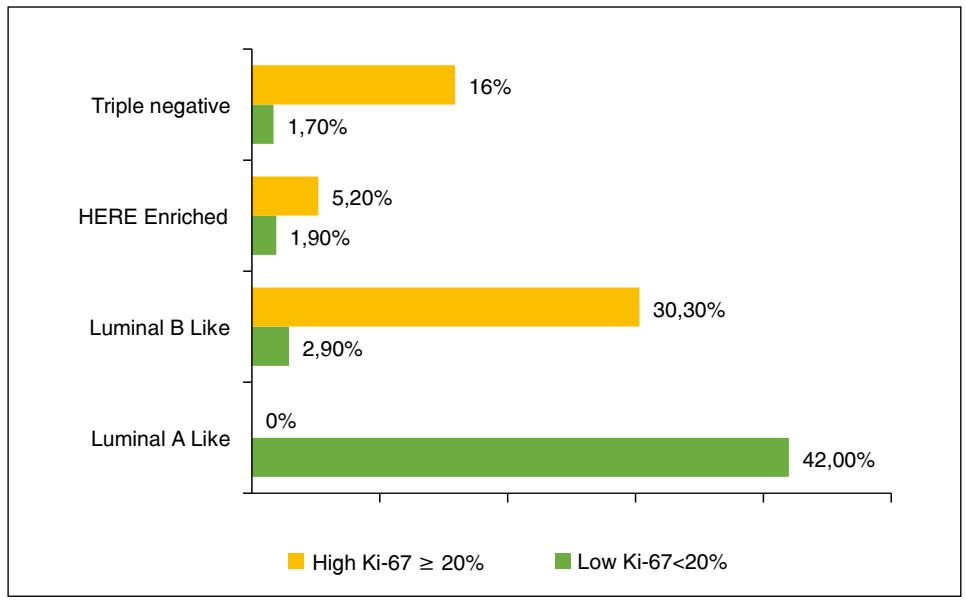

Figure 1. Ki-67 proliferation index value in different subtypes of breast cancers based on immuno-histo-chemistry classification

G0 and early G1 [1, 10, 11]. The Ki-67 proliferative index has value in cancer diagnosis as a cell proliferation indicator, the cancer tissues show a significantly higher expression of Ki-67 proliferative index than in healthy tissues [6]. Nagao et al., in 2011, presented a cohort of 119 patients treated for prostate cancer, the paper concluded that the Ki-67 proliferation index is an independent factor for survival rate, this included tumour grade and stage [12]. Nielsen et al., in 2013, published a result of a prospective 190 patient cohort with primary cutaneous melanoma. Also, this study concluded that Ki-67 proliferation index was a strong prognostic marker in primary cutaneous melanoma [7]. Some recent studies revealed that the administration of antibodies targeted against the Ki-67 protein was shown to result in a slower rate of cell division. This fact makes Ki-67 a promising factor for targeted molecular cancer therapy. ASOs (Antisense oligonucleotide) are small-sized single-stranded nucleic acids that are used as Ki-67 peptide nucleic acid antagonists affects the cancer cells proliferation and apoptosis [13]. Another field where the Ki-67 proliferation index could be useful is monitoring the tumour response to upfront chemotherapy prior to surgery, Mukai et al, in 2014, in research related to 237 HER2 positive breast cancer patients. The response to upfront chemotherapy was assessed using pre-chemotherapy, mid-chemotherapy (3 cycles of paclitaxel and trastuzumab) and postoperative Ki-67 proliferation index. The cohort divided into the control arm or the Ki-67 response-guided arm (Ki-67 arm).

The control arm continued the same treatment regardless of the achieved result of the Ki-67 proliferation index, where Ki-67 arm group further treatment was modified according to the interim Ki-67 index. They have found that there was a linear correlation between the Ki-67 proliferation index reduction rate at interim evaluation and the pathological complete response to upfront chemotherapy [14]. In addition to its diagnostic

Table 3. Conventional and genomic prognostic factors as well as online prognostic tools [1]

Patient factors	Age
	Gender
	Fitness for treatment
	Patient compliance
Tumour factor	Size
	Histological subtype
	Histological grade
	Axillary lymphadenopathy
	Lympho-vascular invasion
	Extra-capsular extension
IHC	ER
	PR
	HER2
	Ki-67 Proliferation index
Genetic mutations	BRCA1
	BRCA2
	TP53
Genomic tests	Oncotype DX
	MammaPrint
Online tools	NPI(Nottingham Prognostic Index) PREDICT

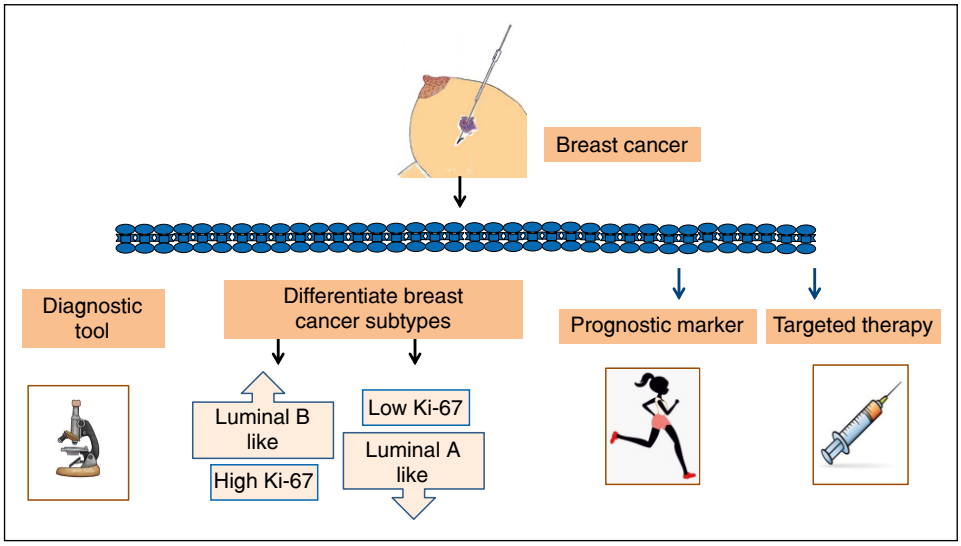

Figure 2. Current and potential future utilization of Ki-67 proliferation index in cancer management

Table 4. Breast cancer molecular subtypes and their criteria [15, 17–19, 25]

Breast cancer subtype	Sex hormone, HER2 and cytokeratins expression	Incidence	Ki-67	Grade	Prognosis
Luminal A	ER+VE and/or PR+VE, HER2-VE, CK5/6–VE, Keratin 8/18+VE	71%	Low	Low	Good
Luminal B	ER+VE and/or PR+VE, HER2+VE, CK5/6–VE, Keratin 8/18	8%			
Luminal B-like	ER+VE, any PR, HER2-VE with high K-i67		High		
Triple-negative "Basal-like"	ER-VE, PR -VE, HER2-VE, CK5/6+VE	15%		High	Poor
HER2-enriched	ER–VE, PR–VE, HER2+, CK5/6–VE	6%		High	Poor
Normal breast-like group	Not classified				

and prognostic value, Ki-i7 proliferation index is used to differentiate between Luminal A-like and Luminal B-like subtypes in ER+VE/HER2–VE breast cancer (Fig.2). The main histological breast cancer subtypes have been identified according to ER (oestrogen receptor), P R (progesterone receptor), and HER2 (*Human Epidermal Growth Factor Receptor — type 2*) expression (Tab. 4). Additional molecular classification is based on gene expression profile studies also is increasingly used to categorize different molecular subtypes of breast cancer. The subtype luminal type A which is the most frequent identified breast cancer subtype is strong ER+VE and/or PR+VE/HER2-VE status. These tumours are known to be of a low histological grade tumour, and usually associated with a good prognosis, it forms about 71% of breast cancers, likely to benefit from hormonal blockade treatment and may benefit from chemotherapy [15, 16] in our cohort, luminal A-like tumours are encountered in 42% of cases. The luminal B subtype is weak/moderate ER+VE and/or PR+VE with HER2+VE (overexpression or amplification), this subtype has higher Ki-67 levels than luminal A tumours, and it is encountered in about 8% of breast cancers. These tumours are likely to benefit from neo/adjuvant chemotherapy and may benefit from hormonal manipulation therapy in addition to the HER2 targeted treatment [17]. Luminal B-like tumours are ER+VE and/or PR-VE with HER2-VE expression, however, has a high Ki-67 index value. The basal-like breast cancer (BLBC), given this name as they are characterized by high expression of genes characteristic of normal breast tissue basal epithelial cells as CK 5/6, CK14, CK15 and CK17. Most of them (but not all) are triple-negative breast cancer (i.e. has a receptor expression ER-VE, PR–VE, HER2–VE), encountered frequently in young premenopausal patients with high BMI. They are high-grade tumours, forms about 15% of all invasive ductal carcinoma of no special type, associated with an aggressive clinical course, often relapsing rapidly either loco-regional or as a distant metastatic disease and linked to a high mortality rate [18–20].The HER2-E (HER2 enriched) subtype tumors have HER2+VE/ER-VE/PR-VE expression, these tumours are less common however some of them are characterized by high-grade histology and poor prognosis [21]. A recent systematic review and meta-analysis published by Schettini et al. from Naples, Italy in 2020, the paper stating that HER2-E tumours are associated with a higher likelihood of achieving a complete pathological response following neoadjuvant anti-HER2-based therapy [22]. Some previous reports has stated that, the triple-negative breast cancer is associated with the highest Ki-67 index values, where the HER2 positive tumours were in second place. Looking at the histological subtypes, the observations revealed that the metaplastic and medullary breast cancers showed a significantly higher Ki-67 proliferative index as compared to invasive ductal carcinoma, NST [23, 24]. Our cohort showing that luminal B-like cancers has the highest Ki-67 index values (30%), followed by triple negative breast cancer (16%). Perez-Lopez et al., in 2016, presented a series of 680 patients, using the Saint Gallen criteria, the cohort was divided in IHC subtypes. The prognosis of the groups was analysed. It was found the luminal B N0 had the most unfavorable prognosis, the other criteria which were associated with this group are those of the luminal B tumours as PR negative, HER2 positive as well as high Ki-67 proliferation index expression [24]. Our results show that in addition to the luminal B-like cancers, other subtypes of breast cancer also has high Ki-67 index values, these subtypes include triple-negative breast cancer (16%) and HER2 enriched tumours (5.2%). These tumours are less common than luminal A tumours, however, some of them are characterized by high-grade histology and poor prognosis. These findings are in accordance with the published researches data.

Conclusion

Generally, this data showed that the majority of the cases of low Ki-67 index expression belongs to the luminal A-like group, where the majority of cases with a high Ki-67 index expression are of non-luminal A-like

subtype as luminal B-Like and triple-negative tumours ($P < 0.00001$). The Ki-67 level is regarded as a helpful biomarker in breast cancer management, its expression is strongly associated with disease aggressiveness and prognosis, also it has an additional value, currently is considered as a promising therapeutic target in breast cancer.

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VIA MEDICA

ORIGINAL ARTICLE

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Cost-effectiveness of levosimendan in patients with exacerbation of chronic heart failure — a single-center perspective

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ABSTRACT

Introduction: Heart failure (HF) places a significant economic burden on the health care system all over the world mainly due to frequent and repetitive hospitalizations. Thus, there is a need for both cost-effective and efficient therapeutic options. The aim of the study was to describe the economic aspect of levosimendan treatment in hospitalized HF patients in one major Polish cardiology unit.

Material and methods: Retrospective observational study included 1086 patients with exacerbation of chronic HF, admitted to the Cardiology Department, University Hospital No 1 in Bydgoszcz, Poland in 2018–2020. We analyzed the cost of therapy, cost and the length of stay of 1057 hospitalizations of patients receiving standard therapy (ST) only and 29 hospitalizations of patients receiving levosimendan (Levo) on top. Levosimendan was used in patients not responding to standard therapy, mostly as a drug of the last chance.

Results: The mean length of hospital stay for the ST patients was 9.4 days compared to 29.1 days for the Levo group. The median total cost of hospitalization of patients receiving ST was significantly lower compared to Levo group [PLN 6,612.5 (IQR 3,624.9—13,301.3) vs PLN 23,854.9 (IQR 10,900.4–40,391.5), $p < 0.001$]. On the other hand, the median daily cost of hospitalization did not differ between the ST and Levo group [PLN 772 (616.4–1,629) vs PLN 1,010.5 (IQR 787.4–1,172), $p = 0.1$]. The total cost of treatment was significantly lower only in the ST subgroup hospitalized for less than 2 weeks compared to the Levo group ($p = 0.008$). An early decision of levosimendan introduction (up to 8 days) resulted in a shorter hospitalization time compared to later drug administration (21 days vs 42 days; $p = 0.019$).

Conclusions: Early administered levosimendan in HF exacerbation seems to be cost-effective in Polish clinical and economic settings. Despite the high cost of drug acquisition, it may provide better outcomes at lower overall costs of HF patient management. A randomized trial will be necessary to address this issue in Poland.

Key words: decompensated heart failure, cost, levosimendan

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Introduction

Despite various treatment options available, heart failure (HF) remains a significant public health problem, with an incidence of up to 37.7 million patients worldwide [1]. It significantly affects life expectancy and deteriorates the quality of life. Moreover, it contributes to the high costs for the health care system. Exacerbation of chronic HF is one of the most common causes of patient rehospitalization that significantly rises health expenditure. Hospitalizations for HF account for 1–2% of all hospital admissions. It is estimated that the total cost of treating patients with HF in the USA will increase from USD 20.9 billion in 2012 to USD 53.1 billion by 2030 [2]. According to data analysis [3], in 2012 the total cost of treating patients with heart failure added up to 108 billion dollars, 60% of which was allocated directly to treatment costs.

Moreover, the treatment of HF remains a substantial challenge for health providers, aimed at improving symptoms and reducing mortality of these patients. The management of HF often requires the administration of multiple agents that act on different processes. Levosimendan — an inodilator introduced recently to clinical practice seems to be the one that compromises multiple desired effects on HF exacerbation. In patients with HF, where the positive inotropic effect and the vasodilating capacity are important, the drug increases the force of heart contraction with reduced preload and afterload without increasing myocardial oxygen demand [4], irrespectively to previous beta-blockers intake. The randomized trials have shown that the drug is effective in reducing the mortality of HF patients [5–7]. Unfortunately, the acquisition cost of the levosimendan is relatively high when compared to other standard drug regimens, eg. dobutamine. Several studies have described the cost-effectiveness of levosimendan therapy in HF patients compared to standard options [8–10]. However, the costs of hospitalization due to HF vary from country to country.

Taken into account a significant health and economic burden of HF on society, there is a need for cost-effective therapeutic options that improve symptoms, reduce rehospitalizations and in-hospital mortality of HF patients. The aim of our study was to describe the economic aspect of levosimendan therapy of HF patients from the perspective of a major Polish cardiology unit. Our analysis was prepared as a pre-trial to build the premises addressed for a randomized clinical trial evaluating the cost-effectiveness of early administration of levosimendan in HF exacerbation.

Material and methods

In this single-center retrospective observational study we included 1086 patients with exacerbation of chronic HF, admitted to the Cardiology Department, University Hospital No 1 in Bydgoszcz, Poland. Patients were hospitalized from 1 January 2018 to 31 December 2020. Exacerbation of HF was diagnosed and managed in accordance with dedicated guidelines of the European Society of Cardiology. The exact costs of each hospitalization were obtained from a dedicated hospital information system. We analyzed the cost of therapy, cost of hospitalization, the length of stay in 1057 hospitalizations of patients receiving standard therapy (ST) for HF exacerbation and 29 hospitalizations of patients receiving levosimendan (Levo). The analysis excluded patients who underwent invasive procedures such as percutaneous coronary intervention (PCI) or implantation of a cardioverter-defibrillator (ICD) during the hospitalization.

The routine practice of introducing levosimendan in HF exacerbation approved in our center was the situation of the inefficacy of ST, including inotropic agents or in cases when the use of drugs with a positive inotropic effect should be considered. The decision of the use of levosimendan was at the discretion of the treating physician.

The normality of the distribution was verified using Shapiro-Wilk test. Continuous variables are presented as median and interquartile range (IQR) or mean ± standard deviation (SD), categorical variables as absolute frequencies and percentages. The comparison between two variables was performed with Mann Whitney U test or appropriate t-Student test according to the distribution. For comparison of more than two variables, Kruskal — Wallis test or ANOVA was used regarding the normality of data distribution. The two-sided p value < 0.05 was considered significant. STATISTICA version 13.1 was used to perform the analyses.

Results

The characteristics of the study groups are presented in Table 1. In the Levo group, there were significantly more patients with diabetes and arterial hypertension. This group also manifested significantly lower left ventricular ejection fraction together with a higher concentration of B-type natriuretic peptide.

The mean length of hospital stay for the ST patients was 9.4 days compared to 29.1 days for Levo group. The median total cost of hospitalization of patients receiving ST was significantly lower compared to Levo group [PLN 6,612.5 (IQR 3,624.9–13,301.3) vs PLN 23,854.9 (IQR 10,900.4–40,391.5), $p < 0.001$]. On the other hand, the median daily cost of hospitalization did not differ between the ST and Levo group [PLN 772 (616.4–1,629) vs PLN 1,010.5 (IQR 787.4–1,172), $p = 0.1$]. The mean cost of levosimendan acquisition was PLN 7,492.47. The mean cost of hospitalization before the drug administration was accounted for PLN 6,730.84.

Treatment costs were compared depending on the length of hospitalization. Interestingly, the total cost of treatment was significantly lower only in the ST subgroup hospitalized for less than 2 weeks ($p = 0.008$). A detailed description of costs depending on the hospitalization period is presented in Table 2.

When analyzed the Levo patients, the drug was administered on average on day 8.3 from the beginning of hospitalization. Thus, we compared the cost of hospitalization between the two subgroups: group 1 ($n = 18$) that received the drug up to the 8th day of hospitalization and group 2 ($n = 11$) received the drug

Table 1. Study group characteristics

	Levosimendan, n = 29	Standard therapy, n = 1057	p-value
Age, years (+/– SD)	73.2 (9.7)	71 (12.4)	0.5
Females, n (%)	7 (24.1)	230 (21.7)	0.7
Arterial hypertension, n (%)	25 (86.2)	672 (63.6)	0.02
Diabetes mellitus, n (%)	18 (62.1)	375 (35.4)	0.006
History of infarction, PCI or CABG n (%)	21 (72.4)	720 (68.7)	0.6
EF LV %, median (IQR)	25 (20–33)	31 (27–38)	0.003
eGFR (estmated glomerular filtration rate) < 30 mL/min/m^2, n (%)	5 (17.2)	130 (12.3)	0.5
BNP (B-type natriuretic peptide) pg/mL; median (IQR)	1,513.4 (874.0–2,415.0)	758.7 (252.2–1,944.75)	0.01

Table 2. Total costs of hospitalization depending on the length of stay in the Levo group vs ST group. Total costs are presented as median (IQR)

Length of hospitalization (days)	Levosimendan (n)	Levosimendan — total cost, PLN	Standard therapy (n)	Standard therapy — total cost, PLN	p-value
0–14	10	9,933.2 (7,916.8–12,743.9)	877	5,439.9 (2,861.2–10,141.8)	0.008
15–30	7	16,289.1 (14,693.9–22,522)	139	13,582.3 (10,489.0–22,407.8)	0.4
31 and more	12	42,159.6 (38,543.3–64,346.9)	41	36,223.2 (26,229.8–81,762.1)	0.3

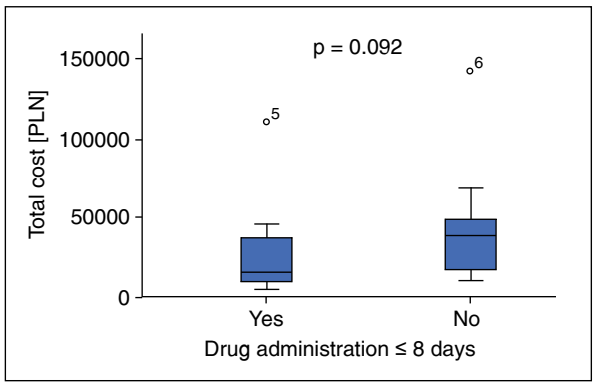

Figure 1. Total cost of hospitalization depending on the time of levosimendan administration (median with IQR)

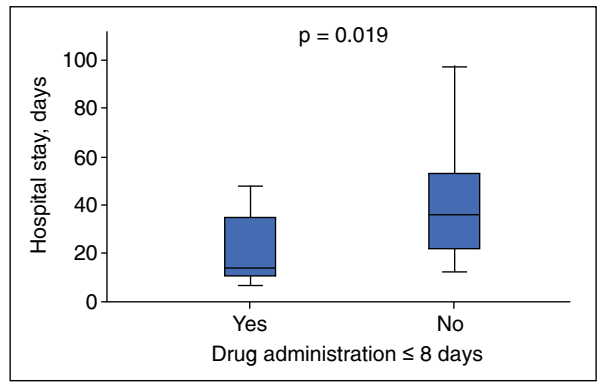

Figure 2. Length of hospital stay in reference to the time of levosimendan administration (median with IQR)

after the 8th day of hospitalization. We have noticed a trend towards significantly lower total median cost of hospitalization in the group 1 vs the group 2 [PLN 16,057.9 (IQR 9,928.5–37,978.34) vs PLN 39,108.3 (IQR 17,375–49,556); p = 0,09] (Fig. 1). The difference of median daily cost between these groups was not significant [PLN 1,033 (IQR 795–1,239) vs PLN 1,002 (IQR 721–1,081), p = 0.4]. The median length of hospital stay was significantly shorter in group 1 [14 (IQR 11–35) days vs 36 (IQR 22–53); p = 0.019] (Fig. 2). Importantly, the subgroups did not differ in baseline parameters, including age, ejection fraction and BNP concentration (p = 0.5).

Discussion

Our observation showed that in the Polish clinical setting and health care system the early administration of levosimendan in patients with HF exacerbation might be associated with favorable economic and health effects.

In our analysis, the Levo group was hospitalized significantly longer when compared to the ST group, together with the higher total cost of therapy. In addition, we noticed a trend towards higher hospitalization costs in patients who received the drug later; these patients were also hospitalized longer. It must be noted that patients receiving levosimendan were more likely to be diabetic and hypertensive, they manifested more severe HF based on lower LV EF and higher BNP concentration. Such conditions and co-morbidities usually demand additional therapies and treatment modalities as well as are correlated with a longer hospital stay. Additionally, levosimendan in our group was added to treatment in situations where conventional therapy was insufficient, often as a last chance therapy. The abovementioned factors may contribute to an increase in resource utilisation and influence our results in reference to incremental costs of the therapy. It is supported by the fact that the daily cost of therapy did not differ between the groups.

Although the cost of levosimendan therapy was higher when the hospitalization lasted up to 2 weeks, in case of longer hospitalization the costs of ST and Levo were comparable. It suggests that if levosimendan was administered later and when the previous therapy was ineffective, this management relatively increased the total costs. The costs were derived not only from the drug itself but also from la onger hospital stay. The cost of treatment until levosimendan administration is also a significant part of the total cost of hospitalization. Therefore our observations support the positive effect of levosimendan both on the clinical and economic outcome and offer preliminary evidence of its cost-effectiveness. When the drug is administered earlier during the hospitalization, it influences the clinical improvement thus reducing the hospitalization period.

Our observations are consistent with other studies that addressed the economic issue and clinical benefit of levosimendan therapy. The LIDO trial showed that the use of levosimendan instead of dobutamine was associated with a reduction in mortality without an increase in the need of hospitalization [6]. Although the difference in absolute drug costs was relatively high, the cost per life-year saved was acceptable from a longer perspective [6]. The study of Fedele et al confirmed that the initial levosimendan treatment for HF was associated with a reduced duration of hospital stay and fewer re-hospitalizations [9]. In REVIVE II trial, patients treated with levosimendan had a shorter length of stay and lower cost for the initial hospital admission relative to patients treated with placebo [11]. Interestingly, Nieminen et al showed that the use of levosimendan for HF decompensation provided savings for hospitals driven by the reduction in the length of hospital stay in every European country considered in the study (Italy, Spain, Greece, Germany, Sweden, Finland, Israel) [12].

Our study is limited mainly by single-center setting, retrospective character and small sample size in levosimendan group. From the global economic perspective, another limitation is the lack of follow-up and rehospitalization rate, as we analyzed the only in-hospital cost of a single admission. Despite these limitations, our analysis contributes substantial insight into the pharmaco-economic issue of levosimendan therapy in Poland. Although levosimendan might increase costs of hospitalization it may also extend the benefits of treatment on the quality of life, rehospitalization rates and survival, thus reducing the global HF burden on the health care system.

In conclusion, early administered levosimendan in HF exacerbation seems to be cost-effective in Polish clinical and economic settings. We believe that the early introduction of levosimendan in HF therapy may reduce the total cost of hospitalization as well as shorten the hospital stay, despite the high cost of drug acquisition. Nevertheless, new trials or registry studies will be necessary to address this issue in Polish health care settings.

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Disclosure of interest

The authors report no conflicts of interest.

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VIA MEDICA

ORIGINAL ARTICLE

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COVID-19 and diabetes: a deadly duo?

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ABSTRACT

Introduction: Among the patients with severe or fatal COVID-19 a high prevalence of comorbidities is noted, diabetes being one of them. The objective of the study was to analyse the relation of COVID-19 and diabetes in respect of their influence on hospitalization's length and outcome.

Materials and methods: The data acquired from the database of Antoni Jurasz University Hospital No. 1 in Bydgoszcz were analysed. The analysis included 1,051 adult COVID-19 positive patients that were hospitalized between March 14, 2020, and April 12, 2021. The collected data included a history of diabetes with differentiation between type 1 and type 2, hospitalization outcome (discharge or death), length of hospital stay.

Results: The prevalence of diabetes in the study group was determined to be 2.09% and 10.18% for diabetes type 1 and 2, respectively, totalling 12.27% (n = 129). Most of the patients (87.54%) have been discharged while 12.46% have died. The diabetic patients accounted for 11.63% of the discharges and 16.79% of deaths. The mortality rates in the group of insulin-dependent diabetes were the highest, namely 27.27% vs. 12.15% in the reaming study population (p = 0.0720). Hospitalization's length did not differ according to diabetes occurrence as on average it amounted to 15.90 days in diabetic patients and 14.44 days in non-diabetic ones.

Conclusions: COVID-19 and type 1 diabetes may constitute a deadly duo. Further studies that include patients with insulin-dependent diabetes are needed to better understand the impact of diabetes and COVID-19 on mortality and hospitalization's length.

Key words: SARS-CoV-2, coronavirus, mortality, length of stay, insulin-dependent, type 1 diabetes, type 2 diabetes

Med Res J 2021; 6 (2): 119–124

Introduction

Nowadays, in the era of coronavirus disease 2019 (COVID-19) global scientific efforts are centred around fighting and understanding the pandemic. More and more research are focused on the impact of concomitant diseases on the outcome and the course of the infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The influence of comorbidities on the severity of COVID-19 cannot be overstated. Among the patients presenting with severe illness and those who died due to the SARS-CoV-2 infection a high prevalence of concomitant diseases is noted, diabetes being one of them [1].

With a global prevalence of 463 million, diabetes is one of the most common chronic conditions worldwide [2]. Hence the diabetic population represents a large vulnerable group of COVID-19 positive patients. Diabetes, especially the most common non-insulin-dependent variant, diabetes type 2, is perceived as a risk factor for a poor outcome in patients with COVID-19 [3]. The proposed reasons for worse prognosis in diabetic patients include but are not limited to their specific characteristics, namely age, sex, and ethnicity, as well as other comorbid conditions including hypertension and obesity [1]. On that account, whether diabetes itself contributes to the infection remains controversial [4]. Nevertheless, possible pathophysiological mechanisms

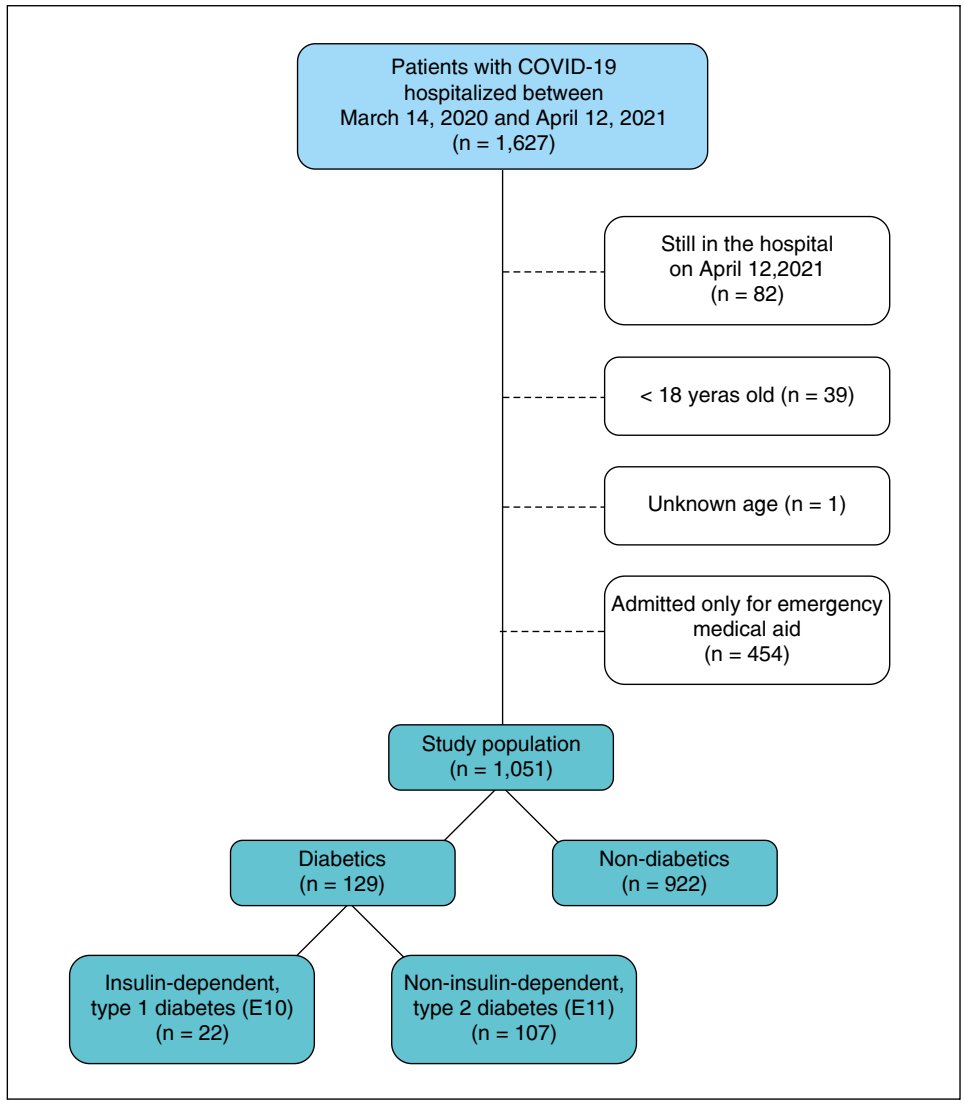

Figure 1. A flowchart of patients included in the analysis

are being proposed including immune response impairment [5]. The role of angiotensin-converting enzyme 2 is also being discussed [6]. The pro-coagulative and pro-inflammatory state exhibited by diabetic patients may be another reason for poor clinical outcome in this population [1]. However, the exact mechanisms are yet to be confirmed.

The matter of SARS-CoV-2 infection with concomitant diabetes still requires better understanding and intensive research to determine whether this combination constitutes a deadly duo. This paper aimed to analyse the relation of COVID-19 and diabetes, considering diabetes types 1 and 2, in respect of their influence on hospitalization's length and outcome with special regard to the issue of mortality. Prevalence of diabetes in COVID-19 positive patients was another objective of the study.

Materials and methods

The data acquired from the database of Antoni Jurasz University Hospital No. 1. in Bydgoszcz were analysed. The analysis included 1,051 adult COVID-19 positive patients that were hospitalized between March 14, 2020, and April 12, 2021. Patients who were still in the hospital at the time of data acquisition (April 12, 2021) were not included in the analysis. Patients under the age of 18 or unknown age, as well as those admitted to the hospital only for emergency medical aid were also excluded. A flowchart of the study is presented in Figure 1. The collected data included:

— history of diabetes defined by the 10th revision of the International Classification of Diseases (ICD-10) as insulin-dependent or type 1 diabetes mellitus (E10) and non-insulin-dependent or type 2 diabetes mellitus (E11);

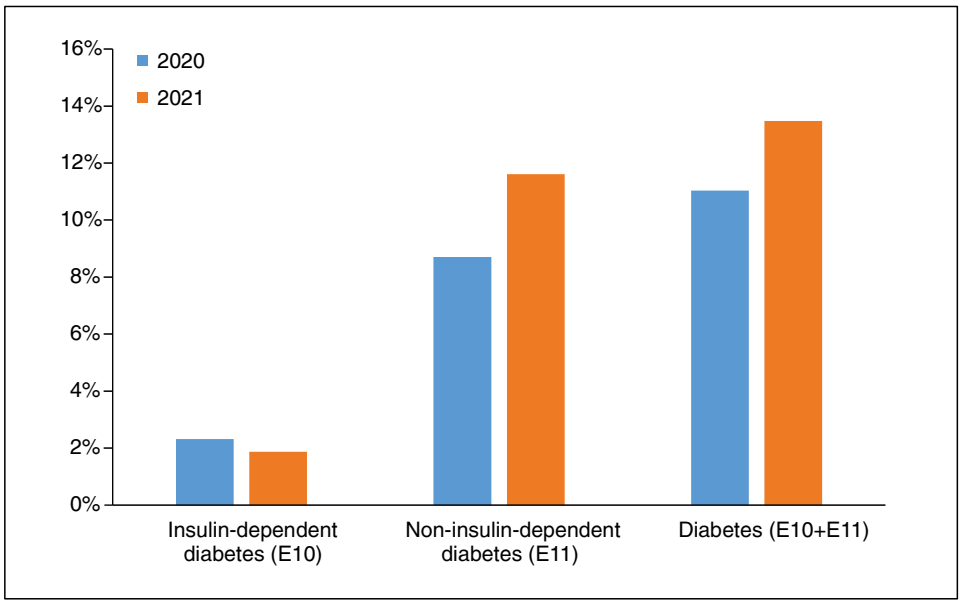

Figure 2. A comparison of diabetes occurrence in the study population between the years 2020 and 2021

Table 1. Hospitalization outcome according to the presence of diabetes and its types

		Discharge (n = 920)		Death (n = 131)	p
Insulin-dependent diabetes (E10)	n	16	n	6	0.0720
	%	1.74%	%	4.58%	
Non-insulin-dependent diabetes (E11)	n	91	n	16	0.4279
	%	9.89%	%	12.21%	
Diabetes (E10 + E11)	n	107	n	22	0.1053
	%	11.63%	%	16.79%	

— hospitalization outcome: discharge or death;
— length of hospital stay.

The statistical analysis was carried out using the Statistica 13.0 package (TIBCO Software Inc, California, USA). Continuous variables were presented as means with standard deviations and medians with interquartile ranges. The Shapiro-Wilk test demonstrated the non-normal distribution of the investigated data. Therefore, for comparison of continuous variables between subgroups nonparametric Mann-Whitney unpaired rank-sum test was used. Categorical variables were expressed as the number and the percentage. Categorical variables were compared using the $\chi 2$ test. Results were considered significant at $p < 0.05$.

Results

Of the 1,051 patients included in the analysis, 22 (2.09%) had insulin-dependent diabetes (E10) and 107 (10.18%) had non-insulin-dependent diabetes (E11), totaling to 129 (12.27%) cases of diabetes (E10 + E11) in the study population (Fig. 1). The comparison of 2020 and 2021 periods regarding the occurrence of diabetes did not yield statistically significant differences ($p = 0.2242$), meaning the prevalence of diabetes did not differ between the patients hospitalized in 2020 (n = 517) and 2021 (n = 534) as it was found to be 11.03% and 13.48%, respectively. In a separate analysis of insulin-dependent and non-insulin-dependent subgroups, statistically significant differences were not found either. The comparison of diabetes occurrence in 2020 and 2021 among the study population is presented in Figure 2.

An analysis of the hospitalization outcome in COVID-19 positive patients indicated that 920 (87.54%) of the patients have been discharged and 131 (12.46%) have died. The data were evaluated regarding diabetes type subgroups as shown in Table 1. In the case of insulin-dependent diabetes (E10) a pronounced, yet not deemed statistically significant, difference in its outcome contribution was noted as it constituted 4.58% of deaths and only 1.74% of discharges.

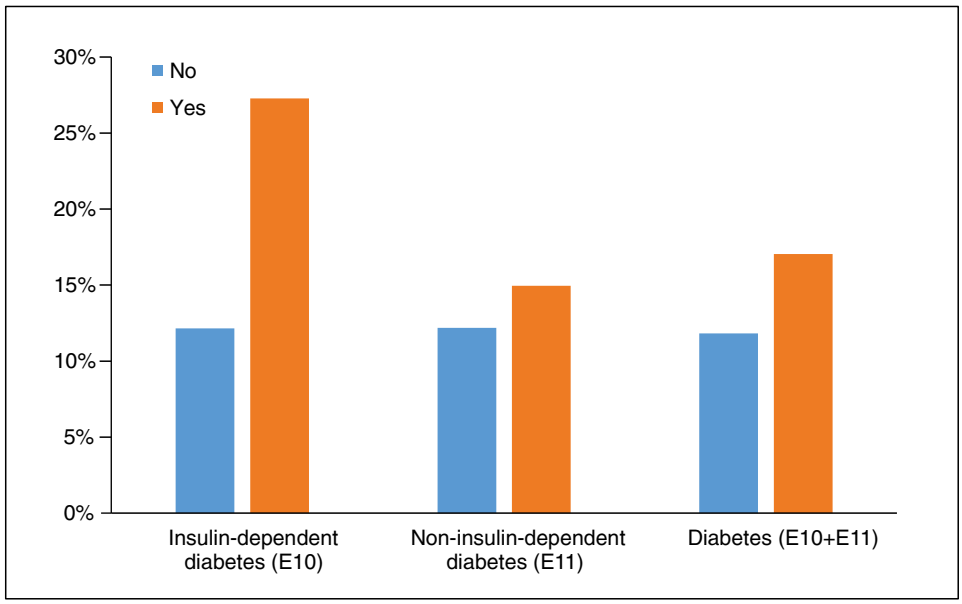

Figure 3. Mortality rates according to the presence of diabetes and its types

Table 2. Length of hospital stay according to the presence of diabetes and its types

	Length of hospital stay [days]						p
	n	Mean	SD	Median	Q1	Q3	
Insulin-dependent diabetes (E10)							
No	904	14.63	25.22	11.50	5.00	16.00	0.9481
Yes	16	13.31	10.73	12.00	9.50	16.00	
Non-insulin-dependent diabetes (E11)							
No	829	14.42	23.77	11.00	5.00	16.00	0.2937
Yes	91	16.35	34.63	12.00	7.00	16.00	
Diabetes (E10 + E11)							
No	813	14.44	23.96	11.00	5.00	16.00	0.3151
Yes	107	15.90	32.18	12.00	7.00	16.00	

A more detailed analysis of hospitalizations that ended in patient's death (n = 131) was performed to determine the mortality rates according to the presence of diabetes, which are shown in Figure 3. The mortality rates in the group of insulin-dependent diabetes (E10) patients were found to be the highest among all the analysed subgroups, namely 27.27% vs. 12.15% in the reaming study population (p = 0.0720).

The data on the length of hospital stay were acquired and analysed for the patients whose hospitalization ended in discharge (n = 920) as presented in Table 2. The average length of hospitalization for patients with any type of diabetes was determined to be 15.90 days vs. 14.44 days for the COVID-19 positive patients without diabetes (p = 0.3151). Considering specific types of diabetes separately, the patients with insulin-dependent and non-insulin-dependent diabetes on average stayed in the hospital for 13.31 and 16.35 days, respectively. No statistically significant differences were found between the groups and subgroups of patients with diabetes and the rest of the study population without it.

Discussion

The present study constitutes a much-needed attempt at analysing the relationship between COVID-19 and diabetes regarding hospitalization's length and outcome. The inclusion of type 1 diabetes patients into this analysis was found to be one of its strong points since most currently available studies only relate to type 2 diabetes. Other distinguishing features of

the present study in the context of available publications include a longer analysis period and a relatively large number of patients for a single centre study.

The prevalence of diabetes among patients with COVID-19 has been analysed in several mostly single centre studies. Seiglie et al. [3] found that in March-April 2020 period at the Massachusetts General Hospital 178 out of 450 (39.6%) COVID-19 patients had diabetes. It is noted that most of the diabetic patients had type 2 diabetes, with only two cases of type 1 diabetes. A one-month-long study (February 26, 2020, to March 26, 2020) conducted by Akbariqomi et al. [7] in a hospital in Iran found that 1 in 4 COVID-19 patients had diabetes (148 of 595; 24.9%). In a study by Vargas-Vázquez et al. [8] based in a Mexican COVID-19 centre during the March-July period of 2020, 50.2% of patients had type 2 diabetes (159 out of 317), with more than one-third of them being previously undiagnosed. However, such a high rate may have been a result of strict patient inclusion criteria as 600 patients were excluded due to e.g., lack of HbA1c measurement on admission. On the other hand, Wang et al. [9] determined the prevalence of diabetes to be 1.7% as it was present in 126 out of 7,283 severe or critically ill COVID-19 positive patients in Wuhan hospitals as of February 25, 2020. Similarly, a low occurrence was reported by You et al. [10] in a study based on the National Health Insurance Service database in Korea in which between January and March of 2020 out of 5,473 analysed patients 495 (9.04%) had type 2 diabetes. A wide variance in diabetes prevalence among COVID-19 patients presented in the aforementioned publications and the present paper could be a reflection of diverse populations from different geographic locations as well as the exclusion and inclusion criteria chosen for each of the studies. Notably, most of the available analyses either do not differentiate diabetes type or only consider type 2 diabetes.

This study results suggest that in the case of concomitant type 1 diabetes, COVID-19 positive patients may demonstrate higher mortality rates. The relation of SARS-CoV-2 infection and diabetes is currently being extensively researched with several studies aiming to establish the mortality rates in COVID-19 patients with diabetes versus those without. You et al. [10] determined the above-mentioned rates to be 5.7% and 1.1% ($p < 0.0001$), respectively, with type 2 diabetes patients presenting with poorer clinical outcomes e.g., higher incidence of pneumonia. In a study by Seiglie et al. [3] the diabetic group was characterized by a higher proportion of mechanical ventilation and admissions to the intensive care unit. The mortality rates among diabetic COVID-19 patients at 14 days were determined to be 15.9% vs. 7.9% ($p = 0.009$) in non-diabetic patients. Based on those results diabetes has been hailed as a risk factor for poor early outcome in COVID-19 patients. A longer observation period of 30 days yielded comparable results and conclusions since the mortality was significantly higher in patients with type 2 diabetes than in the group without (13.6% vs 8.7%; $p < 0.001$) as reported by Sonmez et al. [11]. Moreover, pre-diabetes and undiagnosed type 2 diabetes were also found to be risk factors for severe SARS-CoV-2 infection [8].

The aforementioned studies pertain to either diabetes in general or type 2 diabetes only. The data on type 1 diabetes specifically are far more limited. A UK nationwide study by Ruan et al. [12], which aimed to assess the clinical characteristics and risk factors of adults with both COVID-19 and type 1 diabetes, reported 53 deaths among 194 analysed patients, constituting a mortality rate of 27.32%. This result is very much consistent with the rate of 27.27% determined in this study. Yet, in this analysis, the diabetic group was not compared to a non-diabetic one. Two separate whole-population studies, one conducted in Scotland [13], one in England [14], found that both diabetes type 1 and 2, when adjusted for characteristics such as age, were independently associated with increased risk of fatal COVID-19 compared to the non-diabetic population (Scotland: OR = 2.396 in type 1, OR = 1.369 in type 2; England: OR = 3.51 in type 1, OR = 2.03 in type 2). Interestingly, the multicentre French CORONADO study [15] reported that the primary outcome of tracheal intubation for mechanical ventilation and/or death within 7 days of admission was not affected by diabetes type, meaning there were no differences between diabetes types 1 and 2 in respect of COVID-19 outcome. However, out of 1,317 participants, the study included only 39 patients with insulin-dependent diabetes.

According to these results, the length of hospitalization was not affected by the presence of diabetes. Contrastingly, in a nationwide study based on the Turkish Ministry of Health database, Sonmez et al. [11] reported a significantly higher rate of prolonged hospitalization, defined as a hospital stay of more than 8 days, among 9,213 patients with type 2 diabetes. The median length of hospital stay in the entire study population of 18,426 patients hospitalized for COVID-19 was 8 days. However, the patients with type 1 diabetes were excluded from this analysis. Several single centre studies are consistent with those results. Al-Salameh et al. [16] found the median length of stay to be longer in the case of COVID-19 patients with diabetes (17.1 ± 11.7 days) than in those without (13.5 ± 9.1 days). In this study the group of diabetic patients composed of type 2 diabetes in 96.5%. Alkundi et al. [17] reported comparable results with the length of hospitalization of diabetic and non-diabetic COVID-19 patients of 14.4 ± 9.6 and 9.8 ± 17.1 days, respectively. Here the structure of the study population regarding the type of diabetes was

similar to the one presented in this study as 12.65% of diabetic patients had type 1 diabetes. Most available publications report a significantly longer time of a hospital stay among diabetic versus non-diabetic COVID-19 patients.

Some of the limitations of this study include not considering other comorbidities and patients' characteristics such as age that could have impacted the length of hospital stay and its outcome.

Conclusions

— COVID-19 and type 1 diabetes may constitute a deadly duo characterized by higher mortality rates than in the non-diabetic population.
— Further studies that include patients with type 1 diabetes are needed to better understand the impact of diabetes and COVID-19 on mortality and hospitalization's length.

Statement of competing interests: *The authors report no competing interests.*

List of abbreviations: *COVID-19 — coronavirus disease 2019*
SARS-CoV-2 — severe acute respiratory syndrome coronavirus 2

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REVIEW ARTICLE

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COVID-19 and the economy: job loss and economic shutdown

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ABSTRACT

The COVID-19 pandemic devastated several countries across the globe, having economic, social, and health impacts on all nations, some more than others with over 31 million infection cases and almost 1 million deaths as a result of the pandemic. This has caused a ripple effect on the agricultural sector as seen by the food scarcity and the increase in food spoilage ravaging the sector as many local farmers are unable to transport their produce to consumers. The pandemic has also confronted the hospitality industry with an unprecedented challenge as a result of the temporary closure they had to experience due to the lockdown imposed in affected countries. The transport sector is not excluded though to the positive side as there has been a decrease in air pollution within some countries due to the various travel restrictions and bans placed on the movement of people. Another sector seriously hit by the pandemic is the tourism sector as there has been a projected loss of about $1.2 trillion equivalent to 1.5% of the global Gross Domestic Product (GDP). The same goes for the sports sector as major tournaments have either been cancelled or postponed. This paper discusses the impact of COVID-19 on the global economy and its corresponding implication on job loss in various sectors. With the daily increase in the number of infected cases globally, systems and structures which will be able to neutralize the effects of future pandemics need to be put in place and reviewed from time to time.

Key words: COVID-19, Economy, Agriculture, Tourism, Travel, Sports

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Introduction

The Coronavirus (COVID-19) pandemic devastated several countries across the globe, having economic, social and health impacts on all nations, some more than others. According to the World Health Organization, over 31 million people have been infected and almost 1 million have died as a result of the pandemic. With a fast transmission rate and increased mortality, it became imperative for government to place restrictions on travelling, close borders and put structures in place for a lockdown [1]. While these stringent measures were necessary, they were not without several implications on the global economy. In several countries, particularly major economies, there were predictions about economic recessions as a result of lockdown measures and travel restrictions [2]. The pandemic dealt a strong blow to the economies of several countries across the globe and several sectors of the economy. The pandemic has drastically affected daily operations and the conduct of routine activities including many businesses. There has been a sharp decline in product manufacturing in most countries [3]. Some of the sectors that have been affected by these drastic changes include but are not limited to: Healthcare, Tourism, Agriculture, Sports, Entertainment, Hospitality and Restaurants [4].

The strong interconnectivity of the world points to the fact that the implications of a pandemic would not only be medical but also economic. China serves as a major source of raw materials but with the pandemic beginning in Wuhan, China, a sharp decline in productivity ensued, followed by a decline in consumption and an ultimately negative downturn of the economy [5].

Such a downturn has affected the global economy and the finance of countries around the world. COVID-19 is having major influences on the world economy, and experts have projected that COVID-19 will lower global gross domestic product growth by one-half a percentage point for 2020 (from 2.9% to 2.4%) [6]. There have also been reports showing the negative effects of the pandemic on mental health and psychosocial wellbeing [7]. While this has been strongly linked to several factors such as false news, restrictions on travels, gatherings and education, the financial markets have been hit hard with fake news having effects on stocks [8]. The news of new infections increases the volatility of the financial markets in the US, causing remarkable fluctuations in the financial market [9]. Certainly, the pandemic is accompanied by serious consequences for the global economies. Financial institutions such as banks have experienced severe setbacks in the form of elevated levels of liquidity risk, loan defaults and loss of intermediation revenues [10]. Such volatility eventually tends to have a ripple effect on businesses and individuals alike.

With the inevitable bans placed on travel and movement, both between countries and within countries, there is much impact on the wellbeing of people and their daily lives. Several businesses have had to shut down operations during the pandemic while some have had to downsize staff strength to accommodate changes in the economy. A 2020 study carried out showed that high income earning customers decreased spending, harming small businesses [11]. Several studies examine such negative impact of the pandemic on businesses. One of such studies carried out in the US showed that there were increases in layoffs and closures occurring only a few weeks into the pandemic [12]. Consequently, the closures lengthened as the infection spread. Another study carried out in Canada showed that there was a 32% decrease in working hours as a result of the pandemic, the majority of the workers who lost their jobs earned the lowest [13]. Other evidence shows that unemployment rates increased in the US to 12.99% in workers aged 25–44, with women being more affected by the pandemic-induced unemployment [14]. With the drop in business activity, there was a rise in unemployment.

The economic implication of the pandemic on the health sector has been quite significant. It is estimated that a single symptomatic COVID-19 infection costs about $3045 in direct medical costs [15]. Health care systems need to be able to access extra funding to cover such costs and to withstand the increasing future demands on health care services [16]. Countries having a high burden of COVID-19 will benefit from such expansions. To control the infection rates, movement restrictions included restricted visits to the hospital and cancellation of elective surgeries resulting in a financial downturn for hospitals carrying out these procedures [17, 18]. In the face of these challenges, health innovations such as telemedicine have expanded and there is a greater demand for virtual technologies in health care delivery [19]. The pandemic also decreased access to healthcare and medicines for people living in rural communities in Bangladesh, Kenya, Pakistan and Nigeria [20]. Drastic reduction in the supply of medical devices and Personal Protective Equipment (PPE) required for managing COVID-19 patients and performing routine medical procedures has been reported due to increased demands [21]. The pandemic has equally had significant effects on the retail industry. The report shows panic buying amongst consumers, particularly for food, and supplies such as hand sanitisers [22]. There has been increased spending amongst people for food, while spending on hospitality has decreased drastically [23]. This paper discusses the impact of COVID-19 on the global economy and its corresponding implication on job loss in various sectors.

Review

The Impact of COVID-19 on various sectors of the economy

As with any pandemic, the COVID-19 virus has had a huge effect on the various aspects of human living and the economy. The various strategies such as quarantines, bans on public gatherings and lockdown of various business enterprises among many are some of the strategies which have greatly slowed down the economic growth of various countries of the world. With the virus infecting residents of most continents in the world, its effects are sure to be numerous and well spread. In a publication released by the World Bank, Global Gross Domestic Product (GDP) is expected to decline by 2.1%, while developing countries' GDP is expected to decline by 2.5% and high-income countries by 1.9%. East Asia and Pacific (EAP) countries have been hinted to experience the biggest GDP losses under the global pandemic scenario due to their relatively deep relation through trade and direct impact on tourism, e.g., Cambodia (3.2 %), Singapore (2.1%), Hong Kong SAR, China (2.3%), Thailand (3%), Vietnam (2.7%), and Malaysia (2.1%) [22].

Impact of COVID-19 on agriculture

A release by the Food and Agriculture Organization stated that COVID-19 has affected agriculture in two significant aspects: the supply and demand for food, which is directly related to food security, hence putting food security at risks [23]. Food supply chain refers to

a network that connects an agricultural system (the farm) with the consumer's table, including processes such as manufacturing, packaging, distribution, and storage [24]. Initially, the problem of food insecurity began with the announcements of social isolation which made people go to the supply centres hence generating a shortage of certain products. The food supply has stabilized due to the activities of various non-governmental organizations (NGOs) because it is one of the systems that must be maintained to ensure food security [25]. Food safety was among the four pillars of the food systems affected in the era of the coronavirus (COVID-19) pandemic [26, 29].

Another area which has been greatly affected is the demand for food. Demand generally refers to the willingness and ability of consumers to pay money for a particular good or service, during any particular period [26]. During the COVID-19 pandemic, the demand for food was found to have greatly reduced due to the uncertainty and the reduction of people's spending capacity, although this decrease is still slight; the situation is expected to worsen if the pandemic continues for a long time, due to reduced income and job losses [27]. China where the COVID-19 disease started, represents an important market in world trade; this experience has shown an increase in online demand in the food and beverage sector, due to the quarantine policies [23]. In situations like these, where the mode of transmission of the virus is by contact, contactless delivery services have been embraced by consumers. Some start-up companies and big corporations have adopted the use of drones and online retail stores in reaching their customers. Also, food security ensures that everyone within the society has access to adequate feeding and nutrition. This implies that everyone has unrestricted access to food that allows them to satisfy their basic needs [28]. With the outbreak, this has been difficult to attain as a result of the various travel bans imposed by many countries, as most countries rely on produce from other nations in feeding their citizens. This in the long-run has led to food scarcity at one time or the other during the pandemic. Another negative impact of the COVID-19 outbreak is the increase in food spoilage as many local farmers are unable to transport their produce to consumers.

Little is still understood about the nature of the spread of the virus through food despite the precautionary measures (e.g., during food preparation) being applied at the consumption stage. For example, at the beginning of the crisis, many restaurants, cafeterias, and health authorities in Central Europe stopped serving rare steaks and meats as a general precaution measure [30] against viruses and pathogens even though foodborne transmission of SARS-CoV-2 is yet to be backed up by scientific evidence. Also, in the United States, some of the largest beef-packing and meat processing companies announced plant closures [31]. Nonetheless, the closure of these plants was only affected when employees started testing positive for COVID-19 and not because of the virus transmission from raw meat, which is why FDA did not anticipate that food products need to be recalled from the market [32].

Impact of COVID-19 on restaurant businesses

As a result of the COVID-19 pandemic, the world's economy was put to a halt almost overnight [33]. The pandemic has since then confronted the hospitality industry with an unprecedented challenge. Strategies put in place in an attempt to flatten the COVID-19 curve such as community lockdowns, social distancing, stay-at-home orders, travel and mobility restrictions have resulted in a temporary closure of many hospitality businesses and significantly decreased the demand for businesses that were allowed to continue to operate [34]. Almost all restaurants were asked to limit their operations to only take-outs. This has been an aftermath of the stay-at-home orders issued by the authorities resulting in a rapid decline in hotel occupancies and revenues. However, despite the reopening process which has slowly begun which authorities have started to ease restrictions, for example, allowing dine-in restaurants to reopen at a reduced capacity with strict social distancing guidelines, and gradually reduce restrictions on domestic and international travel [35]. The loss in terms of revenues and income cannot be easily forgotten.

Reports from previous outbreaks (MERS and SARS-CoV) [32, 36] show no evidence that validates food as a means of transmission for the viruses while a study reveals that the acidic status of the stomach (pH < 3.5) inactivates the coronavirus [37]. The MERS and SARS-CoV, which possibly originated from bats, crossed the species barrier and infected humans through an intermediate host which could be a domestic animal, a wild animal, or a domesticated wild animal suggesting that transmission of SARS-CoV-2 could eventually occur in like manner [38, 39]. Based on this fact, some cooking and eating habits may be risk factors for the re-emergence of the virus into the human population [40].

Evidence shows that the Coronavirus may reach fresh food products (e.g., vegetables, fruits, or bakery) or food packaging through an infected person who sneezes or coughs directly on them [41]. Transmission may therefore be possible if the virus is transferred shortly afterwards via the hands or the food itself to the mucous membranes of the mouth, throat, or eyes [42]. With such a protracted impact, many studies have observed that despite the recent easing of lockdown regulations and bans, it would still be difficult for people

to eat together in numbers at restaurants as a lot of fear and panic still surrounds the spread of the virus. For example, a study indicates the psychological acceptance of a good number of customers to the old strategy of restaurant operation only when COVID-19 conditions improve [35]. In a random survey with customers of a restaurant and a hotel, it was discovered that limiting the number of customers served, social distancing implementation, regular cleaning of high-touch surfaces in common areas, and employee training of health and safety protocols are considered as the most important safety precautions, this underscores the need for more behavioural research in determining the effects of these operational strategies on customers' attitudes and behaviours [43]. However, the fact remains that without a cure or definite treatment, owners of food service companies would continue to feel the financial implications of the virus.

Finally, even though the COVID-19 pandemic has dealt with the hospitality industry and academia with uncharted challenges, it has also presented great research opportunities for hospitality scholars [43]. Also, it has provided restaurants with the opportunity to experiment with various forms of digital and social marketing strategies. It has provided them with an avenue to experiment with the latest trends in food delivery service and packaging.

Impact of COVID-19 pandemic on the transport industry

In a study carried out in the UK aimed at exploring the impact of the COVID-19 pandemic on transport concerning the health sector, it was observed that there was a considerable decrease in air pollution within the country due to the various travel restrictions and bans placed on the movement of people. This has been attributed to the reduced use of automobiles during the pandemic lockdown [44]. According to data from Google mobility reports, there is an 80% decrease in the number of passengers that patronize public transit locations in many countries.

Another effect of the movement restrictions and travel ban on transportation during the COVID-19 pandemic is the reduction in the migration of people from a country to another. This in a way has proven to be of importance to maximum utilization of resources available within the country. Another study concluded that the various lockdown responses to coronavirus disease 2019 (COVID-19) have resulted in an unprecedented reduction in global economic and transport activity [45]. Some of the lockdown measures included partial or complete closure of international borders, schools, and non-essential businesses and, in some cases, restricted citizen mobility.

Impact of COVID-19 pandemic on tourism

About a decade ago, a study revealed perceptively that crisis events in tourism were likely to increase in size and frequency as a result of tourism becoming more hypermobile and the global economy ever more intertwined [46]. This has become the case in the situation we've now found ourselves in a vastly diversified and rich economy where over 100 countries have recovered cases of the much-dreaded virus with many of them having imposed inter-country travel bans and local restrictions. In time past, it has been found that the tourism sector is highly vulnerable to disruption by natural hazard events in terms of localized phenomenon such as earthquakes, bushfires, volcanic explosions, tsunamis or floods as well as global events such as disease pandemics [47, 48].

It has also been argued that in a highly connected and globalized world marked by high levels of mobility, the human networks for the diffusion of COVID-19 are vast and open. The spatial spread of the coronavirus is already destroying national and local economies and more so triggering the worst economic and humanitarian crisis since the Second World War. In the tourism sector, the appearance of the COVID-19 pandemic represents an exceptional shock event posing its greatest challenge since the 2008 global financial crisis [49].

The tourism industry contributed the US $8.9 trillion to the world's total gross domestic product (GDP) which represents 10.3% of global GDP, and also equivalent to 330 million jobs (1 in 10 jobs around the world), estimated as the US $948 billion in capital investment (4.3% of global investments) and about US$1.7 trillion of visitor exports, as reported in 2019. [50]. On the 1st of July 2020, the United Nations (UN) conference for Trade and Development revealed that the world's tourism sector is at risk of losing at least $1.2 trillion equivalent to 1.5% of the global GDP, owing to the 4-month shutdown of activities in a bid to mitigate the pandemic spread [51].

The UN's trade and development body also warned against a looming loss of $2.2 trillion equivalent to 2.8% of the world's GDP if the suspension of activities in the tourism industry extends beyond eight months as projected by the UN World Tourism Organization (UNWTO) [51]. According to the UNWTO, this poses the risk of increased poverty in most low and middle-income countries (LMICs) where economic growth rests solely on tourism activities having experienced an increase in value from $490 billion to $1.6 trillion in the last 20 years [51]. It is no surprise that African countries would be some of the most heavily hit by these losses as already revealed in a study carried out in South Africa. According to the study, in an annual report released by the South African Tourism in 2016, the tourism market reached a record level of R102 billion, which comprised

of R26.5 billion from domestic tourism and R75.5 billion from international tourism making about 6.1% of the country's GDP [47]. With the pandemic, it is expected that about 200 municipalities within the country would be hit by the reduction in tourism activities during the lockdown caused by the COVID-19 outbreak. In another study, a critical reconsideration of the exponential growth model for tourism has been suggested; this is in tandem with the risks incurred in global travels and its overall effect on climate change [49].

Impact of COVID-19 pandemic on sports

In a report by United Nations, the global value of the sports industry is estimated at the US $756 billion annually. With the current COVID-19 outbreak, several jobs are at risk globally, not only for sports professionals but also for those in related industries in close partnership with sports events [52]. In another report, it was predicted that if sports remain shut down for a total of three months or more, there might be a projected total loss of $12.3 billion in earnings by mid-June which equates to an average of $133.4 million in earnings every day, or $92.6K every minute [53].

Despite the severity of past infectious cases such as the H1N1 influenza pandemic two mega-sport events still took place: the Vancouver 2010 Winter Olympics and the 2010 Fédération Internationale de Football Association (FIFA) World Cup in South Africa. Also, during the outbreak of the Ebola virus disease in West Africa, the 2015 Africa Cup of Nations (in Equatorial Guinea) took place, along with the Rio 2016 Olympics in Brazil, during the outbreak of the Zika virus, although some athletes refused to attend because of the threat of infection [54]. However, this has not been the case with the COVID-19 virus outbreak. All major sporting tournaments such as the Union of European Football Associations (UEFA) EURO 2020, Summer Olympics in Tokyo, football leagues, tennis tournaments and other contact sports had to be cancelled or postponed. This has mainly resulted in a loss of revenue and investments in economies that are mainly driven by sports. Sports are one of the unifying human activities where everyone can participate and a major form of entertainment.

Recommendation and conclusion

Daily reports show that the number of people infected with the COVID-19 virus continues to rise with total infected cases expected to rise further. Despite the various easing on lockdown restrictions and lifting of bans, it is expected that it would take a while for the world economy to bounce back to normal. The impacts of the COVID-19 virus will still be felt years to come especially in many developing economies and low resource areas. The best we can all do is to provide a helping hand to those that are much more affected by the outbreak, governments and organizations need to direct efforts towards relief plans which will help people gain their footings and proper reseach funding to come up with therapeutic solutions to the virus [55, 56]. To prevent a future breakdown in our economy, we must all be prepared to battle any unforeseeable outbreak by adopting the 'One Health' approach [57, 58]. Systems and structures which will be able to neutralize the effects of future pandemics need to be put in place and reviewed from time to time.

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VIA MEDICA

REVIEW ARTICLE

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SARS-CoV-2 and lung transplantation. What do we know?

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ABSTRACT

Introduction: In 2019, new Coronavirus (SARS-CoV-2) has spread around the globe. The virus can replicate in the cells of the lower respiratory tract, causing pneumonia, oedema and hypoxia. In some patients, the disease will progress to acute respiratory distress syndrome (ARDS) which is a life-threatening condition. Lung transplantation (LuTx) might be the only rescue therapy for severe respiratory failure. Additionally, little is known about the impact of SARS-CoV-2 on lung transplant recipients. The purpose of this systematic review is to present current knowledge about lung transplantation as a treatment method for ARDS associated with COVID-19 infection and to summarize information regarding the management of COVID infection in lung transplant recipients.

Materials and methods: Literature search through different databases was conducted. Only case reports and case series were included.

Results: Out of 525 initial results, 16 studies were included in this systematic review. 7 articles presented patients with LuTx as a treatment option for ARDS and 9 presented management of lung recipients infected with COVID-19. A total of 37 patients were included in this systematic review.

Discussion: The course of reviewed patients with SARS-CoV-2 infection was similar and lung transplantation should be considered as a treatment of last chance when extracorporeal life support cannot be withdrawn. Further research is still required to assess the impact of new coronavirus on graft function in lung transplant recipients. Currently, the treatment strategy involves immunosuppression modification and supplemental oxygen therapy. However, some patients do not present clinical symptoms.

Key words: lung transplantation, coronavirus, COVID-19, ARDS

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Introduction

Since December 2019, medical centers around the world have been struggling with the Covid-19 pandemic. The virus mainly affects the respiratory system; some patients may progress to acute respiratory distress syndrome (ARDS). Advanced age and comorbidities are considered as risk factors for severe disease. In 97% of the patients undergoing acute Covid-19 infection pathological changes in the chest are seen on CT images [1]. In case of irreversible and serious lung parenchyma damage, lung transplantation (LuTx) might be necessary to restore respiratory efficiency. LuTx is a treatment of the last chance performed in patients with end-stage lung diseases when conventional treatment does not provide improvement. According to the International Society of Heart and Lung Transplantation (ISHLT), LuTx might be considered in patients with a 2-year mortality rate greater than 50% without transplant. Furthermore, a 5-year survival rate > 80% is required. In addition, this challenging surgery is associated with a long list of contraindications. For instance, the recent history of malignancy or dysfunction of another organ. Age over 65 years is a relative contraindication [2]. While LuTx is a life-saving surgery for patients with respiratory diseases, severe Covid-19 is associated with higher age and comorbidities that might prevent from becoming a potential candidate for transplantation [3]. There is a limited number of reports of LuTx performed due to Covid-related ARDS in the literature. Furthermore, the current SARS-CoV-2 pandemic represents a significant risk for lung transplant recipients. Little is known about the potential impact of the virus on graft function. Therefore, this systematic review presents

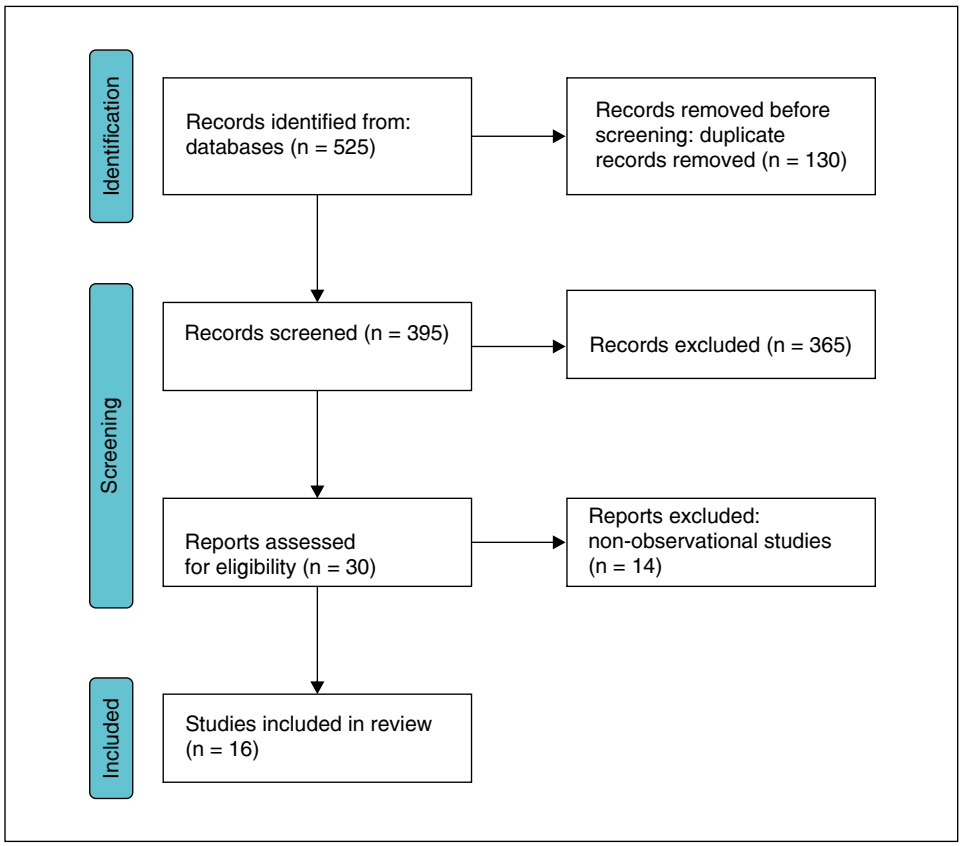

Figure 1. Flow diagram illustrating selection of the articles included in the systematic review

patients who underwent LuTx due to Covid-19 related ARDS and lung transplant recipients with postoperative Covid-19 infection. This systematic review aims to summarize current knowledge about SARS-CoV-2 infection that may lead to lung transplantation. Clinical features and management of patients progressed to ARDS are presented. Secondly, management of lung transplant recipients infected with Covid-19 is depicted as it may be beneficial for the development of future guidelines of postoperative care.

Materials and methods

This systematic review was conducted using PRISMA protocol (Preferred reporting items for systematic reviews and meta-analyses) [4]. Literature search through PubMed/Medline and Embase was performed. Flowchart representing search strategy is depicted in Figure 1. Phrases used for searching included: lung transplantation for Covid-19; lung transplant recipients Covid-19. Only case reports and case series written in English describing patients who underwent LuTx due to SARS-CoV-2 or lung transplant recipients with Covid-19 infection were included. 525 studies were identified after an initial search through databases. 395 studies' titles and abstracts were screened. After exclusion of non-observational studies and articles about transplantation of organs other than lungs, 30 studies remained for full-text assessment. 16 case reports and case series were ultimately included in this systematic review. Two reviewers independently screened titles and abstracts of studies chosen after primary search. Data was extracted manually from included studies. The second evaluation was performed in case of uncertainty. Characteristics (name of the first author, publication year, country, study design and infection status) of reviewed articles are presented in Table 1.

Results

7 articles presenting 13 cases of patients with ARDS were reviewed (Tab. 2). Mean age of presented patients was 54 ± 8,7 years. Presented cases included 4 females and 9 males. Some of the patients suffered from comorbidities like hypertension, diabetes or psoriasis, which might have contributed to the severe course of Covid-19. In all of the presented patients Extracorporeal

Table 1. Characteristics of articled included in the systematic review

Author	Year	Country	Study / number of patients	COVID-19 infection
Han W. [5]	2020	China	Case series / 2	Before LuTx
Lang C. [6]	2020	Austria	Case report	Before LuTx
Chen J.Y. [7]	2020	China	Case series / 3	Before LuTx
Bharat A. [8]	2020	USA	Case series / 3	Before LuTx
Chen Y. [9]	2021	China	Case report	Before LuTx
Hu C. [10]	2021	China	Case report	Before LuTx
Croci G.A. [11]	2021	Italy	Case series / 2	Before LuTx
Aigner C. [12]	2020	Germany	Case report	After LuTx
Koczulla R.A. [13]	2020	Germany	Case series / 2	After LuTx
Morlacchi L.C. [14]	2020	Italy	Case series / 4	After LuTx
Athanazio R.A. [15]	2020	Brazil	Case report	After LuTx
Cozzi E. [16]	2020	Italy	Case series / 2	After LuTx
Raëth J. [17]	2020	France	Case report	After LuTx
Renaud-Picard B. [18]	2020	France	Case report	After LuTx
Verleden G.M. [19]	2020	Belgium	Case series / 10	After LuTx
Desmazes-Dufeu N. [20]	2021	France	Case series / 2	After LuTx

LuTx — lung transplantation

Membrane Oxygenation (ECMO) was applied due to respiratory failure. To support circulation for weeks, veno-venous ECMO had to be applied (bridge to LuTx), while veno-arterious ECMO was required intraoperatively. In 9 of reviewed cases, pulmonary artery hypertension (PAH) was observed. In the presented cases, mean time from Covid-19 confirmation to LuTx was 53,6 ± 14 days which shows how rapid the disease progression might be. Pathological examinations of resected lungs were similar. The mixture of fibrotic and necrotizing tissues was observed. Extensive consolidation and micro-thrombosis were found as well. In the majority of reviewed cases, large improvement was observed postoperatively. Extracorporeal life support has been withdrawn successfully days or weeks after LuTx while it was impossible prior to surgery. Lung function was mostly restored, and saturation was increased. Furthermore, patients regained independence in everyday activities. One death on postoperative day 1 was observed.

In addition, 9 case reports and case series with a total of 24 lung transplant recipients infected with COVID-19 were included (Tab. 3). Mean age of the patients was 51.5 ± 6.7 years. The mean time from LuTx to Covid-19 infection was 63.9 ± 25.7 months and the causes of LuTx included Chronic Obstructive Pulmonary Disease (COPD), Cystic Fibrosis (CF), non-specific interstitial pneumonia, pulmonary fibrosis, pulmonary hypertension, lymphangioleiomyomatosis and bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation. Reviewed patients presented diversified symptoms. These included mild cold symptoms like fever, cough in some patients while others suffered from progressive dyspnea, malaise, hypoxia or thrombosis. In 13 patients ground-glass opacities in chest CT were observed. In 15 cases immunosuppression therapy was changed; cycle cell therapy was stopped (mycophenolate mofetil). In the vast majority of reviewed cases, antibacterial therapy was introduced, for instance, azithromycin, meropenem. In some patients, low molecular weight heparin was introduced. 3 patients had died (1 from multiorgan failure, 1 from graft injury caused by Covid-19 and bacterial infection, 1 from the deteriorated gas exchange).

Discussion

Coronaviruses are known for infections of the upper respiratory tract which cause mild symptoms. However, there are three viruses that replicate in the cells of the lower respiratory tract: Middle East respiratory syndrome coronavirus (MERS-CoV), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and SARS-

Table 2. Reviewed case reports of patients with SARS-CoV-2 related ARDS

Author	Patient age	Sex	Comorbidities	Lung function/radiological images prior to LuTx	ECMO support before LuTx (days)	Pathological examination	Postoperative course	Time from COVID confirmation to LuTx (days)
Han W. [5]	66	Female	–	Oxygenation index < 60 mmHg X-ray manifestations: "white lung" Pulmonary artery systolic pressure 80 mmHg	–	Uneven surface, entirely consolidated in cross-section	Acute rejection treated with steroids ECMO successfully removed on POD 5	–
	70	Male	Hypertension Diabetes Psoriasis	Chest radiographs: Large blurry images of both lungs	10	Extensive consolidations	ECMO withdrawn on POD 2	35
Lang C. [6]	44	Female	Psoriatic arthritis	Gradual worsening of respiratory function	45	Large zones of necrosis Massive alveolar damage Remnants of widespread thromboembolism throughout all lobes	ECMO removed on POD 3 Quick recovery	58
Chen J.Y. [7]	66	Male	Hypertension	Oxygen Index: 60 Pulmonary Artery Pressure: 52	15	Congestive and hemorrhagic necrosis Extensive pulmonary interstitial fibrosis Micro-thrombosis	Death on POD 1	35
	58	Male	HBV infection	Oxygen Index: 104 Pulmonary Artery Pressure: 48	7	Congestive and hemorrhagic necrosis Extensive pulmonary interstitial fibrosis Intravascular organized thrombosis	ECMO removed on POD 2	33
	73	Male	Diabetes Chronic Kidney Disease Coronary Heart Disease Atrial Fibrillation COPD	Oxygen Index: 114 Pulmonary Artery Pressure: 40	19	–	ECMO removed on POD 2	37

→

Table 2 cont. Reviewed case reports of patients with SARS-CoV-2 related ARDS

Author	Patient age	Sex	Comorbidities	Lung function/radiological images prior to LuTx	ECMO support before LuTx (days)	Pathological examination	Postoperative course	Time from COVID confirmation to LuTx (days)
Bharat A. [8]	28	Female	Neuromyelitis optica	Gradual decrease in PaO2 despite mechanical ventilation Right-sided pneumothorax Serratia marcescens pneumonia with left lower lobe necrosis Pulmonary pressure elevation (71/49 mmHg)	–	Severe dense vascular adhesions diffuse alveolar hemorrhage	Separated form VV – ECMO and MV in two weeks Discharged home 4 weeks after LuTx	–
	62	Male	Hypertension	Recurrent pneumonia caused by *Pseudomona aeruginosa*, hemothorax and empyema requiring thoracotomy and lung decortication	100	Loss of normal mediastinal tissue planes; extensive pleuritis diffuse alveolar hemorrhage Lung necrosis secondary to larger thrombi	Four months after LuTx: saturation 97% while breathing room air, independence in common activities	–
	43	Male	Diabetes	Progressive lung fibrosis Severe pulmonary hypertension with right ventricular dysfunction	–	Diffuse alveolar hemorrhage	Three months after LuTx: saturation 95% while breathing room air	90
Chen Y. [9]	66	Female	–	Pulmonary artery pressure: 80 mmHg Respiratory failure with consolidation of the lung seen on X-ray Saturation 74%	14	–	ECMO removed on POD 5 Gradual improvement	–
Hu C. [10]	59	Male	Hepatitis B	Respiratory failure and irreversible lung injury Chest CT: bilateral, ground-glass opacities with consolidations.	–	–	ECMO removed on POD 2 Chest X-ray: significantly improved lung imaging	–
Croci G. A. [11]	18	Male	–	Bilateral pneumothorax Pneumatocele Severe pulmonary hypertension Pulmonary infections	55	Hepatization foci of hemorrhage and consolidation	–	71
	48	Male	–	Severe pulmonary hypertension Right ventricular failure Pulmonary infections	54	Bronchiectasis small peripheral foci of hemorrhage and emphysema	–	70

ECMO — extracorporeal membrane oxygenation; POD — postoperative day; COPD — chronic obstructive pulmonary disease

Table 3. Summary of the case reports and case series findings

Variable		Number of patients/ /number of studies
Male		10/6
Female		13/6
Age > 65 years		6/4
Single lung transplantation		2/2
Bilateral lung transplantation		19/7
Cause of LuTx	Chronic obstructive pulmonary disease	8/3
	Cystic fibrosis	7/6
	Bronchiectasis	2/1
	Non-specific interstitial pneumonia	1/1
	Pulmonary fibrosis	1/1
	Pulmonary hypertension	2/2
	Pulmonary lymphangioleiomyomatosis	1/1
	Bronchiolitis obliterans after hematopoietic stem cell transplantation	1/1
Symptomatic		20/7
Asymptomatic		3/3
Ground-Glass opacities in CT		14/7
CPAP/oxygen therapy/mechanical ventilation		13/6
Immunosuppression modification		16/5
Antibacterial therapy		21/7
LMWH		5/3
Death		3/3

CPAP — continuous positive airway pressure; LMWH — low molecular weight heparin

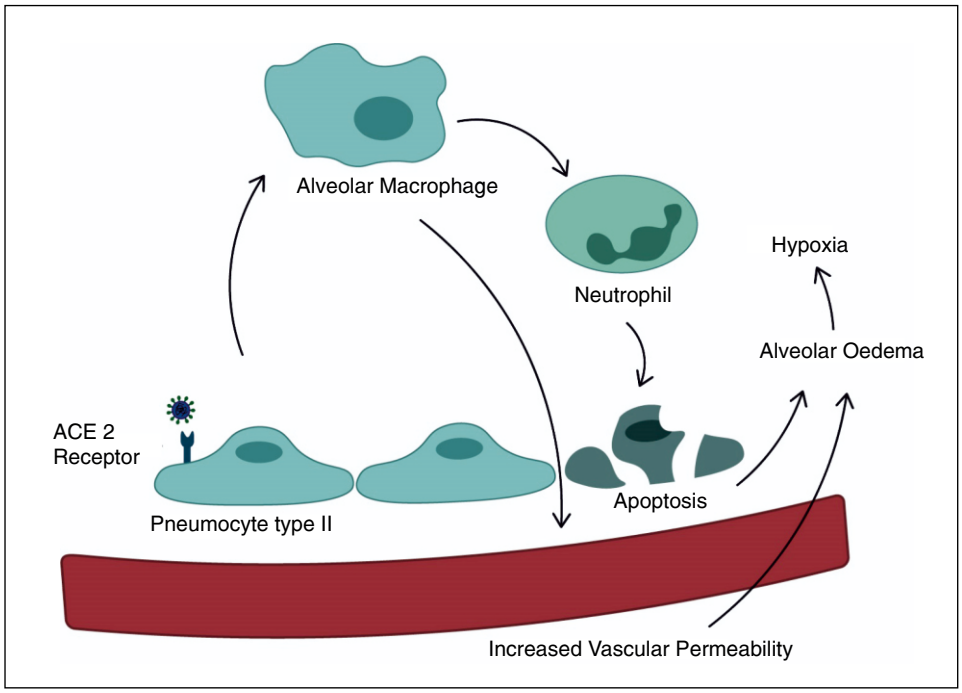

Figure 2. COVID-19 immunopathology

CoV2 [21]. It is considered that the SARS-CoV-2 virus attacks all cells that express angiotensin-converting enzyme 2 receptor (ACE2) which is an entry receptor. Consequently, as the virus replicates its genome, the hosts immunology system is activated and proinflammatory cytokines are secreted. Alveolar macrophages stimulate vascular permeability and recruit neutrophils. Degranulation of these cells is responsible for pneumocytes and endothelial cells damage. Thus, these processes lead to alveolar oedema and hypoxia and are associated with the progressive development of ARDS (Fig. 2) [22]. Chronic inflammation and unsuccessful regeneration contribute to the development of pulmonary fibrosis, leading to damage of lung architecture. It is suggested that recruitment of myofibroblasts and alveolar epithelial damage are causes of most lung fibrosis processes [23]. In some of the reviewed cases, pathological examination revealed thrombosis of pulmonary vessels. Dysfunction of coagulation appears to be common in the course of Covid-19 infection. Vascular enlargement, which can be observed in chest CT, is frequently seen in Covid-19 patients while it is rarely reported in typical ARDS. Furthermore, Covid-19 related ARDS is associated with increased mortality rates compared to typical ARDS [24]. Respiratory failure due to ARDS is a life-threatening condition. In such cases, extracorporeal membrane oxygenation is a rescue therapy, and it was introduced in all of reviewed ARDS cases. Cannulation strategy for acute respiratory distress syndrome is a veno-venous ECMO, as it might support a patient for weeks. Furthermore, early use of VV-ECMO may reduce pulmonary inflammation and lower respiratory-driven pressure. Therefore, with its lung-protective mechanism, it is an accepted treatment for patients with ARDS [25]. However, if trials of ECMO removal are unsuccessful and patients condition does not seem to improve, lung transplantation might be the rescue therapy. However, during LuTx, veno-arterious ECMO should be applied, as VV-ECMO does not support cardiac function. In some patients, pulmonary artery hypertension (PAH) was observed. It is diagnosed when mean pulmonary arterial pressure is greater than 25 mmHg. PAH is associated with an increased risk of severe course of Covid and higher mortality rates [26].

In reviewed articles, the mean time of ECMO support prior to LuTx was 35,4 ± 19 days. Mean time from COVID confirmation to LuTx was 53,6 ± 14 days. In analysis performed by Chen J. et al. out of 249 patients, 8 (3,2%) progressed to ARDS in 4.8 ± 2.4 days after the beginning of symptoms [27] which shows how rapid the disease progression to irreversible pulmonary damage may be.

It is unclear how SARS-CoV-2 infection affects lung transplant recipients and graft function. In reviewed articles, the course of infection varied among patients. In the majority of reviewed articles, patients presented fever, cough, dyspnea or hypoxia. However, three patients underwent Covid-19 infection without clinical symptoms. A total of 13 patients required supplemental oxygen therapy, mechanical ventilation or continuous positive airway pressure (CPAP). Together with noninvasive ventilation, CPAP is introduced in patients with hypoxemic respiratory failure as a result of pulmonary oedema. Due to the lack of randomized control trials, there are no recommendations for using CPAP in viral infections. According to a retrospective review performed by Brusasco C. et al. 64 patients were supported with CPAP due to Covid-19 respiratory failure. Criteria for CPAP application were: $PaO_2/FIO_2 < 200$, $PaO_2 < 60$mmHg, breathing frequency > 30 min and dyspnea at rest. The majority of patients recovered after the use of CPAP (n = 53) and were discharged from the hospital within 28 days [28]. In large number of patients chest CT revealed ground-glass opacities (GGOs). Chest CT is a significant tool in COVID diagnosis due to its high sensitivity. Replicating virus in alveolar epithelium and damage of epithelial surface (leakage) manifest as GGOs. Other changes involve vascular enlargement, consolidation and bronchial wall thickening. These changes usually occur bilaterally [29]. According to a systematic review performed by Salehi S. et. al GGOs may be observed in the early stage of infection (1–2 weeks after exposure). Furthermore, these changes may be observed despite negative COVID-19 PCR results [30]. Thus, chest CT could be beneficial to identify the early stage of coronavirus infection in lung transplant recipients. Immunosuppression therapy for lung recipients consists of three elements: calcineurin inhibitors (tacrolimus), cycle cell inhibitors (mycophenolate mofetil) and corticosteroids. In reviewed cases, mycophenolate was reduced or stopped during infection. This approach was also undertaken by Pereira M.R. et al. in solid organ transplant recipients with Covid-19 [31]. Elevation of proinflammatory cytokines (IL-6, TNF) was observed in patients with severe course of SARS-CoV infection. Those are involved in abnormal clot formation leading to the development of thrombosis. Thus, low molecular weight heparin (LMWH) should be considered to prevent deep vein thrombosis or clot formation in pulmonary vessels. Among reviewed cases, 5 patients were treated with LMWH [32]. According to analysis performed by Coll E. et al., who reviewed 778 solid organ and haemopoietic stem cell transplant recipients, lung transplant recipients (n = 54) had a significantly higher risk of death (OR: 2.5 95% CI: 1.4–4.6). Furthermore, the course of infection was more aggressive compared to recipients of other organs which may be related to more potent immunosuppression and poorer respiratory reserve [33]. According to a report written by

Messika J et. al, among 35 lung recipients, 31 (88,6%) required hospitalization due to Covid-19 infection. The presentation was mostly severe, while 5 patients died due to Covid-19 infection [34]. The early phase of the Covid-19 pandemic reduced the number of lung transplantations performed [35]. Consequently, more patients are on the waiting list and more deaths among those patients has occurred [36]. This systematic review should be considered with several limitations. Firstly, despite a comprehensive search of available studies, some upcoming articles could have been missed due to evolving nature of Covid-19. Secondly, some cases of lung transplant recipients could have been described in studies summarizing recipients of other organs as well, not meeting the inclusion criteria for this review. These factors might be responsible for introducing a bias.

Conclusions

The global pandemic proved to be a critical challenge for healthcare systems and physicians. Lung damage caused by SARS-CoV-2 may be thorough and irreversible. Supplemental oxygen therapy or ventilation is used to support patients in worsening conditions.

However, if the deterioration of lung function progresses, extracorporeal membrane oxygenation might be a rescue therapy. Failure in ECMO withdrawal indicates that lung transplantation is required. As seen in reviewed cases, LuTx provided an improvement and ECMO could be withdrawn few days after the surgery. Therefore, Covid-19 related ARDS might be treated, and mortality rates lowered. However, with limited access to extracorporeal circulatory support devices and an increasing number of Covid-19 patients with ARDS due to ongoing pandemic, this treatment strategy may be approachable only in certain patients. Performing LuTx in patients with severe ARDS associated with Covid-19 is extremely challenging as there are not any official guidelines. Furthermore, the surgery itself is a very invasive treatment. Additional use of extracorporeal life support increases the risk of other serious complications like acute kidney injury, bleeding or thromboembolic complications. Coronavirus pandemic introduced obstacles that have not been previously encountered. For instance, testing donor's lungs for Covid-19; providing surgical facilities with adequate protection level or wearing virus protection suits by the surgical team. In addition, little is known about the potential impact of Covid-19 on lung transplant recipients and further research is required to develop adequate guidelines of postoperative care. We strongly believe that this review may be beneficial as it promotes lung transplantation as a treatment of the last chance in case of patients who progressed to ARDS due to Covid-19 infection. Furthermore, a summary of treatment methods and management of infected lung transplant recipients may be helpful in developing future guidelines.

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VIA MEDICA

REVIEW ARTICLES

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Tibolone among drugs in the therapy of postmenopausal women

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ABSTRACT

The ageing of society is undoubtedly a success, but also a challenge of modern medicine. Postmenopausal women struggle with many health problems, and their treatment recommended so far is often associated with many side effects such as the increased risk of hormone-dependent tumours or thromboembolism. The purpose of this article is to discuss the effects of a relatively new drug called tibolone against the currently recommended treatment. The unique mechanism of estrogenic, progestogenic, and androgenic action of tibolone is due to the breakdown of the parent compound into 3 active metabolites, each selectively acting on different tissues differently. Tibolone is approved for the relief of menopausal symptoms and its effectiveness is similar to that of hormone replacement therapy and the prevention of osteoporosis. The article will also discuss the results of various studies on the risk of cancer during treatment with tibolone, especially in comparison to hormone replacement therapy. Tibolone affects also the cardiovascular system, including reducing the level of lipoprotein a, total cholesterol, triglycerides, and HDL. Tibolone also has a neuroprotective effect and improves mood and libido. Like all medicines, tibolone is not free from side effects such as weight gain, vaginal bleeding, hirsutism, and inflammation of the reproductive organs, so the benefits and risks of therapy should always be considered. There are still no clear conclusions regarding many aspects of the influence of tibolone on the patient's body, therefore large studies are needed to assess the effectiveness and safety of tibolone.

Key words: tibolone, menopause, hormone replacement therapy, neoplasms, osteoporosis

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Introduction

The ageing of societies is a global phenomenon. In 2015, the population of people over 60 years old accounted for 12% of the world's population, and the number is increasing every year. It is estimated that by 2050 the elderly people will constitute as much as 21.5% of the population. These changes are particularly visible in Europe. The data published by the European Commission in 2011 shows that by 2060, approximately 30% of Europe's population will be over 65 years old [1]. While this is undeniably a sign of medical progress, it brings new challenges. In the elderly population, multi-morbidity is characteristic [2]. The typical problems among elderly people include diseases of the musculoskeletal system, the cardiovascular system, the nervous system, metabolic diseases, weakening of the body's defence systems, hormonal changes, and mental and social problems [1]. Preservation of the physical activeness and the quality of life of the elderly, enabling their independent functioning requires the cooperation of specialists in various medical and paramedical fields. This involves taking multiple medications, that are not free from side effects [2]. That is why dynamically developing medicine faces the challenge of improving these therapies. One of the solutions is to look for new, alternative drugs. In this article is presented the application of Tibolone, and its place among other drugs used to treat the postmenopausal women population. About its indications and unique properties, but also the dangers and limitations of the use of this drug.

The unique mechanism of action of tibolone

Tibolone was synthesized in 1964 by Organon Research and Development Laboratories in the Neth-

erlands, but it took 25 years of research to be finally approved for use [3]. It has been widely used in many countries for many years but has not been introduced in the USA yet [4]. It differs from other drugs by selective action on different tissues in a different way. This synthetic steroid has been classified as a selective regulator of estrogenic activity in tissues (STEAR) [3]. The reason why tibolone is so unique is that the parent compound, structurally similar to norethynodrel and virtually no pharmacological activity, is converted in the body into 3 active metabolites: 3α-hydroxytibolone, 3β-hydroxytibolone, and the Δ4 isomer. Each of these compounds has a different effect. 3α-hydroxytibolone and 3β-hydroxytibolone are weak oestrogens and bind to oestrogen receptors in the vagina, brain, and bone with minimal effect on the endometrium. In addition, hydroxymetabolites inhibit the action of sulfatase, which leads to a decrease in the conversion of oestrogen to oestradiol in the breast so that the estrogenic stimulation is lower. Whereas the Δ4-isomer shows progestogenic activity mainly on the endometrium, which reduces its proliferation. Δ4-isomer also has an androgenic effect in the brain and the liver, affecting lipid levels. Regarding the effects on the breasts, the Δ4 isomer inhibits the proliferation of breast tissue and stimulates its apoptosis [4].

Tibolone has been approved for the treatment of climacteric symptoms and the prevention of osteoporosis occurring in women who are at least one year after menopause [5]. It has a positive effect on the mental and sexual spheres. Studies also show that tibolone prevents endometrial proliferation and vaginal atrophy, and also relieves urogenital symptoms.

The overall tolerance of tibolone is also assessed as good [6].

Menopausal symptoms

Every ageing woman experiences physiological hormonal changes in her body. Over the years, ovarian follicles are lost, and the levels of hormones secreted by them decrease. This leads to an increase in FSH levels, which is a major feature of the menopausal transition [7]. Each woman starts menopause individually, usually between the ages of 45 and 52 [8]. In addition to menstrual disorders, this period is associated with the emergence of significant and bothersome clinical symptoms, which increase with the duration of the menopausal transition. First and foremost, they include hot flashes, as well as poor sleep, urogenital atrophy, and unfavourable mood [7].

Most women experience vasomotor symptoms, i.e., hot flushes and night sweats. They are most pronounced a few years before and immediately after their final menstrual period, but a small percentage of women will never be free from them. In addition to reducing the quality of life, hot flushes can negatively affect health because this symptom has been shown to correlate with reduced heart rate variability, which is associated with a higher risk of cardiovascular disease. About a quarter to a third of menopausal women experience vaginal symptoms that, unlike hot flashes and sleep disturbances, do not go away without treatment [7]. They include several troublesome ailments such as itching of the vulva, vaginal dryness, vaginal discharge, dyspareunia, or dysuria [9].

Studies are suggesting the effectiveness of complementary and alternative medicine in reducing stress and the nuisance of symptoms related to menopause, such as cognitive behavioural therapy and phytoestrogens [8]. Patients may also be offered paroxetine mesylate or clonidine for vasomotor symptoms or a low dose of gabapentin at night when hot flushes occur at night, ospemifene (a new selective oestrogen receptor modulator - SERM) for vaginal dryness, and selective serotonin reuptake inhibitors (SSRI) or melatonin receptor agonists for other symptoms. However, most often women with the typical symptoms of menopause are offered hormone therapy [7]. They are effective in combating vasomotor symptoms (they reduce the frequency of symptoms by 75% and their intensity by 87%) and urogenital atrophy, prevent bone loss, reduce the risk of type 2 diabetes and ischemic heart disease, and improve mood and quality of life. Hormone therapy can be divided into oestrogen-only therapy (when the woman has had a hysterectomy) and oestrogen-progesterone therapy (adding a dose of progesterone is necessary because oestrogen alone would stimulate endometrial cell division) [10]. Vaginal oestrogen therapy is the method of choice in the treatment of urogenital atrophy, thanks to which complications related to systemic therapy are not observed [9]. It is important to remember about the side effects of hormone replacement therapy, such as mastodynia, fluid retention, nausea, leg cramps, headache, uterine bleeding, increased risk of thromboembolism (it seems that the solution could be the percutaneous supply of oestrogen, which poses a lower risk of a thromboembolic event) as well as depression, anxiety, bloating and increased appetite if the progesterone component is also included. And in long-term follow-up, they can lead to the development of tumours, which will be discussed in more detail later in this article [10–12].

Alternative therapy is the administration of tibolone, which, due to its unique mechanism of action, also works well in alleviating menopausal symptoms, and studies comparing oral hormone replacement therapy with tibolone shows similar effectiveness. At the same time, the incidence of vaginal bleeding and breast ten-

derness is lower than with standard HRT [11, 12]. In a study comparing transdermal oestrogen (although it was performed in a small group of patients), statistically better results of transdermal oestrogen than tibolone were reported. However, in another study comparing the effects of tibolone and transdermal oestrogen in surgically menopausal women, tibolone was more effective [12].

In conclusion, tibolone should be preferred in women who experienced undesirable side effects after hormone replacement therapy and who have already gone through menopause and are struggling with acute menopausal symptoms [10].

Tibolone and cancer risk

Hormone replacement therapy is undoubtedly a risk factor for cancer of oestrogen-dependent tissues. Women taking combined oestrogen-progesterone therapy have an increased risk of developing breast cancer, while oestrogen-only therapy does not appear to increase that risk. On the other hand, the risk of endometrial cancer is increased with oestrogen-only therapy and the addition of progesterone reduces it [13]. The risk of developing ovarian cancer is increased in both oestrogen and oestrogen-progesterone therapy [14]. Since many women and their doctors are concerned about HRT, another treatment like tibolone could be considered.

The tissue-selective Δ 4-metabolite of tibolone with progestogenic properties prevents the proliferation of endometrial cells, therefore additional progesterone is not required during this therapy. Endometrial atrophy has been observed in several years of clinical observations of the use of tibolone. The safety of tibolone therapy was compared to that of continuous oestrogen-progesterone therapy with a lower percentage of irregular bleeding and spotting from the genital tract. In a small study conducted by the Medical University of Warsaw, none of the women, during the 12-month follow-up, revealed cancer or endometrial adenoplasma. Atrophic changes of the endometrium were found and were associated with a low percentage of vaginal bleeding. However, there have been some reports in the literature of endometrial adenocarcinomas in women treated with tibolone [15].

According to a Danish study, postmenopausal tibolone substitution is associated with an overall increased risk of ovarian and endometrial cancer. This is especially true of serous ovarian tumours and type I endometrial cancer. The risk increases with the longer duration of therapy [14]. An epidemiological study was also carried out in the UK and it was found that women treated with tibolone for at least 2 years had a higher risk of developing endometrial cancer compared to women using hormone replacement therapy, although the authors of this study emphasize that tibolone was not always prescribed under the license for use in women who are at least one year postmenopausal or have been prescribed for women with a previous history of uterine bleeding. Therefore, more detailed research on the relationship between the use of tibolone and the occurrence of endometrial neoplasms is necessary [16].

A complication of hormone replacement therapy (especially when oestrogen alone) may also be the reactivation of endometriosis and stimulation of malignant transformation in women with a history of endometriosis. Due to the lack of high-quality studies, it is not possible to clearly indicate the best treatment option for these women. The authors of some studies indicate that tibolone may be a safer alternative, but there is no clear evidence for it [17].

It is worth remembering that breast cancer is the most common malignant neoplasm of women in developed countries and one of the leading causes of death in women over 60 years old [18]. As already mentioned, studies have shown that in the breast, tibolone metabolites regulate the activity of enzymes that are locally involved in the production of oestrogens (the activity of which explains why the risk of breast cancer does not decrease after menopause) and have antiproliferative and proapoptotic effects on cells. Animal studies in rats, monkeys and nude mice have shown efficacy in inhibiting the growth of breast tumours (at the level of tamoxifen efficacy) and preventing tumour growth. There are also studies that in women with a history of breast cancer treated with tamoxifen, tibolone was effective and safe in relieving menopausal symptoms. Contrary to standard HRT, breast tenderness was less frequent in women treated with tibolone [19].

However, the Million Women Study conducted in the UK found a significant increase in the number of breast cancer cases in women using tibolone. Although it was much lower than with oestrogen-progesterone therapy (leading to an approximately fourfold increase in the risk of breast cancer), it was still slightly higher than with oestrogen-only therapy [20].

Another side effect of HRT is an increase in the density of mammograms, making it difficult to interpret this important breast cancer screening test. Tibolone does not show this effect. Some studies even report a decrease in mammography density after the use of tibolone. Although epidemiological studies show an increased risk of breast cancer in women treated with tibolone, it may be related to the increased detection of cancer in radiological tests [19].

Moreover, some clinical studies suggest that tibolone may reduce the risk of colon cancer [3].

All of this suggests that tibolone may have an advantage over standard HRT in terms of breast cancer risk, but this is not certain enough to make it lose oncological alertness.

The effect of tibolone on the cardiovascular system

Oestrogen deficiency in postmenopausal women is also associated with many changes in the vascular system. With age, the blood pressure value and lipid profile change, vascular reactivity decreases, glucose tolerance is impaired, and thus the cardiovascular risk increases. The effectiveness of HRT in reducing cardiovascular events is so far debatable [21]. A serious complication of HRT is a significantly increased risk of thromboembolism [10]. Also, clinical and observational studies have confirmed that standard HRT doses increase the relative risk of stroke, especially in women over 60 years of age [22].

The tibolone discussed in this article has been shown to reduce Lp (a), total cholesterol, and triglycerides in clinical trials as well as HDL cholesterol levels. High levels of LDL-C, Lp (a) and triglycerides, and low levels of HDL-C are associated with an increased risk of cardiovascular disease [23]. While it is emphasized that Lp (a) is an independent risk factor for cardiovascular disease and lowering Lp (a) levels may be critical in preventing CVD, and changes in HDL-C levels are transient, there are no long-term studies to support the theory that a decrease in Lp (a) does indeed lead to a reduction in cardiovascular events [24]. Moreover, no significant difference was found between the effect of tibolone and standard HRT on Lp (a) concentration [25].

The fall in oestrogen levels may make hypertension more common in menopausal women. Due to the occurrence of hypertension in young women taking contraceptive pills and inconclusive results of studies on the effect of HRT on blood pressure, the influence of tibolone in this aspect was discussed. In a randomized trial in hypertensive women, no clinically significant changes in blood pressure were found between the tibolone and placebo-treated groups. The authors considered tibolone 2.5 mg safe for use in women treated or untreated [26]. However, in the study comparing the effect of Drospirenone combined with 17β-oestradiol (E2) with tibolone, it was concluded that tibolone does not show vascular function resulting from estrogenic properties, most likely due to additional progesterone and androgenic component [21].

Interesting results of the OPAL study also report the progression of atherosclerosis, as measured by the progression of carotid intima-media thickness, in both tibolone and standard HRT therapy compared to placebo, which may be associated with an increased cardiovascular risk. However, other, smaller studies do not confirm this relationship [27].

Other factors that appear to increase the risk of cardiovascular disease are increased levels of fibrinogen and low levels of antithrombin III. Despite previous reports on the profibrinolytic activity of tibolone, the meta-analysis of studies does not suggest either a significant reduction in fibrinogen concentration or changes in plasma ATIII concentration, regardless of the duration of treatment with tibolone. The authors of this meta-analysis suggest that this form of therapy is neutral in terms of the occurrence of thromboembolic events [4, 27].

Concerns about the safety of tibolone arose during the Fracture Incidence Study in the Elderly Osteoporosis Population (LIFT), which was discontinued due to an observed increased risk of stroke [3, 27]. However, results from the General Practice Research Database indicate that tibolone was not associated with an increased risk of stroke [22]. The differences may be because women in the LIFT study had a more severe medical history [3].

In conclusion, there is still a lack of conclusive and reliable scientific data to determine the overall effect of tibolone on cardiovascular morbidity and mortality [26].

Osteoporosis

Four main groups of drugs are used during osteoporosis: bisphosphonates, selective oestrogen modulating receptor, parathyroid hormone derivatives and strontium ranelate. The limitations of pharmacotherapy with bisphosphonates include gastrointestinal complaints, atrial fibrillation or significant impairment of functions, i.e., diseases occurring among geriatric patients. Raloxifene - a selective oestrogen receptor modulator - may increase vasomotor symptoms and increase symptoms of thromboembolism. Parathyroid hormone derivatives have serious ineffectiveness among people with kidney failure or hypercalcemia. The use of strontium ranelate in concomitant dysfunction of the kidney will prove to be inappropriate. The numerous options of the above-mentioned drugs encourage the search for alternative therapies, which include tibolone [28].

In postmenopausal women, the risk of osteoporosis increases significantly due to the decreased synthesis of oestrogens, especially 17-b-estradiol [29]. The role of these hormones is to inhibit osteoblast apoptosis and reduce the viability of osteoclasts due to the interaction with cytokines that regulate the death processes of these cells [30]. In addition, oestrogens reduce calciuria, which also helps to maintain the body's calcium-phosphate balance [29]. Scientific studies have

shown that tibolone, due to the content of oestrogens, reduces the risk of vertebral and extra-vertebral osteoporotic fractures [31]. An additional advantage is the presence of androgens that stimulate the synthesis of new bone tissue, which in turn causes a greater increase in bone density compared to oestrogen-only therapy. The anti-resorptive effect of tibolone is dose-dependent - 2.5 mg of the drug inhibits resorption more effectively than the use of 1.25 mg [30]. It is suggested that the lower dose should be used in asymptomatic patients or as part of maintenance therapy, and the higher dose in the presence of severe symptoms of menopause [32]. Tibolone turns out to be particularly beneficial in women after an osteoporotic fracture or with the presence of risk factors for such a fracture, in the case of contraindications to the use of denosumab and bisphosphonates, as well as in patients with particularly severe vasomotor symptoms of menopause [33, 34]. Due to the proven cartilage-protective properties of some selective oestrogen receptor modulators, one study raised the question of whether such an effect would also be observed in the case of tibolone. However, no such relationship has been demonstrated, which may be related to the effect on receptors other than oestrogen receptors [35].

Central nervous system

Sex hormones also regulate many processes within the central nervous system. There are two types of oestrogen receptors in the brain. Within the hypothalamus, the majority are alpha receptors, while beta receptors dominate within the structures responsible for motor and cognitive functions [30]. In animal studies, the stimulating effect of oestrogens on the synaptogenesis process in the hypothalamus and increasing the number of spines of dendritic pyramidal cells in the hippocampus has been proven. It is assumed that the disappearance of dendritic spines is caused by the activity of the GABA-ergic system, which increases with oestrogen deficiency. Particularly noteworthy is the fact that androgens act antagonistically to GABA receptors [36]. Progesterone also stimulates the process of synaptogenesis and myelination [37]. Therefore, tibolone has a positive effect on the learning process and memory, and in particular, improves semantic memory [38]. However, there are reports of an adverse effect of tibolone on the performance of activities requiring concentration and task planning [39].

It has also been shown that oestrogens influence the processes regulating oedema, astrogliosis and the inflammatory response following brain damage [40]. Their protective effect against astroglia and microglia cells under inflammatory conditions was also observed. It is worth emphasizing that progesterone also protects nerve cells against the influence of factors inducing oxidative stress [42]. Interestingly, tibolone regulates the phagocytosis of astrocytes more effectively in women than in men [42].

When discussing the various implications of tibolone pharmacotherapy, one should not forget about the increase in the level of neurotransmitters in the cholinergic and serotonergic systems. In addition, the drug regulates the phosphorylation of the Tau protein, which plays a key role in the pathogenesis of tauopathies such as, for example, Alzheimer's disease. Its neuroprotective effect should be considered in the context of its use in the treatment of postmenopausal neurodegenerative diseases [38].

Mood and cognitive functions

Neuroendocrine and metabolic changes taking place during menopause adversely affect the mental sphere of patients - symptoms of depression or anxiety often appear [39]. Lowered mood and libido may also result indirectly from vasomotor symptoms [43]. After the tibolone therapy, an improvement in mood was observed, and beneficial effects were also noted in women struggling with the problem of chronic fatigue or reduced motivation [30].

The positive influence on the mental aspects can be explained by several mechanisms. Firstly, scientific studies have shown that oestrogens affect serotonergic, dopaminergic and adrenergic neurotransmission and increase the concentration of beta-endorphins in both plasma and pituitary gland [30,39]. It is presumed that the increase in the level of androgens positively correlates with the level of beta-endorphins [39]. These chemical compounds are endogenous opioids influencing thermoregulation, behavioural functions and showing analgesic properties [44]. It was also proved that tibolone increased their concentration and stimulated the synthesis of allopregnanolone - a neurosteroid that acts agonistically in relation to the GABAa receptor [39, 44]. Stimulating the activity of this receptor reduces the level of anxiety and has a sedative effect [39].

Sexual functions

In the menopausal period, a frequently reported complaint is a decrease in the level of satisfaction with sex life [43]. Oestrogen deficiency predisposes to the development of atrophic vaginosis and urethral syndrome. These diseases are one of the causes of dyspareunia, which negatively affects the quality of sexual life [30]. In addition, decreased libido may be

a result of a decrease in androgen levels, as well as a consequence of accompanying mood disorders. Oestrogens positively influence the function of nerves in the genital system and increase vaginal lubrication [43]. It has been shown that tibolone reduces the symptoms of atrophic inflammation, stimulates vaginal blood flow and stimulates lubrication [30, 45]. Thanks to its affinity to androgen receptors and the reduction of SHBG concentration in the plasma, it increases the concentration of free testosterone, which is responsible for maintaining normal libido. As a consequence, patients more often undertake sexual contacts and report an increase in desire, excitement and satisfaction with intercourse [39].

Other side effects

Side effects in patients taking tibolone not covered in the above considerations include abdominal pain, weight gain and bloating. Some patients reported vaginal bleeding, breast tenderness, genital pruritus, headaches, the hirsutism. [5] Short-term increases in serum transaminases were also noted in clinical trials. Several cases of liver injury correlating with treatment have been reported. Treatment has been identified as causing clinical liver injury, but the mechanism is unknown. So far, there have been no cases of acute liver failure, death, or chronic hepatitis [46].

Two studies suggest that tibolone may worsen the vaginal infection, although neither of them has provided an aetiology. One study reports urinary tract infections [47]. There was a case of a patient with polycythaemia secondary to the use of tibolone [48]. In in vitro studies, tibolone induces the proliferation of glioblastoma cells, which may be related to its activity at oestrogen and progesterone receptors. However, it does not affect the migration or invasiveness of neoplastic cells [49].

Conclusions

According to data published by the European Commission, every third adult will be over 65 by the end of 2060. The progressive ageing of society is not only an economic challenge but also a medical one, which is why it is so important to focus the scientific development on ailments that often occur among geriatric patients. This idea led us to discuss drug therapy with tibolone. Its uniqueness and the possibility of utilizing pleiotropic effects is because, despite being classified as a selective regulator of estrogenic activity, it also has progestogenic and androgenic effects. Tibolone may be used as an alternative therapy in patients who do not tolerate conventional hormone replacement therapy because it shows similar effectiveness and greater effectiveness in reducing breast tenderness or vaginal bleeding. The effect on cancer development is uncertain – studies describing an increased risk of endometrial cancer and a decreased likelihood of developing breast cancer compared to HRT are emerging. The effect of tibolone on the cardiovascular system remains inconclusive - some studies suggest that it accelerates the progression of atherosclerosis and is pro-fibrinolytic, but other articles present just the opposite conclusions. Tibolone reduces the risk of vertebral and non-vertebral fractures, especially in women with a previous fracture or with risk factors. Concerning the central nervous system, a neuroprotective effect, improvement in semantic memory and learning, as well as an unfavourable effect in the field of task planning, have been noted. In the described studies, tibolone turned out to be effective in patients with increased anxiety or decreased motivation, which most likely results from the increased concentration of beta-endorphin in the body. Due to the increase in vaginal flow and lubrication, women reported an increase in sexual satisfaction. The most common side effects include weight gain, headaches and abdominal pain, vaginal itching and bleeding, and hirsutism. Summarizing this article, the mechanisms of action and clinical implications of tibolone are still not fully understood. It is necessary to conduct further research on this drug, which may significantly affect the effectiveness of pharmacotherapy in the population of geriatric patients.

Conflict of interests: *The authors declare that they have no competing financial interests.*

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VIA MEDICA

REVIEW ARTICLE

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Starting from scratch: building a new curriculum for faculty development program in emergency medicine by repurposing from a systemic review

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ABSTRACT

Introduction: As we move towards globalization, health care professionals may find themselves working in a healthcare system that has a different patient population and disease epidemiology than their training. This study aims to develop a curriculum for a faculty development program for emergency medicine health care professionals in a private hospital in Kuwait who find themselves in such a situation.

Material and methods: Using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines, the authors systematically searched PubMed, CINAHL and ERIC from the inception of the database until June 2018, for search terms that would capture curriculum development for faculty development programs in emergency medicine or trauma. Two independent reviewers for relevance reviewed abstracts; included studies were retrieved for full-text analysis. A curriculum was developed using the topics requested by the needs assessment using the recommendations from the systematic review.

Results: A total of 92 papers meeting the search criteria were identified of which 5 were included in the analysis. All 5 articles had education as the main objective of the curriculum for the faculty development program. All 5 articles had a faculty development program that was in the classroom setting. Four articles (80%) included a target audience of senior staff. Four articles (80%) recommended mentoring as an effective method for faculty development.

Conclusions: The most effective method of the faculty development program was through mentorship. Further research is needed to dictate faculty development focusing on non-educational objectives.

Key words: faculty training

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Introduction

As we move towards globalization, physicians may find themselves training in one type of healthcare system to attain formal certificates and degrees, only to find themselves practising in a different system. Health care professionals may find themselves working in a healthcare system that has a different patient population and disease epidemiology than where they trained. Each healthcare system with its unique challenges brings forward a need to develop and enhance a certain skill set. Furthermore, the challenging health needs and advanced knowledge in health and medical science are constantly evolving, resulting in a need to further update medical practice. Many of the skills required to practice medicine are achieved in formal training at the beginning of one's career such as in residency. Aside from these formal training programs, a faculty development program is the primary means of expanding beyond existing skills, which will assist healthcare professionals in multiple roles, ranging from clinical to leadership skills. There are, however, limited opportunities available to formally develop professional skills needed to maintain the practice in the evolving fields of medicine. Healthcare professionals have either acquired skills "on the job" or seek training specific to the needs they feel they need to acquire [1]. Except for clinical updates and leadership roles, faculty develop-

ment programs may aim to develop several objectives that do not fall in these categories, such as developing inter-professional collaboration and understanding social interaction with patients. Steinert highlighted the importance of faculty development to respond to advances in medical education and healthcare delivery, to continue to adapt to these growing responsibilities and requirements of healthcare professionals in their respective fields in medicine and to expand their focus and consider different training methods and formats and encourage new partnerships and collaborations [2]. Faculty development should also take into consideration as mentioned by Gappa et al, the evolving factors that have important implications on healthcare professionals and their continuing education [3]. These factors include the increasing diversity of learners who come from different cultural and academic backgrounds. Furthermore, effective faculty must support the learning of those learners with diverse learning needs and develop curricula and teaching strategies appropriate to the practice environment.

This evolution of practice is demonstrated in emergency medicine, a speciality that continues to grow in scope, activity and serves as an essential component to patient safety. This consistent evolution covers both scopes of the day-to-day treatment needs as well as the planning and leadership roles for disaster preparedness. There are more than thirty countries that have recognized emergency medicine as a speciality. In those countries where the field is not yet recognized, many are pursuing speciality recognition and developing training programs [5, 6]. With the increasing complexities of medical training, emergency physicians who take on education leadership roles require an in-depth understanding of knowledge transition to be able to identify, train and evaluate the needs of a faculty [4]. Curriculum design for a faculty development program should focus on the desired outcomes that the program aims to achieve to allow healthcare professionals to become more competent. The competency-based education approach allows learners to increase their ability to acquire and integrate knowledge, skills and attitudes in medical practice.

As a country, Kuwait developed a residency program in emergency medicine in 2010, having graduated the first cohort of board-certified emergency medicine consisting of two doctors in 2015. Presently, there is a deficit in the number of board-certified emergency physicians across the seven ministries of health hospitals. This means that physicians working in the emergency departments in Kuwait have a unique challenge in that they have very minimal training in emergency medicine having mostly trained in internal medicine or general surgery. These physicians who have not trained in Kuwait are not aware of the healthcare system or patient population in the country. Healthcare in Kuwait has emergency departments seeing 1000–1300 cases per day. This high flow of cases accompanied by limited electronic data of the patients' previous history including previous labs, ECGs and medications make treating patients a challenge. Kuwait also has very limited use of the family physicians making the main health contact the emergency department. Therefore, a faculty development program is required to educate these healthcare professionals to become updated in emergency medicine practices as well as team science in day-to-day clinical needs and disaster preparedness. Many patients in Kuwait view emergency physicians as non-specialized junior doctors that only triage patients. Patients believe that the more experienced specialists are the in-house departments such as internal medicine and general surgery, thereby calling on emergency physicians to consult the in-house services. These misconceptions have to be addressed especially with the growing number of specialists in the field that are overseeing the care of patients. Faculty development programs are the cornerstones needed to bridge the gap between board-certified and non-board-certified emergency physicians.

Literature notes that curriculum development for faculty development programs requires strategies for deep interrogation of the needs and gaps. Curriculum development can be achieved using several theories. One of which is Kern's curriculum development which aims to identify the problem through a needs assessment to transform the current approach to an ideal approach and tapering it to fit the learner and the learning environment [7]. In addition, the use of backward design, a method of designing an educational curriculum by setting goals before choosing the instructional methods and forms of assessment is also helpful. It focuses on the required outcomes using the end goal as the driver to construct objectives of the curriculum.

Fink uses the taxonomy of significant learning and focuses on learner development such as that of a faculty [8]. In understanding and addressing the motivational drivers of learners and incorporating them as a part of a curriculum, learners can be more engaged in the learning process. When learners learn something about themselves or others, these human dimensions enable them to interact more effectively to understand the personal and social implications of what they have learned. Using needs assessment to construct the objectives and curricula will give motivational energy to what learners are learning. Lastly, integrating within the curriculum on how to be a better learner will allow learners to be more self-directed and become more effective learners.

Material and methods

Literature search

A systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA). Three databases were systematically searched: PubMed, CINAHL and ERIC from their inception until June 2018 for relevant English-language studies. Institutional Review Board approval was not required for this study as it was a systematic review of the published literature. Literature search strategies in these databases used a combination of subject headings and index terms as well as keywords relating to faculty development, curriculum development and emergency medicine. Multiple searches were performed in each database and an example in PudMed and CINAHL is shown below.

Search #1

In the primary search, the search terms used were ("faculty development" or "faculty training") and "needs assessment" and (emergency or trauma). This yielded 12 results in PubMed and 3 results in CINAHL.

Search #2

In the secondary search, curriculum development or curriculum design was used as a broader search instead of needs assessment. This was not to miss any other methods of curriculum design. The search terms were ("faculty development" or "faculty training") and ("curriculum development" or "curriculum design") and (emergency or trauma). This yielded 9 results in PubMed and 6 results in CINAHL.

Search #3

In the third search, to cover the database ERIC, there were no specific articles related to Emergency Medicine. Two ERIC searches were conducted that used more expanded terms related to medical school faculty in general. The target population to cover graduate medical school was the closest to emergency medicine depicting postgraduate study. The search terms were (DE "Faculty Development") AND (DE "Medical School Faculty" OR DE "Graduate Medical Education" OR DE "Medical Education" OR DE "Medical Schools") AND (DE "Needs Assessment"). This yielded 12 results.

A secondary search was done in ERIC with the substituted term needs assessment for curriculum design and curriculum evaluation as follows, (DE "Faculty Development") AND (DE "Medical School Faculty" OR DE "Graduate Medical Education" OR DE "Medical Education" OR DE "Medical Schools") AND (DE "Curriculum Development" OR DE "Curriculum Design" OR DE "Curriculum Evaluation"). This yielded 50 results.

Criteria for eligible papers

Eligible manuscripts had to be full-length peer-reviewed publications that outlined faculty development programs. Broad inclusion criteria included articles that based their research primarily on emergency medicine. Articles were considered if they included a target population of learners that had no formal training in the field, they were currently practising in. Papers were excluded if they were not related to faculty development programs and their curriculum development. The objectives of the faculty development programs were to address both clinical knowledge and non-clinical knowledge such as the flow of patients and leadership skills. Articles outlying the roles or needs of emergency medicine physicians were also reviewed.

Article review process

The process for reviewing and selecting articles is presented in Figure 1. A total of 92 abstracts were independently reviewed by two authors (SQ and EA). 86 articles remained after removing duplicate articles. Of these, 76 publications were excluded based on abstract review. Abstract inclusion decisions that were discordant between the two reviewers were reconciled between themselves without a third party. 10 papers for full-text review were retrieved, of which 5 were deemed to be eligible for inclusion.

Data analysis

Two reviewers (SQ and EA) independently extracted data from the 5 papers using a standard data collection protocol that included speciality, faculty development program objectives (whether clinical, educational or administrative), training setting (classroom, clinical setting or simulation), trainee level (junior or senior), curriculum length and methods of instruction. When there were different conclusions between reviewers, further joint discussion led to a final consensus.

Results

Of the 5 publications between the start of the search engine to June 2018, 2 (40%) were published in the last 5 years. A summary of key findings is presented in Table 1 with specific characteristics. The objectives of the faculty development program were subdivided into (1) clinical such as cases or bedside teaching, (2) administrative such as leadership roles and (3) business

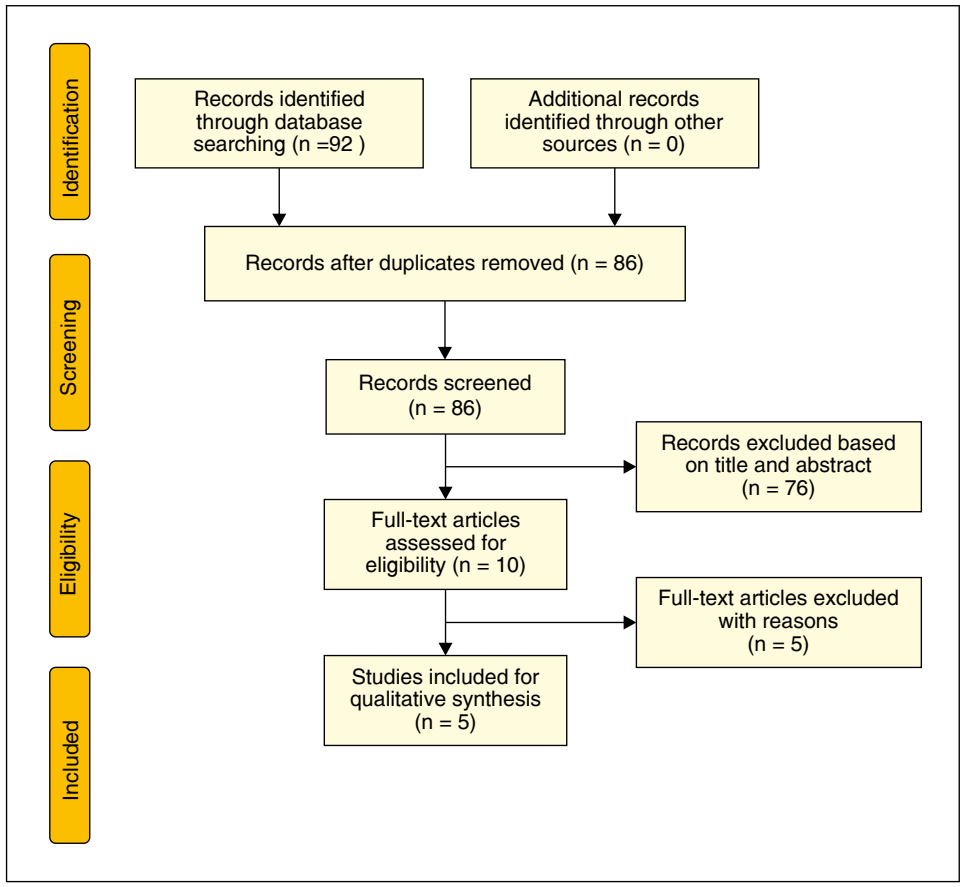

Figure 1. The process of reviewing and selecting articles

Table 1. Summary of key findings extracted from articles used for this study

Author objectives	Speciality	FDP	Setting	Level	Length	Recommended instruction
Woods et al.	EM	Educational	Classroom	Senior	Not specified	Mentorship
Brown et al.	EM	Clinical, educational, administrative	Classroom, simulation, clinical research	Junior, Senior	Not specified	Need for FDP
Farley et al.	EM	Clinical, educational, administrative	Classroom, clinical, simulation	Junior	Not specified	Mentorship, bedside, research
Bandiera et al.	EM	Educational	Classroom	Senior	Half-day	Objective setting, feedback, seeking teaching opportunities
Alagappon et al.	EM	Clinical, educational	Classroom, clinical research	Junior, Senior	Variable	Mentoring, fellowships, rotations

EM — emergency medicine

models, educational or research. The level of the learner was subdivided into junior or senior, defined as less than or greater than 10 years in the field respectively. Recommended instruction that originated out of the article included mentorship or coaching techniques that gave a one-on-one level of training while the learner was applying what was learnt.

All 5 articles had education as the main objective of the curriculum for faculty development programs. 3 of the articles had more than one objective, 3 articles had clinical objectives, 2 articles had administrative objectives and 2 articles had a research objective. All 5 of the articles had a faculty development program that was in the classroom setting; they were in lecture format

as the instructional design of the teaching. Of those five articles, three had a faculty development program that included more than one instructional design as a teaching format. Simulation appeared in all 3 articles and clinical appeared in 2 articles.

Four articles (80%) included a target audience of senior staff. This included senior emergency physicians either as the sole learners or with junior staff. Four of the articles (80%) recommended mentoring as an effective method of faculty development. One of the articles recommended faculty development program was needed through a conducted needs assessment without going into detail on the instructional design of the program.

Discussion

Faculty development programs have continued to be the main form of faculty development after formal training. Emergency medicine being a fast-evolving speciality requires continuity of education to achieve the fast-developing skills. Few opportunities exist during medical training to formally develop these required professional skills [2]. The results of this systematic review suggest that a mentorship or coaching method is recommended as part of faculty development

for learners to learn the required skills. This is particularly true if the skills needed were that of an educational objective.

Apart from formal training certificate and degree programs, faculty development is the primary means of expanding beyond existing skill sets. Faculty development provides "the broad range of activities that institutions use to renew or assist faculty members in their multiple roles. [9]" More recently, the faculty members themselves through focus groups and surveys are constructing the content and format of such programs [10–12]. These needs assessments are useful in identifying the specific gaps in knowledge or training that faculty development can address [13,14].

Limitations

The current report has several limitations such as not capturing faculty development curricula that have not been published at all, or in the traditional peer-reviewed literature. In addition, although used broad search criteria, the search was focused on emergency departments and limitations of this search were finding studies that conducted their research on a similar target learners' population as the one in Taiba Hospital; healthcare professionals with no training in emergency medicine, although working in an emergency department for many years. The search studies classified the learners as juniors undergoing emergency medicine training or seniors, having completed their residency training. As a result, the faculty development programs focused mostly on non-clinical objectives such as research, educational and administrative needs. Despite searching multiple databases there are likely faculty development programs that have addressed a similar issue but have not published on them.

Conclusions

Faculty development programs provide the majority of post-residency education and training to keep with the evolving field of Emergency medicine. The most effective method of the faculty development program was through mentorship and pairing healthcare professionals to support each other with clinical and administrative challenges. In follow- up, taking into account the results of the systematic review, a needs assessment was conducted to bring together a curriculum for an inter-professional faculty development program for emergency medicine physicians and nurses at Taiba Hospital in Kuwait. A faculty development program titled Emergency Department Faculty Development Program (ED-FDP) was structured by pairing the board-certified Emergency Department (ED) staff physicians with the non-board-certified staff physicians to provide mentorship for any clinical and/or administrative issues. Further research is needed to dictate faculty development focusing on non-educational objectives.

Appendix

Demographic

— What is your job in the hospital?
— How many years have you been working in the ED department since the start of your career?
— Have you attended a faculty development program before?

Curriculum structure

— Have you used medical database search engines such as PubMed to give a lecture?
— Which topics would you like a faculty development program to focus on?
— Would you like sessions on-spot diagnosis of cases? E.g., pathognomic rashes, X-ray findings?

Doctors: How confident do you feel while performing the following procedures?

— Point of care ultrasound
— Suturing
— Intubation and airway management
— Casting
— Eye exam

— Central line insertion
— Managing special populations e.g., pregnant women, paediatrics
— Documentation
— Other: please specify ……..

Nurses: How confident do you feel performing the following procedures?

— Triaging
— Assisting in critically ill patients
— Managing special populations e.g., pregnant women, paediatrics
— Other: please specify ……..

Instructional design

— Do you feel you would like to focus on the theory of these topics in lecture format?
— Would you like to focus on the clinical component discussing cases
— Do you feel you would like to focus on the partial components?
— Have you attended a design thinking session before?
— Do you agree for the lectures to be recorded?
— Have you ever attended a simulation session before?
— How confident are you in critical appraisal of medical journals?

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VIA MEDICA

REVIEW ARTICLE

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A narrative review on the use of lip trainer (Patakara) in oral rehabilitation

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ABSTRACT

The spent time on body exercising is usually given more interest than the exercise of lips, especially after the wide evidence-based demonstrated effects of strong lips on the general health and hence the quality of life. Oral rehabilitation leads to a powerful closure of the lip that can be the first-line defensive mechanism against the many oral dysfunctions as halitosis, snoring, mouth breathing and dryness, and dysfunctions of the oro-gastrointestinal system. The strong lip seal or closure gained from the continuous use of lip muscle trainer (Patakara) not only limits the deteriorated normal physiological oral functions that are associated with the ageing process but also can be considered a good oral rehabilitation device to many oral dysfunctions such as halitosis, snoring, mouth breathing and dryness, and dysfunctions of the oro-gastrointestinal system. Incorporating the use of lip muscle trainer in traditional physiotherapy and rehabilitation programs — especially for geriatrics — is a fundamental part of the whole treatment plan. Physiotherapists must direct their attention toward Patakara utilization in future oral rehabilitation studies to augment and affirm more benefits for this hopeful device. Advising the family relative or caregivers to encourage the elderly to use the lip muscle trainer for maintaining a strong lip is very important.

Key words: Patakara, oral rehabilitation, oral health, lip muscle trainer

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Introduction

The complex feature of lip closure can be accomplished by the integration of variant numbers and types of movements of the orbicularis oris muscle (OOM), with additional face muscles that have fibres moving in all directions around the perioral complex [1]. Since it can influence various daily activities, the functional strong lip is vital to remember [2]. Many functions — such as talking, chewing, and swallowing — belong to the action of OOM [3].

The process of ageing-related steady decline in muscular quality, strength, and mass is the general definition of sarcopenia [4]. Sarcopenia-related functional and structural changes appear in all body parts involving the tongue and lip muscles, oral and perioral complexes, and oral sensation [5]. Increased ageing-related tooth loss is a predisposing factor for weak tongue and labial muscles [6]. Atrophy, smaller fascicles and bundles, and changed fibre shape are the main reported form and consistency ageing-related changes of OOM [7].

It is important to maintain an effective labial closure because the strength of OOM decreases with the ageing process, resulting in an incomplete labial closure and unhealthy oral medium due to the saliva evaporation. Weak labial closure and decreased tongue movements — in cerebrovascular neurological insults — negatively impact chewing, digestion, and swallowing in the oral cavity [3].

Strength of orofacial musculature and, hence a strong labial closure is gained by the repeated performance of oro-facial muscle contractions via electro-stimulation [8] or oral rehabilitation devices including lip muscle trainer (Patakara) [9]. Although Patakara is not a relatively new device, studies on it are very limited. This narrative analysis, therefore, seeks to discuss the benefits of Patakara on oral health.

Origin and history of Patakara

In the early 1900s, in the field of orthodontic therapy, with the help of orofacial muscular training, Rogers introduced oro-myofunctional appliances (OMFA) to

the patients with growing maldentition to correct the unusual pattern of deglutition, treating the myofunctional and/or myoskeletal problems [10], focusing on the normal swallowing and nasal breathing, improving the balance of oro-facial musculature, and to promote mandibular development [11].

Oro-facial training is an individualized rehabilitation regimen of resisted or active free oro-facial movements. Oro-facial training aims to correct or affirm the normal tongue posture, treat the imbalance of facial musculature, regain the tongue-cheek muscular balance, correct the abnormal chewing and swallowing patterns, and normalize the neuromuscular functions of the oro-facial complex [12]. OMFA emerged the idea of OMT-based devices because in 2000 Dr Akihiro, a Japanese dentist, invented the Patakara. This is a simple, non-invasive, easy-to-use, oral-rehabilitation device used to enhance oral health (by strengthening labial closure), and hence the quality of life (QoL) of the elderly [13].

Segments of Patakara

The highly elastic plastic Patakara [14] is made from a polyester-elastomer material (this material is a very highly elastic rubber-polymer-plastic composite) [9]. Due to its resilience, Patakara is designed to be placed between the upper and lower lips in the oral cavity to improve the conditioning of oral musculature [14]. Patakara consists of two parts: the first part (enters that oral cavity and is called as Pataleara which is considered as the fundamental big part with two sides, upper and lower sides) and the second part (plastic tabs) (Fig. 1).

Guidelines of Patakara use

Firstly, close the mouthpiece. Insert the Pataleara between teeth and lips. Without clenching the teeth, the person must contact the upper side to the lower side of Pataleara via closing lips for five minutes. During this time, the patient is ordered to constantly touch the tip of the tongue to the incisive papilla. During the five-minute lip closure, the person is ordered to perform at least 10-repetition stretching-movement by maximally drawing the plastic tabs of Patakara to front, right, left, upper, and lower directions without letting the device to be released from the oral cavity (this can be applied by the continuous firm closure of upper and lower lips during the exercise). This five-minute session may be repeated 5 times daily [15].

Patakara indications

Patakara can be used to address many oral dysfunctions as snoring, mouth breathing and dryness, halitosis, and oro-gastrointestinal dysfunction [13].

Restoring the normal breathing from the nose

Respiration is normally conducted from the nose. Conduction of respiration from the mouth or nose and mouth more than six months is defined as the habit of mouth breathing (MB). MB is related to ageing-related OOM and labial closure weakness, halitosis, mouth dryness, dental caries [16], the tongue's low resting position, weakness of oro-facial muscles [17], and dysfunction of dilating muscles of airways that present in obstructive sleep apnoea (OSA) [18].

OOM is the fundamental muscle included in the labial closure. From the middle of the fifth age decade, labial closure strength (LCS) begins to decrease to meet its minimum value at over 80 years [19]. Weak LCS and tongue elevation induce mouth breathing and snoring during sleeping. The gained appropriate LCS and tongue elevation by Patakara correct the breathing from oral to the nasal pattern. Patakara declines the apnoeic symptoms in patients with OSA by increasing the strength and force of OOM [15] in addition to improving the oxygen saturation [20].

Snoring problem

In the elderly, snoring is a very common health problem with some related risk factors, such as obesity and a large neck circumference [21]. It is understood that during sleep, most snorers exhibit a pattern of mouth breathing. Snoring can be theoretically decreased by increasing the pharyngeal airway space by shifting the tongue anteriorly to recompense for the lost neuromuscular function of genioglossus muscle (the main muscle of pharyngeal opening) [22]. Repetitive anterior placement of the tongue to the incisive papilla during the Patakara oral training may enlarge the upper airway space. Wide upper airway space corrects snoring by shifting the breathing pattern from oral to nasal breathing [15].

Halitosis (bad mouth malodour)

Halitosis negatively affects the social and psychological QoL in many subjects suffering from this embarrassing health problem [23, 24]. Development of malodorous substances and, hence halitosis is produced from the dry mouth that induces the growth of anaerobic and gram-negative bacteria. OSA, ageing, mouth breathing [20], and systemic disorders such as diabetes [25] are commonly associated with dry mouth. Using Patakara increases saliva flow [20] that eliminates halitosis by lowering the number of oral bacteria and enhancing the wetness of oral mucosal tissue in geriatrics [26]. Also, increased upper airway space in patients with OSA in addition to the return to normal nasal breathing pattern [15].

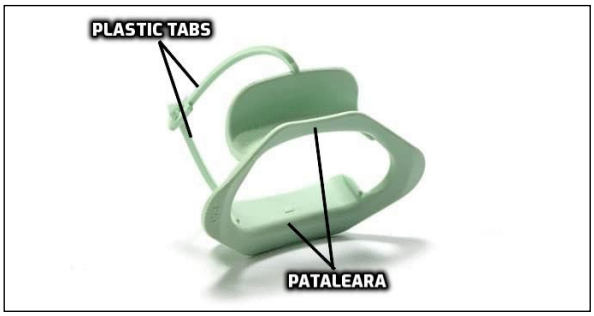

Figure 1. Segments of Patakara

Mouth dryness

The subjective symptom of decreased saliva secretion is the definition of dry mouth or xerostomia, whereas the objective finding of low saliva flow is hyposalivation [25, 27]. Xerostomia and hyposalivation are risk factors for periodontitis, dental caries, local oral and systemic infections, feeding and swallowing problems, and upper gastrointestinal dysfunctions [28].

Oral training by Patakara can improve the saliva flow, wetness of oral mucosa [14], and oral pain that may present in geriatric-related chronic periodontitis [26]. Hypofunction of the salivary reflex arch (afferent arm, salivary nucleus, and efferent arm) in addition to the progressive cellular loss of the motor nervous system (including the facial nerve and its supplying facial muscles) — is reported with the ageing process. Repeated contractions and stretching to oro-facial muscles — with the help of Patakara training– trigger the afferent receptors and branches of the facial nerve in facial muscles that, in turn, stimulate the salivary nucleus in the brain that activate the efferent arm (salivary glands) to increase the production saliva flow [14].

Oro-gastrointestinal dysfunctions

Ageing-associated physiological hypofunctions occur in many physiological processes of the body including swallowing. This changed swallowing process in the elderly occurs due to the declined neuromuscular reserve [29], teeth loss, less-efficient mastication, decreased density and cross-sectional area of jaw muscles [30], declined volume and pressure of tongue muscle (it produces the adequate force to transit the chewed food parts to the pharynx), down-shifted location of the larynx in some geriatrics, the overspread of pharynx cavity, and the large-timed and small-sized opening of the upper-oesophageal sphincter [29].

The involved tongue isometric strengthening exercises [31] during Patakara training [15] can improve swallowing dysfunctions. The repeated isometric exercises of the tongue can improve the ageing-related declined capacity of motor functions of the tongue, enhance tongue pressure and strength, control the food bolus, and hence improve the dietary-intake functions in the geriatric mouth [32].

In eating disorders, Patakara can boost the geriatric QoL as the oro-facial muscle training can boost nasal respiration due to the corrected integration between the nasal cavity, the location of the tongue, the larynx, and the airways. Patakara-induced parasympathetic stimulation may be the cause of improved salivation in addition to the enhanced subjective symptoms of gastrointestinal dysfunction such as epigastralgia, early satiety, constipation, and anorexia especially in geriatrics with poor nutrition [19].

To gain the normal dietary functional intake, it is noted that using food in oral rehabilitation raises the risk of pulmonary aspiration. The frequent use of a lip muscle trainer (Patakara) in the rehabilitation of oral and/or eating dysfunctions can lower the risk of pulmonary aspiration and further raises the value of geriatric lip closure training [33].

Conclusions

The strong lip seal/closure gained from the continuous use of lip muscle trainer (Patakara) not only limits the deteriorated normal physiological oral functions that are associated with the ageing process but also can be considered a good oral rehabilitation device to many oral dysfunctions such as halitosis, snoring, mouth breathing and dryness, and dysfunctions of the oro-gastrointestinal system. Physiotherapists must direct their attention toward Patakara utilization in future oral rehabilitation studies.

Conflict of interests: *The author declares no conflicts of interest.*

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VIA MEDICA

CASE REPORT

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Minimally reduced levels of anti-Spike IgG after nine COVID-19 convalescent plasma donations: a case report

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ABSTRACT

Despite intensive research, the physiology of the serological response to SARS-CoV-2 infection and its dynamics during the recovery period remain incompletely understood. Regulation of the immune response seems all the more important as it plays a role in both virus clearance during infection and the potential development of long-term resistance to reinfection. A case of convalescent plasma donor is described in whom was observed a prolonged enhanced immune response to infection in the form of a persistently high level of anti-Spike IgG despite subsequent plasma donations. The presented donor experienced COVID-19 interstitial pneumonia, requiring pharmacotherapy in a hospital setting (therapy involving azithromycin, chloroquine and protease inhibitors), which allowed him to achieve remission. The described donor donated plasma nine times during convalescence, each time showing a satisfactory level of anti-Spike IgG. The presented case highlights the multifactorial regulation of the serological response in the course of SARS-CoV-2 infection, which may include the long-term effect of pharmacotherapy, especially in the field of antiretroviral drugs. While the authors are not yet able to clearly define the importance of antiretroviral therapy in regulating the humoral response in COVID-19 patients, it is supposed it may be important in the subsequent antibody production.

Key words: antiretroviral, azithromycin, chloroquine, convalescent plasma, COVID-19, SARS-CoV-2

Med Res J 2021; 6 (2): 157–160

Introduction

The SARS-CoV-2 virus, which is the cause of the global pandemic, is the subject of intense research involving almost the entire world of science. Many aspects of viral biology remain unknown, including the physiology of the serological response to infection and the mechanisms regulating its severity in both asymptomatic and symptomatic (including those developing the COVID-19 disease) patients [1]. Understanding the regulation of the immune response as a reaction to SARS-CoV-2 infection seems to be all the more important as it plays a role in both viral clearances during infection and the potential development of long-term immunity to reinfection. While the half-life of anti-SARS-CoV-2 IgG antibodies has been determined to be around 36 days [2], due to the relatively short time of observation of the virus, determining the overall duration of the immune response is not possible yet. It is worth noting that the key elements in the long-term response to infection are ultimately differentiated B-cell lines, known as antibody-secreting cells (ASCs), which determine the humoral immune response and mechanisms that regulate their function [1]. An extremely important issue here seems to be the directing of the B-cell differentiation process towards long-lived or short-lived plasma cells [3], which may determine resistance to reinfection or be no less important in the context of obtaining convalescent plasma for the needs of later transfusions. It should also be assumed that further understanding of the immune response also requires an evaluation of the influence of pharmacotherapy on the modulation of the immune response, both during an ongoing infection and upon extinction of the immune response, understood as the

recovery phase. A case report of a man with a history of SARS-CoV-2 infection is presented, complicated by COVID-19 interstitial pneumonia, in whom was observed a prolonged enhanced immune response to infection in the form of a persistently high level of anti-SARS-CoV-2 antibodies in the IgG class despite subsequent plasma donations.

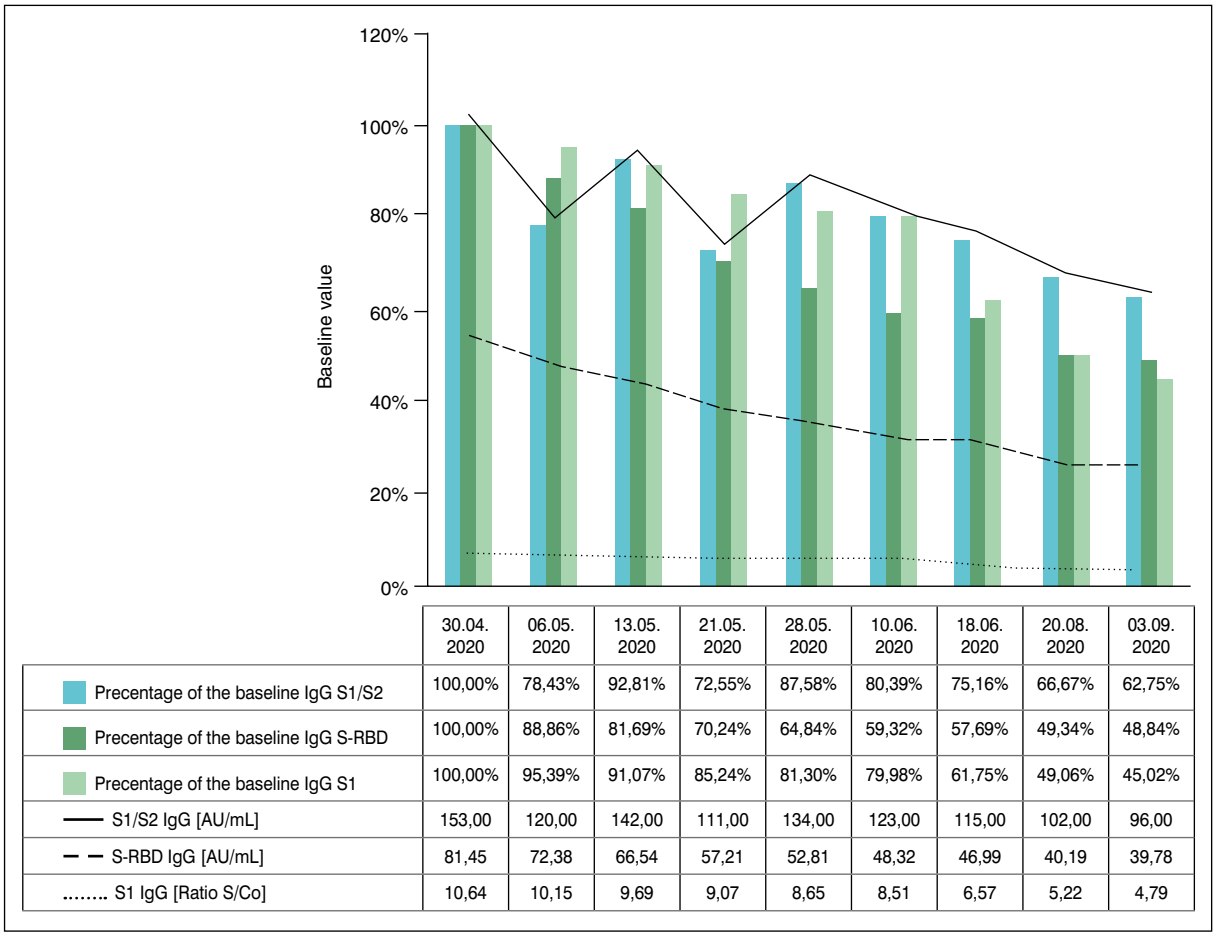
Case report

A 52-year-old man came to the facility for a convalescent plasma (CCP) donation having been previously infected with the SARS-CoV-2 virus, complicated by the development of COVID-19 interstitial pneumonia, requiring hospitalization in the Department of Infectious Diseases. The diagnosis was made based on a positive real-time PCR test (nasopharyngeal swab taken on March 30th, 2020) and the presence of characteristic clinical symptoms (fever > 38°C and cough, which appeared 3 days after returning from a trip to Georgia). In the laboratory tests performed on admission to the hospital, apart from an increased concentration of C-reactive protein (CRP) (14.25 mg/L, normal range: 0.00–5.00 mg/L) and an increased level of D-Dimer (907.00 ng/mL, normal range: < 500 ng/mL), no significant laboratory abnormalities were found. The complete blood count was within the normal range and the parameters of the white blood cell differential count were as follows: WBC 4.45 x 10^3/mL; NEU 2.92 x 10^3/mL; LYMP 1.04 x 10^3/mL, MONO 0.46 x 10^3/mL, EO 0.01 x 10^3/mL; BASO 0.01 x 10^3/mL. After the initial stage, during which only febrile episodes and persistent cough were observed, the patient's general condition deteriorated with the development of dyspnoea requiring passive oxygen therapy and interstitial pneumonia, confirmed by a CT scan of the chest. For this reason, treatment with a macrolide antibiotic (azithromycin) was initiated. Due to increasing values of the inflammatory markers (CRP 40.39 mg/L), deterioration of the patient's clinical condition and progression of changes in the radiological image (appearance of new lesions with morphology characteristic of COVID-19 pneumonia), antiretroviral therapy (protease inhibitors combination - lopinavir/ritonavir) and chloroquine were added to the pharmacological treatment in an attempt to reverse disease progression. In the following days of hospitalization, improvement in the clinical condition, a decrease in the concentration of inflammatory markers and gradual disappearance of changes in the radiological image were observed. Analysing the clinical course and the results of laboratory and imaging tests, the course of the disease was classified as moderate, based on the developed guidelines for the management of COVID-19 [4]. At discharge from the hospital, the white blood cell differential count presented as follows: WBC 5.62 x 10^3/mL; NEU 2.91 x 10^3/mL; LYMP 1.92 x 10^3/mL, MONO 0.63 x 10^3/mL, EO 0.11 x 10^3/mL; BASO 0.03 x 10^3/mL. After nearly four weeks of hospitalization, the patient was discharged home in good general condition.

On April 30, 2020, five weeks after obtaining a positive (+) PCR test for SARS-CoV-2 virus RNA and two weeks after the last negative (–) PCR test for SARS-CoV-2 virus RNA, the said donor reported to the facility for the first time. Following the qualification procedure, in line with the European Commission's convalescent plasma collection and transfusion program [5], 750 mL of plasma was collected using an automated plasmapheresis system. No adverse reactions were observed during and after plasmapheresis. In total, nine plasma donations were obtained over four months, at varying intervals, dictated by the work schedule of the donor. In samples taken before each plasma donation, the levels of IgG anti-SARS-CoV-2 antibodies against Spike S1 (Euroimmun, USA), Spike S1/S2 (DiaSorin, Italy) and S-RBD domain (Snibe, China) were determined using the enzyme-linked immunosorbent assay (Spike S1) and chemiluminescent immunoassays (Spike S1/S2 and S-RBD domain). According to the manufacturer's recommendations, the result was considered positive for the following test values: Euroimmun S1 IgG ≥ 1.1 [S/Co]; Diasorin S1 / S2 IgG ≥ 15 [AU/mL]; Snibe S-RBD IgG ≥ 1.0 [AU/mL].

Even though the determination of IgG antibodies against the S1 antigen of the SARS-CoV-2 virus indicates significant dynamics of decrease in the level of antibodies over time, the determination of IgG antibodies against the S1/S2 antigens and S-RBD domain of the virus showed much lower dynamics of decrease. Based on the observations of the described donor, it can be concluded that the time between confirmation of the infection in the PCR-RNA test and the moment when the antibody test is still positive amounts to 157 days.

Importantly, in each of the anti-SARS-CoV-2 S1/S2 antibody determinations, the antibody concentration values remained above 80 AU/mL, which, according to the available literature data [6], seems to correlate with the satisfactory level of neutralizing antibodies (nAbs). Also, concerning the anti-S-RBD antibodies, a strong correlation was demonstrated with the titre of neutralizing antibodies [7]. These observations are all the more valuable as conducting tests for the presence of neutralizing antibodies is time-consuming and involves several complicated procedures, such as providing a laboratory with a high microbiological safety class, which limits the implementation of this kind of tests by several institutions. The obtained results are presented in Figure 1.



	30.04. 2020	06.05. 2020	13.05. 2020	21.05. 2020	28.05. 2020	10.06. 2020	18.06. 2020	20.08. 2020	03.09. 2020
Precentage of the baseline IgG S1/S2	100,00%	78,43%	92,81%	72,55%	87,58%	80,39%	75,16%	66,67%	62,75%
Precentage of the baseline IgG S-RBD	100,00%	88,86%	81,69%	70,24%	64,84%	59,32%	57,69%	49,34%	48,84%
Precentage of the baseline IgG S1	100,00%	95,39%	91,07%	85,24%	81,30%	79,98%	61,75%	49,06%	45,02%
—— S1/S2 IgG [AU/mL]	153,00	120,00	142,00	111,00	134,00	123,00	115,00	102,00	96,00
– – S-RBD IgG [AU/mL]	81,45	72,38	66,54	57,21	52,81	48,32	46,99	40,19	39,78
..... S1 IgG [Ratio S/Co]	10,64	10,15	9,69	9,07	8,65	8,51	6,57	5,22	4,79

Figure 1. The level of anti-Spike IgG antibodies in subsequent convalescent plasma donations

Discussion

The presented case suggests that one should not forget about possible immunomodulation related to the applied pharmacotherapy while analysing the humoral response in the course of SARS-CoV-2 infection. Patients whose course of the disease is classified as moderate or severe deserve special attention as it is then that the pharmacotherapy that interferes with the immune system is used to eliminate the virus or stop its intracellular penetration, but also for fear of developing a "cytokine storm". According to the literature, the azithromycin and chloroquine used in this case are associated primarily with suppression of the immune system, including control of the production of pro-inflammatory cytokines such as IL-1 and IL-6 [8]. Direct evidence for the role of drug-induced immunomodulation was provided by studies involving the murine vaccination model, which showed that prior azithromycin therapy led to a significant reduction in the primary humoral response during pneumococcal vaccination [9]. Concerning proteasome inhibitors, the situation is much more complex as they both have a suppressive effect on selected proinflammatory cytokines, being at the same time also characterized by an ability to stimulate T-cell proliferation, which is the most desirable action in their primary indication - HIV infection. Importantly, it has been proved that antiretroviral therapy also significantly affects the proliferation and function of B cells, enhancing the humoral response to both HIV and non-HIV antigens [10]. Although the authors do realize that it is extremely important in obtaining an appropriate immune response during immunization in HIV positive patients [10], they are not yet able to define the significance of this interference with the immune system in the context of COVID-19 patients treated with antiretroviral therapy.

Conclusion

Although a long-term donor follow-up was conducted, the observations are limited due to single-subject analysis, which makes it difficult to draw firm conclusions. The authors are aware that much more cases are needed to support the presented hypothesis and findings. Nevertheless, the presented report shows the

multifactorial regulation of the serological response in the course of the SARS-CoV-2 infection, the understanding of which seems to be crucial in the further fight against the ongoing pandemic.

Author contributions: *Concept and drafting of the manuscript: TW, KR; critical revision of the manuscript for important intellectual content: AR, BBR, PR.*

Conflict of interest: *The authors declare no conflict of interest*.

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Gluteal subcutaneous calcifications on a patient with chronic back pain

Key words: calcification, granuloma, injection-site reaction, subcutaneous fat, computed tomography

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A middle-aged man presented to the emergency department with a three-day history of macroscopic haematuria and mild discomfort on his right lower back. He denied fever or other urinary complaints. His past medical history was significant for chronic low back pain, benign prostatic hyperplasia, and obesity, for which a bariatric surgery was performed 21 years earlier. In face of the clinical suspicion of nephrolithiasis, a computed tomography scan of the abdomen was ordered, confirming the hypothesis by showing nonobstructive micro calculi on the lower pole of the right kidney.

Surprisingly, though, multiple bilateral subcutaneous calcifications were seen on the gluteal region (Fig. 1). When questioned, the patient affirmed having received intragluteal injections of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids multiple times in the past for his low back pain.

A diagnosis of injection site granuloma was made. There is no data on the literature about the prevalence of subcutaneous calcification on the gluteal region secondary to inadvertent injection of an intramuscular drug on the fat tissue, with reports having been published about granuloma formation after administration of several medications, such as opiates, NSAIDs [1], leuprorelin [2] and Sandostatin [3].

However, given that about half of the intended intramuscular injections are mistakenly applied subcutaneously [4], injection site granuloma may not be a highly uncommon entity. Its importance resides on the possible differential diagnosis with more severe conditions, such as soft-tissue sarcoma, dermatomyositis and systemic sclerosis.

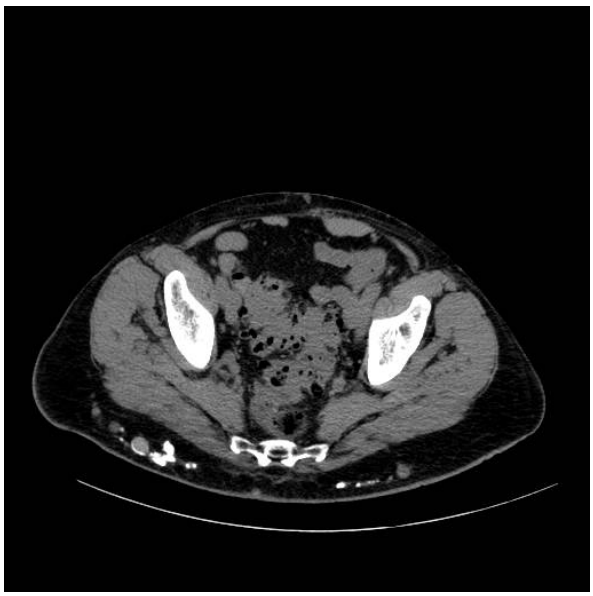

Figure 1. Axial scan of CT of abdomen evidencing well-demarcated lesions on the subcutaneous fat tissue, either fully or rim calcified

Bilaterality and lesion stability over time speaks against malignancy. The absence of muscle weakness or typical skin lesions makes dermatomyositis quite unlikely. For systemic sclerosis, one would expect an antecedent of the Raynaud phenomenon, sclerodactyly

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and digital ulcers. Heterotopic ossification usually has an identifiable trigger event, such as a history of trauma or joint replacement surgery. Accurate history taking may lead to the final diagnosis, obviating further workup [5].

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