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Diagnostic and Therapeutic Model of Sepsis and Purulent-Inflammatory Diseases

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Abstract

In this study, the method of fluorescence spectroscopy was used to improve the diagnostics and prediction of sepsis, pyo-inflammatory diseases and postpartum endometritis. At the first stage of the study, the researcher explored the fluorescence spectra of dilutions of serum with centrifuged and non-centrifuged bacterial culture (6-day crop sugar broth with Staphylococcus aureus), distilled water, 20% albumin and sugar broth. The focus was on the influence of treatment, including infusion therapy, on the fluorescence spectral characteristics of a patient's serum. At the second stage, the method of fluorescence spectroscopy was used for the diagnosis of sepsis *in vivo*. At the third stage, the analyst scrutinized the peculiarities of pregnancy, childbirth, and the postpartum period (totally, 40 parameters) in patients with postpartum pyo-inflammatory diseases and in the control group.

Keywords

Pyo-Inflammatory Diseases, Sepsis, Postpartum Endometritis, Method of Fluorescence Spectroscopy

1. Introduction

Despite an in-depth attention to the global epidemiological problem of sepsis, it has not been fully resolved yet. The focus has been on the selection of effective antibiotic regimens and other aspects of treatment. At the same time, the microscopic mechanisms of the aetiology and pathogenesis of sepsis have not been debated satisfactorily. It develops in over 30 million people annually and kills over 6 million out of them [1]. The prevalence of sepsis is the highest in low- and middle-income countries. Every year 3 million newborns and 1.2 million children suffer from sepsis [2]. Three out of ten deaths from neonatal sepsis are

likely to be caused by drug-resistant pathogens.

One tenth death due to pregnancy and childbirth is caused by maternal sepsis. In this case, 95% of maternal sepsis deaths occur in low- and middle-income countries [3]. One million newborns die every year due to maternal infections, including maternal sepsis [4].

Given the significant urgency of sepsis, particularly within the most recent thirty years, congresses and conferences were held around the world. Much attention is paid to the search for etiological factors, as well as the objective markers of the severity of patients' conditions (respiratory rate, heart rate, leukocyte level in the general blood test, etc.). There is enough adequate information on the pathogenetic factors of sepsis, but the molecular changes occurring at the molecular level are not well understood. This understanding is very important for explaining and exploring the pathogenetic component of treating sepsis. Treatment may not be as effective as necessary without the in-depth understanding of these aspects.

The recent achievements of medicine are closely linked to the successful development of biomedical research, in particular in the field of biological chemistry. Significant progress in these studies has made it possible to elucidate numerous complex mechanisms in the vital activities of the human body both in normal and pathological conditions. Today's methods of preventing and treating diseases involve the widespread use of biochemical research methods for their diagnosis, choice of drugs and treatment methods, as well as for monitoring the effectiveness of treatment.

The progress of studies and technology in the second half of the last century has led to the widespread use of physical methods for the diagnosis of diseases. Researches from the last few decades have shown that fluorescence spectroscopy is one of the most common and universal methods for studying biological tissues and liquids. In this paper, the main advantages of this method, such as high sensitivity, accuracy, expressiveness, will be used for the reliable diagnosis of sepsis and for the improvement of therapeutic tactics.

2. Literature Review

Due to the great significance of the sepsis problem, world congresses are dedicated to it. In 1991, the sepsis classification meeting in Chicago proposed the classification of sepsis based on the systemic inflammatory response syndrome to any inflammatory or non-inflammatory injury. The next definition of sepsis was discussed in 2001. The presence of clinical signs of systemic inflammatory response syndrome and suspected or proven infection at the time were the basis for the diagnosis of sepsis [5] [6] [7]. These criteria for the clinical diagnosis of sepsis and its classification, offered by the American College of Chest Physicians/Society for Critical Care Medicine (ACCP/SCCM), are still the basis for today's experts. But in recent years, additional information contributed to the understanding of this problem. Besides, clinicians needed clearer characteristics

to detect sepsis at the early stages of its development. So, at the 45th Orlando Intensive Care Congress in 2016, the Society of Critical Care Medicine and the European Society of Critical Care Medicine organized a working group of 19 specialists who gave a new definition of sepsis, *i.e.* Sepsis-3. According to their definition, sepsis is a life-threatening organ dysfunction caused by impaired regulation of the body's response to infection. The aim of the changes, proposed in 2016, was the acceleration of the diagnosis and improving the treatment of sepsis. In particular, clinical signs of sepsis are infection and organ failure due to the presence of this infection. The latter is measured according to the qSOFA scale, covering quick Sequential Organ Failure. It includes the impaired consciousness, systolic blood pressure less than 100 mm of mercury and respiratory rate greater than 22 per minute. However, the problem of sepsis still remains relevant and has not been resolved. Simple qSOFA criteria help to identify patients with suspected sepsis, but they don't offer effective diagnosis, including that at the preclinical level, and more effective treatment.

It should be noted that in the presence of pyo-inflammatory diseases, including sepsis, there is a blockage of serum albumin molecules by the products of bacterial metabolism, which leads to a significant decrease in the number of complete albumin molecules capable of performing their transport functions in the human body [8] [9]. The very increase in the number of inferior albumin molecules leads to an increase in the severity of the disease. Unfortunately, the aforementioned was beyond sepsis experts' attention. It suggests the need for intensive infusion therapy for patients with sepsis with a 20% solution of albumin. This process will help to replenish the body with complete albumin. It is an important pathogenetic component of treatment that, in combination with antibiotic therapy, can significantly increase its effectiveness.

Thus, the use of fluorescence spectroscopy enables the diagnostics of pyo-inflammatory diseases and sepsis, including those at their early stages, as well as controls the whole treatment process.

Therefore, the purpose of this paper is to build a diagnostic and therapeutic model of sepsis, based on the pathogenetic concept of the development of this pathology.

3. Data and Methodology

3.1. Data Source

The overall research was carried out from December 2001 to December 2018.

The clinical data for this particular investigation were provided by the Lviv city clinical emergency hospital and the department of gynaecology at the Vinnytsia city clinical hospital. The luminescent laboratory of the department of experimental physics at the Ivan Franko National University of Lviv provided experimental data. The measurements were performed using the aperture monochromators MDR-2 and MDR-12.

The objects of the study were "spectral-fluorescence modelling of changes in

blood serum (BS) in sepsis *in vitro*" (dilution of BS by centrifuged and non-centrifuged crops (CP and NCP) of bacterial culture of Staphylococcus aureus), dilution of BS with distilled water, 20% solution of albumin, sugar broth, 100 patients with a surgical profile (15 of whom have sepsis), 75 women with postpartum endometritis and 40 control subjects (women with uncomplicated course of postpartum period).

Research methods are: clinical, laboratory, biochemical, instrumental methods, including the method of fluorescence spectroscopy (MFS), as well as mathematical and statistical methods.

3.2. Research Results

In the study, MFS was used to improve the diagnosis and prognosis of pyo-inflammatory diseases. Fluorescence spectra (FS) were investigated via the excitation of BS samples by light with the wavelength of 280 nm, corresponding to the luminescence region of human serum albumin. The results of the experiment were displayed in the graphical and numerical form and processed graphically and statistically.

This method is based on the peculiarities of changes in the characteristics of BS in pyo-inflammatory diseases and sepsis. In the presence of endogenous intoxication in the body, the interaction of albumin molecules with the products of bacterial metabolism due to the ability of albumin molecules to complex takes place. The total number of albumin molecules remains constant. At the same time, the number of complete albumin molecules in the serum samples decreases. These changes cannot be recorded by the methods used in the standard algorithm for the diagnosis of pyo-inflammatory diseases and sepsis. At the same time, the MFS allows us to record these changes. The luminescence (fluorescence) of albumin molecules is due to the presence of the amino-acid residues of tryptophan in it. In the healthy people of the control groups, FS of BS look like a λ-type curves with maximum fluorescence in the region of 330.1 - 335.1 nm. The main indicators used for the analysis in the conducted work are the values of fluorescence intensity If and the position of fluorescence maxima λ_{max}. In patients with purulent-septic complications, a decrease in the intensity of fluorescence is observed. This occurs due to the fact that some binding centres of albumin interact with the products of bacterial metabolism and give glow in the longer wavelength region. Therefore, when the septic process develops, there are changes in the spectral-fluorescence characteristics of BS immediately, which can be detected only with the help of MFS. Initially, these changes are accompanied by a decrease in the fluorescence intensity, and subsequently, a long-wave "septic peak" is formed. These changes are a negative prognostic sign. If the long-wave shift is greater and the "septic peak" is higher, the prognosis is worse for patients. In particularly critical cases, the major peak caused by complete albumin is reduced to minimum, and the patient has only a "septic peak" in the long-wave area. Then there is a risk of even exitus letalis. At the same time, as

patients improve, changes in the spectral-fluorescence characteristics of BS occur in reverse order: there is an increase in the fluorescence intensity of the main peak, and the "septic peak" gradually shifts into the short-wave region and gradually disappears.

In the first phase of the study, the dilutions of BS by non-centrifuged and centrifuged bacterial culture (6-day sowing on the Staphylococcus aureus sugar broth), distilled water, 20% donor albumin, and sugar broth were studied. The problem of the influence of therapeutic measures, in particular infusion therapy, on the spectral-fluorescence characteristics of BS patients was also discussed [10].

The dilution of BS with 20% donor albumin leads in the cases of low concentrations to the slight shift of λ_{max} and a slight increase of the intensity; at high concentrations, If and λ_{max} are virtually unchanged. These results are actually consistent with the spectral characteristics of a 20% donor albumin solution. We focused on the study of spectral-fluorescence features of the pathognomic pathogenic for sepsis pathological constellation serum + bacterium − the phenomenon of bacteremia. To assure the validity of our assertions, we created the fluorescence-spectral model of sepsis *in vitro* by breeding BS by non-centrifuged (NCF) and centrifuged (CF) bacterial culture of bacteria [10]. In the *in vitro* studies, the FS of 11 dilutions of serum by NCF and CF cultures of bacteria [10] were measured for two similar experimental series of dilutions with concentrations starting from 100% of the standard serum down to the pure bacterial cultures (NCF/CF, respectively) with an experimental step of 10% dilution. It has been proven that starting with 10% of bacterial culture content in BS (proportions that are appropriate to the clinical model of sepsis), there appeared in vivo shifting by 7 - 10 nm in the long-wave region that is typical for sepsis (**Figure 1**, **Figure 2**, **Table 1**, **Table 2**). It should be noted that the changes of FS of BS in the dilution of NCF and CF of bacteria have a specific character and form the basis for the development of MFS for the early diagnosis of sepsis by studying the spectral-fluorescent model of sepsis *in vivo*.

At the second stage, MFS was used for diagnosing sepsis in vivo for patients with inflammatory diseases, sepsis and patients with burn injury [11]. In the study of the spectral-fluorescence characteristics of BS in patients with purulent-septic complications, two probable qualitatively significant tendencies were recorded, namely: the shift of fluorescence band maxima for patients with pre-septic pathology and sepsis in long-wave region and a significant reduction in their intensities (maximum up to 70% - 80%) of the donor unit. Both vectors of change had no correlation with the standard laboratory-biochemical parameters of conventional control of these patients, but correlated properly with the integrated clinical criteria for the severity of the patient's condition and the phenomenon of verified bacteraemia [12]. It should be noted that the revealed changes in the spectral-fluorescence characteristics of BS in patients with sepsis in most cases were preclinical in nature: they were usually recorded 24 - 48

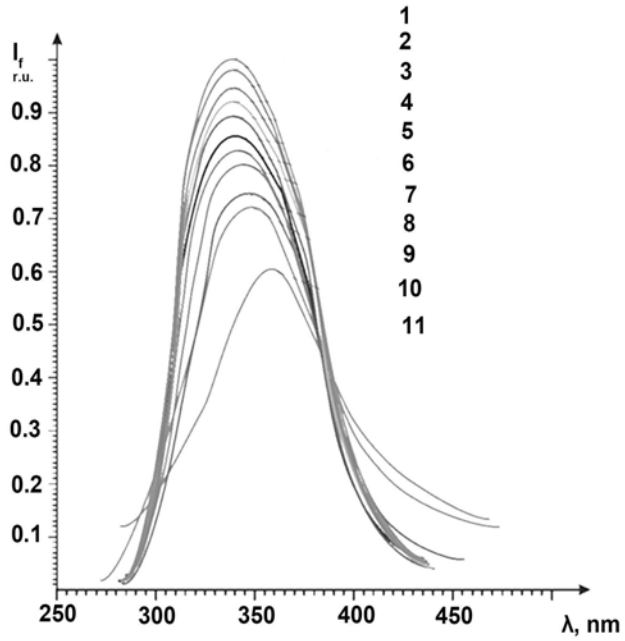

Figure 1. Effect of dilution non-centrifuged (NCF) crops on fluorescence spectra of donor blood serum (BS) (1—blood serum (BS); 2—90% BS; 3—80% BS; 4—70% BS; 5—60% BS; 6—50% BS; 7—40% BS; 8—30% BS; 9—20% BS; 10—10% BS; 11—CF crops). λ_{ex} = 280 nm.

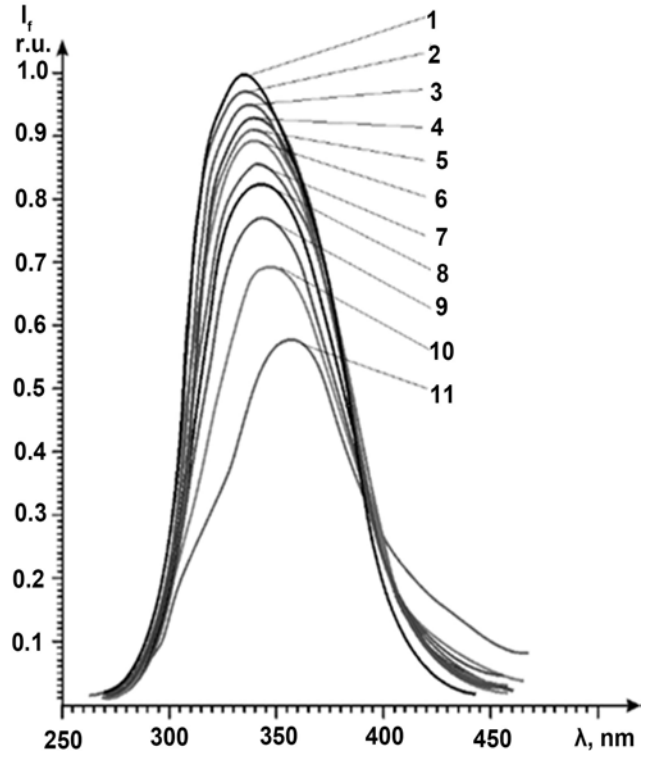

Figure 2. Effect of dilution centrifuged (CF) crops on fluorescence spectra of donor blood serum (BS) (1—blood serum (BS); 2—90% BS; 3—80% BS; 4—70% BS; 5—60% BS; 6—50% BS; 7—40% BS; 8—30% BS; 9—20% BS; 10—10% BS; 11—CF crops). λ_{ex} = 280 nm.

Table 1. Influence of dilution by non-centrifuged bacterial cultures on spectral-fluorescence characteristics of blood serum.

N	1	2	3	4	5	6	7	8	9	10	11
λ_{max} nm	339	339	339	339	339	340	341	344	347	348	358
I, r.u.	1.00	0.98	0.95	0.92	0.89	0.85	0.83	0.8	0.75	0.72	0.60

Table 2. Influence of dilution by centrifuged bacterial cultures on spectral-fluorescence characteristics of blood serum.

N	1	2	3	4	5	6	7	8	9	10	11
λ_{max} nm	335	335	337	340	340	340	341	343	343	347	357
I, r.u.	1.00	0.97	0.95	0.93	0.91	0.89	0.86	0.82	0.77	0.69	0.58

hours before the appearance of obvious clinical and laboratory signs of a significant change in the general somatic status of patients (Ukraine's Patent 76953) [13] [14]. At the same time, the structure of the excitation spectra of the fluorescence of donors and patients with sepsis is generally similar, but the patient's intensity of the excitation spectra is much lower than that of the donor.

Interesting are the results of the study of FS of BS in patients with pyo-inflammatory diseases. At first, we will present and discuss the results of individual, most revealing studies, in particular, of serial examinations of three patients with sepsis, for whom the dynamics of FS in different pathogenetic scenarios at different stages of the disease are studied. Figure 3 summarizes the results of a study of FS of the BS donor and patient (aged 33) with severe sepsis, which was treated in Lviv's city clinical emergency hospital. At the time of hospitalization, a critically difficult condition of the patient and verified bacteremia (blood seeding at the time of hospitalization: Staphylococcus aureus).

Figure 3 shows that the maximum of the fluorescence band of the patient's BS is shifted to the long-wavelength region by $\Delta\lambda = 40$ nm (curve 1) relative to the donor fluorescence band, and the fluorescence intensity (If) was 0.3 related unites (r.u.) from the donor If. This curve is, in fact, a septic peak, signalling a critical condition of the patient. The intensity of this curve in the region of 340 nm indicates a small amount of complete albumin in the BS of the patient. After surgical intervention and the elimination of the source of infection and intensive antiseptic therapy and prolonged bacteremia, the significant improvement and stabilization of the patient's condition were achieved: the analysis of the FS of the patient on the seventh postoperative day revealed that the shift of her band of fluorescence was significantly reduced and constituted $\Delta\lambda = 7$ nm (Figure 3, Table 3).

Undoubtedly, the considerable increase in the fluorescence band intensity of its BS mentioned above was connected with the decrease in septic symptoms. Our *in vitro* studies of the spectral-fluorescence characteristics of standard

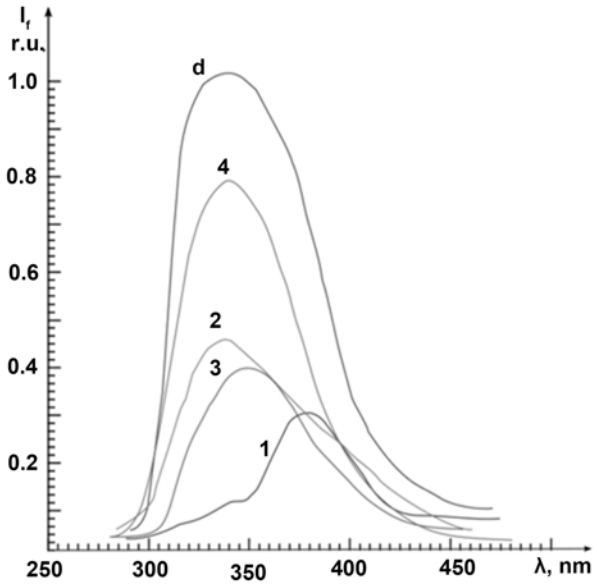

Figure 3. Fluorescence spectra of serum in Patient 1 with sepsis: 1—28.12; 2—04.01; 3—12.02; 4—19.03; 5—04.06 and donor of BS (d). *λ*ex = 250 nm.

Table 3. Changes in spectral-fluorescence characteristics of serum of a patient with sepsis.

N	control group	1	2	3	4	5
λ_{max} nm	340	380	345	337	349	340
I, r.u.	1.0	0.3	1.07	0.46	0.39	0.79

dilutions of the donor BS with distilled water (**Figure 4**, **Table 4**) clearly confirmed the correctness of our supposed explanation of the reported phenomenon of increase in the fluorescence band of this patient's fluorescence (**Figure 3**, curve 2).

After all, the decrease in the content of BS in the samples after the addition of distilled water also leads to a significant increase in the intensity of fluorescence bands. An additional confirmation of this assumption is the fact that after a change in the mode of infusion therapy associated with the reduction of septic symptoms and the dominance of the cardiovascular disorders regular for this stage, in the absence of significant changes in laboratory biochemical parameters, a decrease in the intensity of the fluorescence to 0.39 r.u. was observed and exceeded the baseline (**Figure 3**, curves 3, 4 relative to curve 1).

Later, under the influence of intensive complex therapy, a gradual improvement of the patient's condition with corresponding dynamics of changing spectral-fluorescence characteristics of her BS was observed: the gradual increase of fluorescence band intensity and the reverse shift of its maximum in the spectral region 337 nm (**Figure 3**, curves 3 - 5). The significant approximation of the fluorescence parameters of the patient's BS to the corresponding indicators of

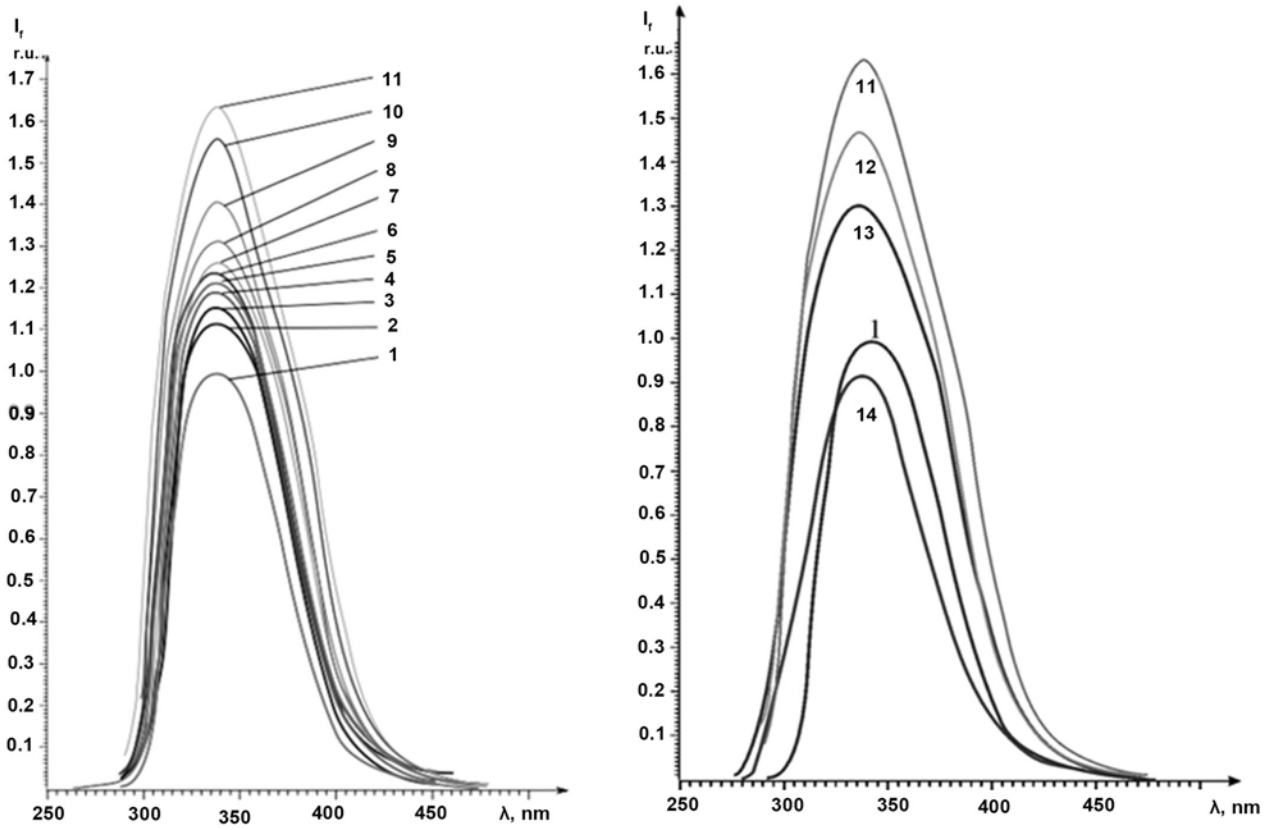

Figure 4. Effect of dilution with distilled water (DW) on the fluorescence spectra of donor blood serum (BS) (1—BS; 2—90% BS; 3—80% BS; 4—70% BS; 5—60% BS; 6—50% BS; 7—40% BS; 8—30% BS; 9—20% BS; 10—10% BS; 11—5% BS; 12—DW:If = 0).

Table 4. Influence of dilution by with distilled water on spectral-fluorescence characteristics of blood serum.

N	1	2	3	4	5	6	7	8	9	10	11	12	13	14
λ_{max} нм	338	338	337	337	337	337	338	339	338	338	338	336	336	338
I, в.о.	0.99	1.11	1.15	1.19	1.21	1.24	1.26	1.31	1.40	1.56	1.63	1.47	1.30	0.92

the donor BS was revealed 2.5 months later after her leaving hospital. Thus, according to our studies of the BS of the above-mentioned patient, the decrease in the intensity and the shift of the fluorescence band take place due to the presence of an advanced septic process and correlates with the integral indicators of the severity of the clinical condition and bacteremia. The dynamics of changes in the FS of the BS objectively reflect the course of sepsis and correlate with the effectiveness of therapeutic tactics.

Remarkable was also the results of the study of the FS of BS of another person with severe sepsis, who was treated at Lviv's city clinical emergency hospital. The major difference between these two cases is that, due to the timely hospitalization and early surgical elimination of the source of the infection, the septic process was considerably lower that was much reflected in the dynamics of changes in the spectral fluorescence (Figure 5, Table 5).

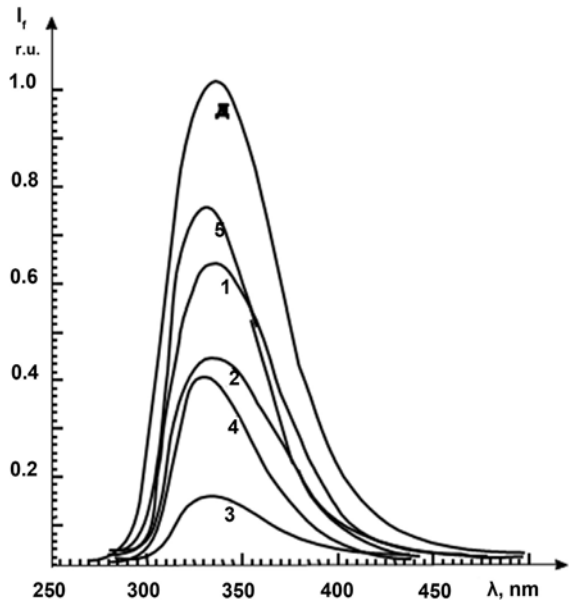

Figure 5. FS of BS in Patient 2 with sepsis: 1—03.06; 2—05.06; 3—06.06; 4—07.06; 5—10.06 and donor of BS. λ_{ex} = 280 nm.

Table 5. Changes in the spectral-fluorescence characteristics of serum of a person 2 with sepsis.

N	control group	1	2	3	4	5
λmax, nm	336	336	334	333	330	331
I, r.u.	1.0	0.64	0.44	0.16	0.41	0.76

Analyzing the results in this figure, one can conclude that after eliminating the source of the infection background by an intensive antibiotic therapy, this patient with clinically insignificant course of sepsis during a certain period experienced bacteremia (Klebsiella pneumonia) (curves 1-3). At this stage of treatment, the decrease in fluorescence band intensity reached maximum (0.16 If) only at the end of the bacterioemic period. Subsequently, during the gradual recovery of the person under study, there was a significant increase in the fluorescence intensity of the BS up to 0.75 If (**Figure 5**, curve 5).

Noteworthy are the results of studies of the spectral-fluorescence characteristics of BS in patient with sepsis and diabetes (**Figure 6**, **Table 6**).

The patient's condition during the observation period was steadily worsening, despite surgery and intensive antibiotic therapy, which may well be explained by the presence of a number of serious comorbidities and her older age. It should be remarked that the negative dynamics of the condition of this patient is reflected by the unfavourable dynamics of the parameters of the spectral-fluorescence characteristics of her BS: a constant decrease in the intensity of fluorescence bands (**Figure 5**, curves 1, 2, 3). The patient died as a result of an advanced process of generalizing infection and multiple organ failure.

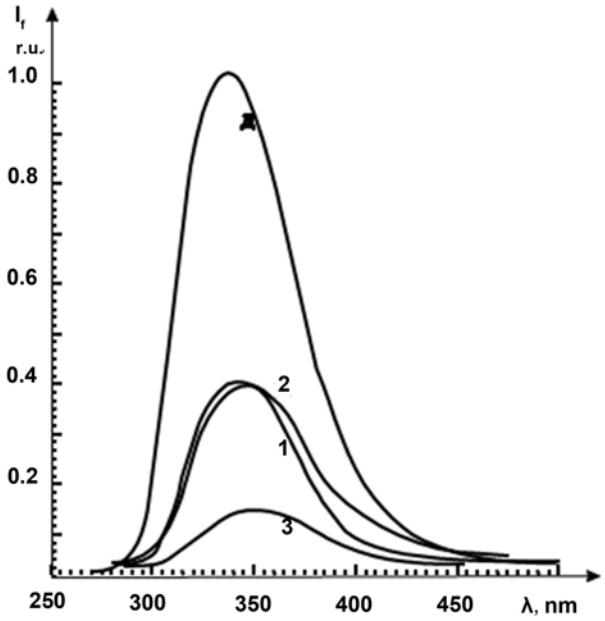

Figure 6. FS of BS of patient 3 with sepsis and diabetes: 1—03.06; 2—05.06; 3—06.06 and donor BS. λ_{ex} = 280 nm.

Table 6. Changes in the spectral-fluorescence characteristics of serum of a person 3 with sepsis.

N	control group	1	2	3
λmax, nm	338	342	347	351
I, r.u.	1.0	0.41	0.40	0.15

The above results indicate three most likely scenarios for sepsis. The dynamics of changes in the spectral-fluorescence characteristics of BS in patients with sepsis objectively reflect the clinical features of the disease, which significantly depends on the quality of diagnosis and correlates with the effectiveness of therapeutic tactics. MFS makes us able to use effective therapeutic tactics and correlate its correction depending on the change of the patient's condition. It should be noted that the first stage of the disease significantly reduces the intensity of fluorescence of the BS, which is associated with an increase in the number of defective albumin molecules in the BS, blocked by toxins. Therefore, an important element of therapeutic tactics for pyo-inflammatory diseases, including sepsis, is the infusion of 20% solution of albumin, which allows to replenish the amount of complete albumin in the patient's blood.

At the third stage, the peculiarities of the course of pregnancy, childbirth and the postpartum period (40 parameters in all) were analyzed in 75 women in postpartum period of the main group with postpartum endometritis and 40 people of the control group with the uncomplicated course of the postpartum period. MFS (of Ukraine's Patent 133472) was also used for the diagnosis of postpartum pyo-inflammatory diseases [15]. Extragenital pathology, gynecolog-

ical diseases, risk of miscarriage, complicated pregnancy, colpitis, the presence of TORCH infection, childbirth duration over 12 hours, presence of anomalies of childbirth, foetal distress, age of up to 35, length of stay in hospital within 3 - 5 days, decrease in fluorescence intensity and the presence of a long-wave shift are the reliable prognostic factors for the development of postpartum endometritis (PE) [16] [17].

It has been shown that in patients with PE, the decrease in the fluorescence intensity and the shift of the λ_{max} of the FS of BS into the long-wavelength region correlates with the severity of the disease. At the same time, it has been found that the spectral-fluorescence parameters of BS in patients are dynamic indicators that respond immediately to any—even minimal—changes in their clinical status and are integral characteristics of the health of the human body (**Figures 7-10** and **Tables 7-10**).

Figure 7 presents the results of a study of the FS of the BS of a woman 60 with PE, which was hospitalized in the gynaecological department on the 13th day of the postpartum period.

This patient had a gynaecological disease (cervix erosion), and an episiotomy was performed during the labour. In the postpartum period, mild anaemia and 3rd-degree vaginal cleanliness were revealed. The ultrasound diagnostics also showed an anomaly of uterine development with enlarged cavity with hyperechogenic content. Three blood samples were taken to see the dynamics. The fluorescence intensity of BS was slightly decreased for the second sample (curve 60'). She had some complaints (general weakness, fever up to 39.5˚C). At that time, the vacuum aspiration of the walls of the uterine cavity was performed for therapeutic purposes. As a result, the patient's condition improved (curve 60''), and subsequently, she left for home in a satisfactory condition.

Quite interesting are the results of the study of the FS of the BS of the woman after labour, depicted in **Figure 8**. This patient was treated mycoplasmosis and extragenital pathology (chronic bronchitis). There was the threat of a premature childbirth at the 32nd week of her pregnancy. There was a 1st-degree rupture of the cervix during the delivery. During the analysis of vaginal output, bacterial vaginosis was detected. Complaints, *i.e.* the lower abdominal pain and fever up to 38˚C in the patient, appeared on the 23rd day of the postpartum period. Patient 61 was admitted to the gynaecological department on the 24 days of her postpartum period. After the vacuum aspiration of the uterine cavity walls on 02 February 2015, the endometrial histological study revealed endometritis [16] [17].

Table 7. Spectral-fluorescence characteristics of patient with postpartum endometritis (60) and a patient with sepsis (1', 3', 4').

N	albumin	control group	60	60'	60''	1'	3'	4'
λmax, nm	330,1	330.1	337.1	337.1	336.1	376.8	339.8	349.5
I, r.u.	1	0.91	0.54	0.51	0.69	0.29	0.45	0.39

Table 8. Spectral-fluorescence characteristics of patient with postpartum endometritis (61) and a patient with sepsis (1', 3', 4').

N	albu min	2	61	61'	61"	61"	1'	3'	4'
λmax, nm	330.1	330.1	339.1	339.1	336.1	329	376.7	339.8	349.5
I, r.u.	1	0.91	0.56	0.53	0.72	0.88	0.29	0.45	0.39

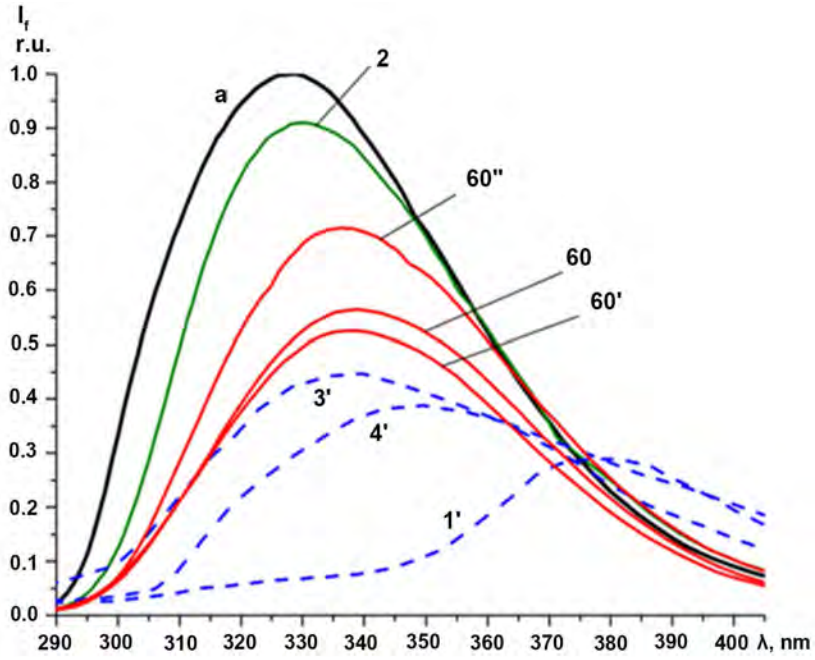

Figure 7. Fluorescence spectra of blood serum in the patient with postpartum endometritis in dynamics (60—24.02.2015; 60'—26.02.2015, 60"—29.02.2015), women with uncomplicated course of postpartum period (2), patient with sepsis (1', 3', 4') (see **Figure 3**) and 20% donor albumin (a) (λ_{ex} = 280 nm).

Within four days, there took place a decrease in the fluorescence intensity of the BS of the patient from 0.56 r.u. (curve 61) to 0.53 (curve 61') followed by the normalization of its condition as a result of effective antibiotic therapy (curves 61" and 61'"). As a result, we observed a positive dynamics of changes in the spectral-fluorescence characteristics of Patient 61's BS, which reflects the dynamics of the healing process.

After manual vacuum aspiration during the next two days, there was a decrease in the fluorescence intensity of the BS from 0.56 ppm. (curve 61) to 0.53 (curve 61') followed by its normalization as a result of effective antibiotic therapy (curves 61' and 61'"). Thus, we recorded the positive dynamics of the change in the spectral-fluorescence characteristics of the BS of Patient 61, which qualitatively reproduces the scenario of recovery of the patient for sepsis (curves 1', 3', 4').

Quite informative are the results of the study of the spectral-fluorescence characteristics of the BS of another woman with endometritis after the childbirth,

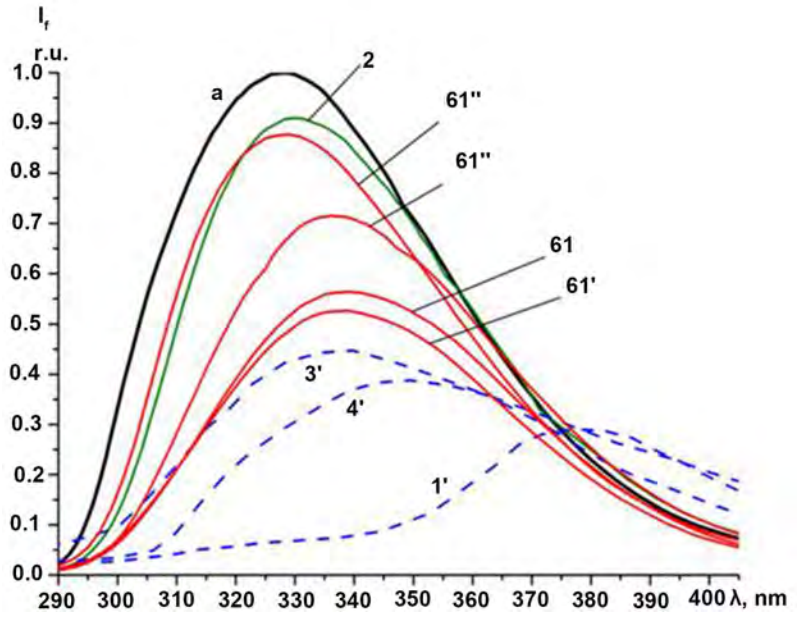

Figure 8. Fluorescence spectra of blood serum in patient with postpartum endometritis in dynamics (61—2.02.2015; 61'—4.02.2015, 61"—6.02.2015, 61'"—30.04.2015), women with uncomplicated course of postpartum period (2), patient with sepsis (1', 3', 4') (see **Figure 3**) and 20% donor albumin (a) (λ_{ex} = 280 nm).

shown in **Figure 9** and **Table 9**. She had a complicated somatic anamnesis (transferred pleurisy in 2013, urolithiasis), chronic adnexitis. In childbirth, the anhydrous period duration was 6 hours 30 minutes. In the postpartum period, anemia, proteinuria, 3rd-degree purity of the vagina and the expansion of the uterine cavity according to ultrasound were revealed.

After the manual vacuum aspiration of the walls of the cavity of the uterus of Patient 62, antibacterial and uterotonic therapy was performed. We investigated the FS of the BS as of 15 July 2015 and revealed a significant decrease in the fluorescence intensity to 0.35 r.u. and a noticeable long-wave shift of its band (curve 62). In the following experiment, a marked increase of If of BS of this patient was recorded up to 0.6 r.u. and the shift into the shortwave region (see curve 62') was fixed. The results of the FS of BS are also present in the picture (see 1', 3', 4', **Figure 3**).

Figure 10 and **Table 10** present the FS of the BS of two more women with postpartum endometritis. It should be noted that the growth of If of Patient 69 from 0.59 r.u. (curve 69) to 0.96 r.u. (curve 69') correlates with the improvement of her condition during treatment. In the initial study of the FS of the BS of Patient 70 revealed a considerable decrease of If of BS (curve 70). After the vacuum aspiration on 20 February 2014 and the following treatment, the patient's condition improved significantly. This is evidenced by the results of the study of the FS of her BS (curve 70').

This makes it possible on the basis of the detailed information on the spectral-fluorescence parameters of the BS of patients to prescribe them effective treatment on time and to preserve the reproductive health of women in

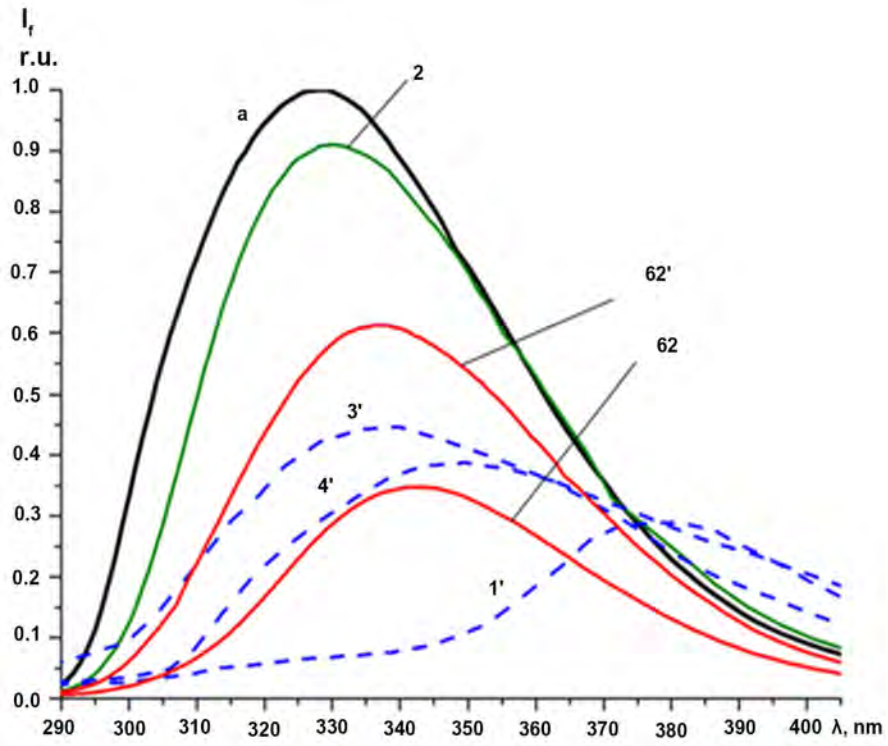

Figure 9. Fluorescence spectra of blood serum in the patient with postpartum endometritis in dynamics (62—14.02.2015; 62'—17.02.2015), the woman with uncomplicated course of postpartum period (2), patient with sepsis (1', 3', 4') (See **Figure 3**) and 20% donor albumin (a) (λ_{ex} = 280 nm).

Table 9. Spectral-fluorescence characteristics of patient with postpartum endometritis (61) and a patient with sepsis (1', 3', 4').

N	albumin	2	62	62'	1'	3'	4'
λmax, nm	330.1	330.1	343.1	337.1	376.7	339.8	349.5
I, r.u.	1	0.91	0.35	0.61	0.29	0.45	0.39

childbirth. Further systematic studies of the FS of BS in the framework of MFS in patients with pyo-inflammatory diseases will make MFS an effective method of diagnosis in obstetrics and gynaecology and in medical practice in general.

It should be noted that in pyo-inflammatory diseases, including sepsis, there are changes in structures of albumin molecules and a decrease in the level of complete albumin in BS, capable of performing its functions, including detoxification. Therefore, the pathogenetic components of the treatment of these diseases are antibiotic therapy and infusion therapy with albumin solutions to replenish the amount of complete albumin in BS. According to the latest International Guidelines for the treatment of severe sepsis and septic shock, experts propose to use albumin in large volumes for infusion-transfusion therapy [18] [19] [20] [21].

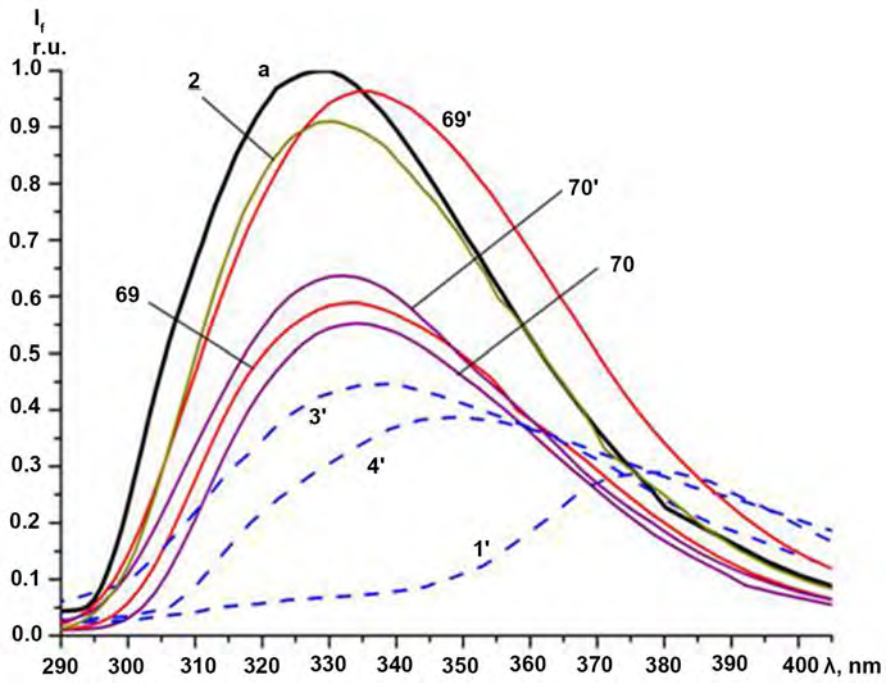

Figure 10. Fluorescence spectra of blood serum in the patient with postpartum endometritis in dynamics (69—20.02.2014; 69'—10.03.2014., 70—20.02.2014; 70'—24.02.2014.), uncomplicated course of postpartum period (2), patient with sepsis (1', 3', 4') and 20% donor albumin (a) (λ_{ex} = 280 nm).

Table 10. Spectral-fluorescence characteristics of patients with postpartum endometritis (61) and a patient with sepsis (1', 3', 4').

N	albu min	2	69	69'	70	70'	1'	3'	4'
λmax, nm	330.1	330.1	334.1	336.1	334.1	332	376.7	339.8	349.5
I, r.u.	1	0.91	0.59	0.96	0.55	0.64	0.29	0.45	0.39

4. Conclusions

1) It has been established that the bacterial culture dilution of BS, starting with 20% of the content of centrifuged or non-centrifuged cultures of bacterial culture in serum, makes possible the *in vitro* reproduction of proportions consistent with the clinical model of sepsis *in vivo*. A decrease in the fluorescence intensity of BS dilutions by over 30% and a long-wave shift of the FS maximum of over 10 nm were detected.

2) A method for diagnosing sepsis and pyo-inflammatory diseases is first proposed. Three plausible scenarios for sepsis were identified. It has been shown that the structure of FS BS is an effective marker of the severity of the disease, which can assess quickly and qualitatively the threat of critical purulent-septic complications as well as monitor the treatment process.

3) The spectral-fluorescence characteristics of BS in childbirth with PE were under study.

Fluorescence spectroscopy makes it possible to perform diagnostics at the preclinical stage, to assess quickly and qualitatively the threat of critical purulent-septic complications and to monitor the treatment process. The spectral-fluorescence characteristics of BS are found to be reliable markers for the diagnosis of pyo-inflammatory diseases in obstetric and gynaecological practices. The study of their dynamics enables them to prescribe the effective treatment on time and to prevent the development of obstetric sepsis.

4) In pyo-inflammatory diseases, including sepsis, there may happen the blockage of albumin molecules by the products of bacterial metabolism, which leads to a significant decrease in their ability to perform transport functions. The infusion therapy with a 20% solution of albumin will help to replenish patients' body with complete albumin. It is an important component of pathogenetic treatment that, along with antibiotic therapy, can significantly increase its effectiveness. The method of fluorescence spectroscopy will effectively monitor the treatment process.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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Application and Reliability of Caprini Thrombus Risk Assessment Scale in Risk Assessment of Venous Thromboembolism in Acute and Severe Uygur Patients

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Abstract

Background: To explore the application and reliability of Caprini thromboembolism risk assessment scale in the risk assessment of venous thromboembolism in acute and severe uygur patients. **Methods:** 160 cases of acute and severe Uighur patients with venous thrombo embolism (VTE) that were treated in our hospital from December 2017 to December 2018 were selected as the research group. 160 cases of acute and severe uygur patients without VTE admitted to our hospital in the same period were selected as the control group. Caprini thrombus risk assessment scale and Padua thrombus risk assessment scale were used to evaluate in both groups. The general data of the two groups were compared. The results of the two groups were consistent using Caprini and Padua blood clot risk assessment scales. Clinical efficacy of two different thrombosis risk assessment scales in risk assessment of VTE. **Results:** Group and control group in the gender distribution, backlog of red blood cells and platelet count have no significant difference ($P > 0.05$), the team average age, average hospitalization days were significantly less than control group ($P < 0.05$), the team hemoglobin level was significantly higher than that of control group ($P < 0.05$), the team of white blood cells were significantly lower than control group ($P < 0.05$). Caprini thrombosis score was used to evaluate 156 high-risk patients and 164 low-risk patients. A total of 75 cases of high-risk patients and 245 cases of low-risk patients were assessed by Padua thrombosis score, and the results of the two assessment methods were significantly different ($X^2 = 6.956$, $P < 0.05$). Consistency (Kappa coefficient) was 0.58, indicating medium consistency. The specificity of Caprini thrombus score was significantly lower than that of Padua thrombus score ($P < 0.05$),

the sensitivity and negative predictive value of Caprini thrombus score were significantly higher than that of Padua thrombus score ($P < 0.05$), and there was no significant difference in the positive predictive value between the two groups ($P > 0.05$). **Conclusion:** The sensitivity, negative predictive value and positive predictive value of Caprini thrombosis risk assessment scale in VTE risk assessment of acute and severe uygur patients are very prominent, and the clinical efficacy is better, which is worthy of application.

Keywords

Venous Thromboembolism, Critically Ill Patients, Uygur, Risk Assessment, Clinical Effectiveness

1. Introduction

Venous Thrombus Embolism (VTE) is a common complication during the clinical treatment of critical ill patients [1]. Caprini thrombosis risk assessment scale was developed and named by Caprini, a foreign scholar. After it was introduced into domestic clinical practice, it was revised in 2009, and many large sample retrospective studies have been carried out in western clinical practice. Its feasibility and effectiveness have been proved [2]. However, most clinical studies have focused on medical or surgical patients, and studies using the Caprini thrombotic risk assessment scale for severely ill uyghur patients are very rare. This study applied the control-pathology method and retrospectively analyzed the VTE risk assessment of uyghur patients with acute and severe diseases by using Caprini thrombus risk assessment scale and Padua thrombus risk assessment scale, as reported below. The purpose of our study was to explore the application and reliability of Caprini thromboembolism risk assessment scale in the risk assessment of venous thromboembolism in acute and severe uygur patients.

2. Data and Methods

2.1. General Information

160 critical uygur patients with venous thrombo embolism (VTE) admitted to our hospital from December 2017 to December 2018 were selected as the study group. The mean age (62.4 ± 13.8) was 84 male patients and 76 female patients. Inclusion criteria: 1) Age ≥ 20 years; 2) > 2 d was accepted in ICU; 3) Meet the clinical diagnostic criteria for acute and severe patients; 4) It meets the clinical diagnostic criteria for DVT; (5) complete previous clinical data.

160 critical uygur patients without VTE were selected as the control group. The mean age was (51.6 ± 11.9), including 87 years for males and 73 years for females. The study was approved by the ethics committee. Inclusion criteria: 1) Age ≥ 20 years; 2) > 2 d was accepted in ICU; 3) No VTE occurred during hospitalization; 4) Complete previous clinical data.

2.2. Methods

General data collection: gender, age, relevant laboratory biochemical indicators of the two groups were collected and analyzed retrospectively and recorded into the statistical system.

Padua thrombosis risk assessment scale: there are eleven risk factors in the scale.

The risk factors include: corticosteroid therapy, the obese (IBM 30 or higher), acute infections or rheumatoid disease, acute myocardial infarction, heart or lung failure, old age (more than 65 years), traumatic surgery within 30 days, high tendency to thrombosis disease, low mobility, history of VTE and active cancer patients. The score range of each of the 11 risk factors mentioned above was 1 point to 3 points, and the total score accumulation degree of all factors was divided into two grades: low risk: ≤3 points, high risk: >3 points [3].

Caprini thrombus risk assessment scale: using the revised version of 2009, including 40 risk factors. Both control and study groups were assessed for thrombus risk. The assessment score range of each risk factor: 1 - 5 points. When there is no risk factor, 0 points will be scored. According to the assessment score, the risk rating and risk grading were carried out: low risk: ≤1 point, medium risk: 2 points, high risk: 3 - 4 points, super high risk: ≥5 points [4].

2.3. Observation

General data were observed and compared between the two groups. To observe and compare the consistency of assessment results between the two groups using Caprini thrombus risk assessment scale and Padua thrombus risk assessment scale. To observe and compare the clinical efficacy of two different thrombus risk assessment scales in risk assessment of VTE. Padua thrombus score included two grades: low risk: ≤3, high risk: >3; Caprini thrombus score results include four levels: low risk: ≤1 point, medium risk: 2 points, high risk: 3 - 4 points, super high risk: ≥5 points. When comparing the consistency of the above evaluation results, Caprini thrombus score was divided into two grades: low risk: ≤2 points and high risk: >2 points, in order to facilitate the comparison of clinical efficacy of the two groups, including specificity, sensitivity, negative predictive value and positive predictive value. ROC analysis method was used for comparative calculation.

2.4. Statistical Analysis

Descriptive statistics were utilized to analyze for demographic, clinical, and outcome parameters. Continuous data are presented as the means and standard deviations (SDs) or medians and interquartile ranges. Categorical data are summarized as a total number and percentage of the cohort. All continuous variables were compared using Student's t-test or the Wilcoxon signed-rank test in the absence of a normal distribution. Categorical variables were compared using the Chi-squared test. A P-value < 0.05 was considered statistically significant with

95% confidence intervals (CIs) also reported. These statistical analyses were performed using SPSS 19.0 software (SPSS, Chicago, IL, USA).

3. Results

3.1. Characteristics

There was no significant difference in the gender distribution, backlog of red blood cells and platelet count between study group and control group ($P > 0.05$). The average age, average hospitalization days in the study group was significantly less than control group ($P < 0.05$), the hemoglobin level in the study group was significantly higher than that of control group ($P < 0.05$), the white blood cells in the study group were significantly lower than control group ($P < 0.05$). The characteristic was seen in Table 1.

3.2. Consistency of the Two Groups

Consistent results between the two groups were evaluated, using the Caprini thrombotic risk assessment scale and the Padua thrombotic risk assessment scale. Caprini thrombus score was used to evaluate 156 patients with high risk and 164 patients with low risk. A total of 75 patients with high risk and 245 patients with low risk were evaluated by Padua thrombus score. The results of the two assessment methods were significantly different ($X^2 = 6.956$, $P < 0.05$). The Kappa coefficient was 0.58, indicating moderate consistency. See Table 2 for details.

3.3. Clinical Efficacy of Two Scales

The clinical efficacy of two different scales was compared in risk assessment of VTE.

The specificity of Caprini thrombus score was significantly lower than Padua thrombus score ($P < 0.05$). The sensitivity and negative predictive value of Caprini thrombus score was significantly higher than Padua thrombus score ($P < 0.05$), and there was no significant difference in the positive predictive value between the two groups ($P > 0.05$), the results were shown in Table 3.

4. Discussion

Clinical VTE is divided into two types: Pulmonary Embolism (PE) and Deep Vein Thrombosis (DVT) [5]. Generally speaking, the condition of severe

Table 1. Characteristics of control and study groups.

Group	Case	Gender		Age	hospital days	hemoglobin	WBC	HCT	PLT
		Male	Femal	(year, $\bar{x} \pm s$)	(d, $\bar{x} \pm s$)	(g/l, $\bar{x} \pm s$)	($\times 10^9$/l, $\bar{x} \pm s$)	(%, $\bar{x} \pm s$)	($\times 10^9$/l, $\bar{x} \pm s$)
Control	160	87	73	51.6 ± 11.9	11.8 ± 2.6	131.6 ± 16.5	6.8 ± 2.1	38.4 ± 3.7	198.5 ± 48.2
Study	160	84	76	62.4 ± 13.8	17.6 ± 2.1	124.9 ± 36.1	10.7 ± 4.8	37.2 ± 4.1	197.6 ± 47.6
χ^2/t	/	1.624		15.462	13.274	11.837	16.649	1.362	1.023
P	/	>0.05		<0.05	<0.05	<0.05	<0.05	>0.05	>0.05

Table 2. Consistency evaluation between the two groups using Caprini scale and Padua scale.

		Caprini thrombus risk assessment scale		
		High risk	Low risk	Total
Padua thrombus risk assessment scale	High risk	70	5	75
	Low risk	86	159	245
	Total	156	164	320

Table 3. Clinical efficacy of two different thrombotic risk assessment scales in risk assessment of VTE.

Risk assessment scales	sensitivity	specificity	negative predictive value	positive predictive value
Caprini scale	73.4%	70.9%	71.2%	72.3%
Padua scale	85.6%	32.2%	55.8%	69.1%
X^2	6.294	7.023	5.493	0.516
P	<0.05	<0.05	<0.05	>0.05

emergency patients is relatively serious and critical. During the course of clinical treatment, patients may suffer from coma, dehydration, infection and long-term postoperative limb immobilization [6]. Patients with severe condition may even have combined cardiopulmonary dysfunction, thereby increasing the risk of VTE [7]. The American College of Chest Physicians (ACCP), in the 9th edition of its clinical practice guidelines on antithrombotic and thromboembolic prophylaxis, proposed that all patients with acute and severe clinical conditions should be assessed for VTE risk during clinical treatment [8]. For patients with high risk of VTE, corresponding preventive intervention measures should be applied to reduce the rate of patients with VTE [9]. Therefore, it is of great clinical significance to select a reliable, comprehensive and rapid VTE risk assessment scale.

The results of this study suggested that the sensitiity of risk assessment for Padua thrombi scale was low with only 32.2%, suggesting that its predictive effect was not very satisfactory when assessing the risk of VTE in critically ill patients. This is consistent with relevant other research results [10]. VTE risk grading based on the Padua risk assessment scale was less effective and reasonable.

In the 1990s, a foreign physician and scholar named Caprini proposed for the first time to assign values to patients with existing thrombotic risk factors, classify patients according to the score, and implement different preventive interventions for patients according to different grades [11]. In the clinical guidelines of ACCP, Caprini thrombus risk assessment scale was a prediction and screening tool for clinical surgical patients with the risk of VTE. Although there is no rigorous statistical calculation method, it can provide a more reasonable classification for clinical patients in the process of risk assessment of VTE, and it is very simple and easy to use [12].

The results of our study indicated that there was a significant difference between the two evaluation methods ($X^2 = 6.956$, $P < 0.05$). The sensitivity and negative predictive value of Caprini thrombus score was significantly higher than Padua thrombus score ($P < 0.05$). Consistent with the results of similar studies, the validity and reliability of risk assessment using the Caprini thromboembolic risk assessment scale for patients with acute and critical illness is significantly higher. The reason may be that the content and quantity of relevant risk factors included in the two different assessment scales are inconsistent. The Caprini thrombotic assessment scale includes a total of 40 risk factors, while the Padua thrombotic assessment scale only includes 11 risk factors. As a result, many related VTE risk factors in the Padua thrombus risk assessment scale could not be effectively reflected and applied in the evaluation process of patients, thereby reducing the effective prediction rate of patients at high risk of thrombus [13]. A study reviewed the medical records of a certain VTE patient (65-year-old male and a BMI of 29 kg/m^2). Clinical diagnosis was acute pancreatitis and central venous catheterization was used. After the patient was assessed using Caprini thrombotic risk assessment scale, the score was 6, indicating the risk of VTE with high risk. However, the Padua thrombi risk assessment scale was used to reassess the condition, with a score of 1, indicating a low risk of VTE [14].

The results of our study suggested that the study group and control group has no significant difference ($P > 0.05$) in the gender distribution, backlog of red blood cell and platelet count. The average age and hospitalization days in the study group was significantly less than control group ($P < 0.05$), the hemoglobin level in the study group is significantly higher than that in control group ($P < 0.05$), the white blood cells in the study group were significantly lower than that in the control group ($P < 0.05$). The study results confirmed that the risk factors influencing the occurrence of VTE in patients with acute and severe clinical diseases included age, hemoglobin level, white blood cells, etc. This is consistent with relevant research results [15]. At the same time, the length of hospital stay in the study group was significantly longer than that in the control group, which indicated that the occurrence of VTE in the patients would have a serious adverse impact on the recovery speed and recovery quality of the patients. Therefore, VET risk assessment of patients is conducive to the early prevention and intervention of patients with high risk of VTE, which can effectively reduce the risk of VTE in patients. At the same time, VET risk assessment can also speed up the recovery of patients.

In conclusion, when applying Caprini thromboembolism risk assessment scale to evaluate the risk of VTE in critical uygur patients, the sensitivity, negative predictive value and positive predictive value of the assessment are very outstanding, and the clinical evaluation is more effective and worthy of application.

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Conflicts of Interest

There are no conflicts of interest.

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Improved Angina Symptoms Following Coronary Sinus Flow Reducer Implantation in a Patient with Refractory Angina and Chronic Total Occlusion: A Case Report

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Abstract

Background: Due to the aging population and increased survival of the patients with coronary artery disease, there is an increasing number of patients with debilitating angina refractory to optimal medical treatment who are not candidates for revascularization. In case of low ischemic load, the treatment of stable refractory angina is aimed at symptom reduction. There are several new treatment methods targeting myocardial ischemia available, including coronary sinus flow reducer (CFR) implantation. **Case Report:** We report a case of a patient suffering from CCS class IV angina despite optimal medical therapy, with further revascualrization options exhausted, who was successfully treated with coronary sinus flow reducer (CFR). Besides technical skill to reach ostium of coronary sinus, the most important technical tip is precise positioning of the CFR. The reduction of angina symptoms started after epithelisation of CFR frame, usually 6 - 7 weeks after implantation. At 6-month follow-up, the patient reported a marked reduction of angina symptoms, with CCS grade improving by three classes (from IV to I). At 10-month follow-up, the sustainment of CCS grade I angina symptoms was reported by the patient. **Conclusions:** We conclude that CFR can be safely and successfully implanted in patients suffering from refractory angina. Considerable improvements in CCS grade may be experienced in certain cases.

Keywords

Chest Pain, Refractory Angina Pectoris, Myocardial Ischemia, Coronary Sinus Flow Reducer, Chronic Total Occlusion

1. Introduction

Advancements in drug and device therapy, along with the aging population, have increased the life expectancy of the patients with coronary artery disease (CAD) [1]. This has also resulted in the increased prevalence of those CAD patients who have chronic angina pectoris refractory to medical treatment and who are ineligible for further surgical or percutaneous revascularization [2] [3]. Patients with reversible ischemia-related angina lasting ≥ 3 months despite optimal medical therapy and revascularization options exhausted are said to have refractory angina (RA). This group of patients comprises an estimated 5% - 10% of all diagnosed angina cases. They often use several anti-ichaemic drugs, experience a poor quality of life due to deleterious symptoms and are frequently hospitalized [3].

Coronary sinus flow reducer (CFR) stent is an implantable device aimed at reducing angina pectoris symptoms by decreasing the cross-section of the coronary sinus (CS) and increasing venous back pressure. This in effect redirects blood flow to subendocardium, increases collateral blood flow and, presumably, induces neoangiogenesis [4] [5]. Combined, these mechanisms increase perfusion of the more ischemic regions of the myocardium, resulting in alleviation of angina symptoms, improved myocardial contraction and reduced left ventricular end-diastolic pressure [6].

CFR is a stainless steel balloon-expandable hourglass-shaped stent inserted into the CS via transjugular approach. It is a percutaneous analogue of surgical partial ligation of the CS that was first performed by Beck and Leighninger in 1954 and was—despite significantly improving angina symptoms and reducing 5-year mortality rate—later discontinued in part due to widespread acceptance of the coronary artery bypass graft (CABG) surgery [7].

Studies of CFR so far have demonstrated the device and its implantation procedure to be feasible, safe and efficacious. The COronary SInus Reducer for treatment of Angina (COSIRA) multicentre, prospective, double-blind, sham-controlled study showed significantly higher percentage of patients with Canadian Cardiovasular Society (CCS) classification improvement of at least one functional class in the treatment group in comparison to the sham-controlled group (71% and 42%, respectively) [8]. Two smaller studies also demonstrated significant improvements in objective myocardial ischemia measures, such as exercise time or the mean change in wall-motion index assessed by dobutamine echocardiography [9] [10]. Our heart centre has been employing CFR in RA treatment since 2016 with overall results so far closely matching the COSIRA trial outcomes.

In this case report, we describe a patient with multiple coronary diseases, after CABG and unsuccessful PCI of CTO RCA. He was suffering from CCS class IV angina with multiple comorbidities, including diabetes and aortic valve replacement. After CFR implantation he showed a sustained improvement of angina symptoms at 6- and 10-month follow-up, demonstrating the safety and

efficacy of CFR implantation in such patients.

2. Case Report

80-year-old man with a history of hypertension, dyslipidemia, type 2 diabetes treated with oral antihyperglycemic therapy, benign prostatic hyperplasia, peripheral arterial disease, atrial fibrillation, non-ST-elevation myocardial infarction, CABG using left internal mammary artery (LIMA) grafted to left anterior descending coronary artery (LAD) and venous graft grafted to obtuse marginal 1 (OM 1), and aortic valve replacement using bioprosthetic valve presented to our clinic with CCS class IV angina despite optimal medical therapy (acetylsalicylic acid 100 mg, nebivolol 5 mg twice daily, ramipril 5 mg twice daily).

Cardiac echography showed impaired left ventricular systolic function with EF of 48% - 50%, with basal, inferior, inferior septal and inferior lateral wall motion abnormalities. Aortic bioprosthetic valve showed normal function.

Coronary angiography showed 2-vessel coronary artery disease with RCA chronic total occlusion (CTO) with left to right Rantop 2 collateral flow and an important stenosis of proximal LAD. Surgical revascularization was our first option. After patient refused surgery we performed proximal LAD stenting with DES (Synergy 3.0 × 12 mm). PCI CTO with different approaches (antegrade, retrograde) was not successful. Finally, dissection of the mid RCA occurred during PCI attempts (**Figure 1**). Due to RA persisting 3 months after PCI despite optimal medical therapy (bisoprolol 5 mg, perindopril 10 mg, ranolazine 2 × 500 mg, rosuvastatine 30 mg), a multi-disciplinary heart team decided that CFR implantation was the optimal treatment approach for this patient.

Ultrasound-guided right internal jugular vein puncture was performed, followed by multipurpose catheter insertion and coronary sinus ostium cannulation using fluoroscopic guidance. A 9 French guiding catheter with the CFR stent (Neovasc Inc., Richmond B.C., Canada) was placed inside the coronary sinus at the appropriate insertion point, *i.e.* at least 2 cm distal to the ostium to exclude small cardiac veins draining the right coronary artery (RCA) venous return, all the while excluding the larger, more distal side branches draining the left coronary artery (LCA) venous return. The catheter-mounted hourglass-shaped balloon was inflated at 5 atm for 30 seconds, expanding the reducer stent into its functional shape (**Figure 2**). The recommended 10% - 20% device oversizing relative to the coronary sinus cross-section was achieved in order to ensure proper anchoring, prevent device migration and induce endothelization of the stent's mesh structure. After balloon deflation and the removal of the catheter, venography showed successful reducer stent position and anchoring. Complications such as stent occlusion, coronary sinus dissection or perforation, or bleeding at the jugular puncture site were excluded. The patient received dual antiplatelet therapy comprising acetylsalicylic acid and clopidogrel for the duration of 6 months.

The reduction of angina symptoms began 6 - 7 weeks after implantation. At 6-month follow-up, the patient showed marked reduction of angina symptoms,

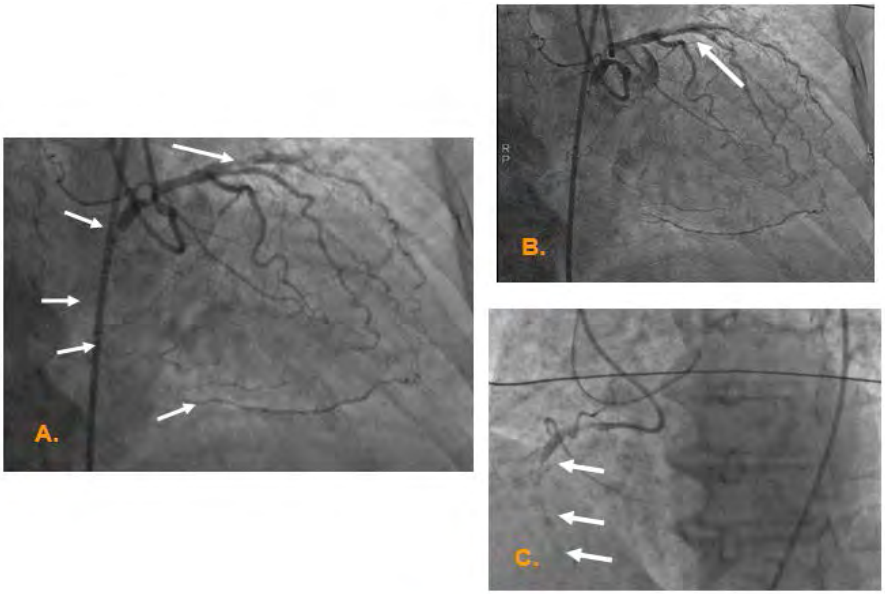

Figure 1. Coronary angiography. (A) Biradial injection of LM and RCA. Proximal occlusion of RCA. Severe stenosis of proximal LAD; (B) LAD after DES stenting; (C) Unsuccessful PCI of CTO RCA: combined tehnique (antegrade/retrograde). Note the disection of RCA.

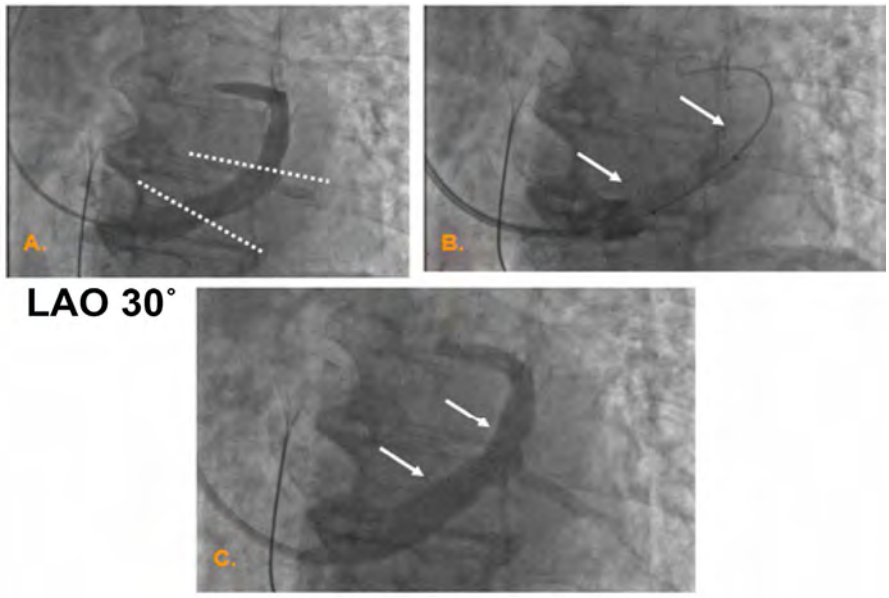

Figure 2. Coronary flow reducer (CFR) implantation. LAO 30˚. (A) Coronary sinus angiography. Right jugular approach. Left amplatz 1 shaped catether. Anatomic target position for CFR implantation; (B) Coronary sinus angiography during CFR-balloon inflation. Note the supportive wire (Amplatz extrasupport). No parallel flow to expanded CFR (5 atm continuous pressure delivered through indeflator); (C) Final position of the CFR after successful implantation.

with CCS grade improving by three classes (from IV to I). At 10-month follow-up, the sustainment of CCS grade I angina symptoms was reported by the patient.

3. Discussion

Patients with CAD have increased life expectancy, to some extent due to advancements in drug and device therapy and in part due to the aging population. In general, we are faced with an increased number of patients with RA. Despite having a long-term mortality of under 4% per year, approaching that of the patients with chronic coronary syndrome (1.5% per year, 6.1% in 5 years for patients with no prior MI, 10.8% in 5 years for patients with prior MI) , the incapacitating nature of angina has a significant negative effect on quality of life in patients with RA [3] [10] [11]. Up to 30% of stable CAD still experience angina symptoms 1 year after revascularization [12]. Data derived from cardiac cath-lab registries showed that 6% - 12% of the patients referred to angiography with evidence of ischemia were ineligible for traditional revascularization [13].

Several methods have been under investigation to mitigate the symptoms of RA. First-line treatment options include beta-blockers, ivabradine, calcium channel blockers, nitrates, ATP-sensitive potassium channel openers, late sodium current inhibitors and rho-kinase inhibitors [14]. According to Diamond recommendations and novel ESC guidelines on chronic coronary syndrome, patients should be treated with a combination of event prevention and angina relief medical therapy [15] [16]. Approximately 10% of RA patients receiving one or more of the medical treatment choices remain symptomatic [17].

There are some additional treatment options of RA, including external enhanced counterpulsation, extracorporeal shockwave therapy, spinal cord stimulation, internal mammary artery implants, transmyocardial laser revascularisation, cell therapy and gene therapy. None of these approaches, however, have yet become widely used [18].

Lately, the CFR implantation has shown promising results in alleviating angina symptoms and improving quality of life. 70% - 80% of patients experience improvement in CCS class, while according to the COSIRA data there is also up to 30% of placebo effect in angina symptoms' improvement [8]. Since RA treatment is aimed at symptom reduction, its goal is achieved even in the placebo population. According to ESC guidelines, CFR is included as a B evidence level, IIb recommendation class RA treatment option [16]. Available clinical data suggest CFR should be indicated in RA patients with proven ischemia in LAD and LCX territory. Positive effects of CFR implantation were also proven in microvascular angina [19]. In a single case with RA following successful CABG, CFR implantation was followed by complete disappearance of nocturnal events, significant improvement in exercise tolerance and angina improvement by two CCS classes (IV to II) at 3-month follow-up were reported [14]. We found no other published data on angina improvement following CFR implantation in CTO RCA patients.

In spite of regular selection of patients, we may expect a non-response cohort of patients up to 20% - 30%. Some possible mechanisms may be: ischemia arising from the territory of RCA, symptoms caused by heart failure rather than ischemia, non-ischemic chest pain, the presence of an alternative drainage ven-

ous system of the myocardium into the right ventricle (the Thebesian venous system), and incomplete endothelization of the stent with inadequate pressure gradient across the device [20]. Some of the proposed mechanisms need further clinical evaluation. It has been shown that peri-procedural measurement of the differential pressure between right atrial pressure before implantation and coronary sinus systolic pressure during balloon occlusion might be able to identify the non-responder population; the patients who achieve a high peri-procedural differential pressure are more prone to have a high post-implantation, post-endothelization pressure gradient across the device and thus a higher probability of good response regarding angina symptoms [21].

CFR implantation is a safe procedure, with only one coronary sinus perforation reported so far [22]. Other potential complications include migration of the device, thrombotic occlusion of the stent's lumen and dissection of the coronary sinus. In our case report, we present a successful CFR implantation with good clinical reduction of angina. At this point, we cannot prove the mechanism of the improvement. Nevertheless, the clinical dynamic ensued according to previous clinical data, *i.e.* the improvement of angina symptoms appeared 6 - 7 weeks after CFR implantation. This is the expected time period necessary for CFR mesh endothelization, which is the critical point for hemodynamic effects resulting in venous backpressure build-up to take place.

So far we have experience with 5 CFR implantations in CTO RCA patients. Reduction of RA in this population seems to be lower than in the overall CFR population, 60% vs. 75%, respectively. We may speculate that CFR might not be as effective in the cases of large ischemic area. Additional clinical data are required to support our hypothesis.

There is an ongoing discussion concerning the possibility of using CFR in patients with chronic angina who are candidates for percutaneous revascularization of CTOs. There are data from our CTO registry confirming the clinical efficacy of successful PCI of LAD, RCA, LCX in reducing RA in 6-year follow-up (55%, 35%, less than 5%, respectively) [23]. However, in the light of the recent CTO studies' conflicting results, there is still a debate regarding the clinical efficacy of CTO interventions at improving angina frequency, physical limitation and quality of life [24] [25]. In addition, CTO revascularizations do not offer prognostic benefits but rather aim at improving angina symptoms, which is exactly what the Reducer has already proven to achieve. Furthermore, while CTO revascularization is technically challenging and often time-consuming, CFR implantation is a relatively simpler and usually shorter (~30 - 45 minutes) procedure [26]. Additional clinical data are necessary to define ischemic load burden that might be addressed by either CFR implantation or CTO PCI, both aiming at reduction of angina symptoms.

4. Conclusion

Optimal medical therapy is the initial treatment approach to stable CAD. In case

of proven ischemia exceeding 10% of the myocardium, revascularization options should be considered [27]. However, patients with angina refractory to optimal medical treatment and with revascularization options exhausted make up a substantial portion of all patients with CAD and their number is expected to increase in the years to come. CFR implantation has proved to be an effective and safe RA treatment method. Both wider acceptance of this novel technique into regular clinical practice and broadening of the patient population (e.g. including patients with RA due to CTO) are expected in the near future. We have shown a case of a patient with remarkable CCS class improvement of angina symptoms, demonstrating the potential of CFR implantation to have a transformative impact on the quality of life of patients with RA. Further clinical studies are required to evaluate CFR implantation as a complementary treatment strategy in addition to optimal medical therapy and/or revascularization.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Placental Malaria and Pre-Eclampsia from the Lagos State University Teaching Hospital, Ikeja, Lagos Nigeria

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Abstract

Objective: To determine the relationship between placental malaria infection and pre-eclampsia in a holo-endemic zone. **Design:** Prospective case-control study. **Materials and Methods:** One hundred and twenty seven (127) pregnant women with a diagnosis of pre-eclampsia in labour or having caesarean section served as cases while controls were 127 normotensive parturient women. They were recruited from the maternity unit of Ifako Ijaiye and Isolo General Hospitals, Lagos that served as secondary care centers. At delivery, either spontaneous vaginal delivery or by caesarean section, a 2.0 cm × 2.0 cm placenta tissue was cut with scalpel and fixed in 10% formaldehyde in a specimen bottle and sent to the pathologist. Following this, 2.5 mls of Cord blood and 2.5 mls of the maternal venous blood were taken into separate EDTA bottles properly labeled at delivery, samples were sent to the haematology laboratory immediately for peripheral thick film smear for malaria parasite. Results were obtained from the laboratory and together with data from the case files, they were entered into SPSS version 16 for analysis. Independent Student t-test was used for significance for continuous variables while Chi-square was used for qualitative data. The significance was set at 0.05. **Results:** There were statistically significant differences between the cases and controls regarding the maternal age, number of pregnancies, $p < 0.05$ but none in the gestational age at delivery and birth weight, $p > 0.05$. There was statistically significant difference between the two groups regarding the diagnosis of placental malaria as well as past history of alcohol intake and occupation, $p < 0.05$. Binary logistic regression analysis showed that chronic placenta malaria infection was an independent risk factor for preeclampsia. **Conclusion:** Placental malaria infection was more common in patients with preec-

lampsia than their matched normotensive patients in our environment. At the same time, chronic malaria was found to be an independent risk factor for preeclampsia. More concerted efforts by all stake holders should be geared towards primary prevention together with early diagnosis and treatment of malaria especially in early pregnancy. This may reduce the incidence and complication of preeclampsia in our environment.

Keywords

Placental Malaria, Preeclampsia, Holoendemic Zone

1. Introduction

Malaria is a life-threatening parasitic disease transmitted by female anopheles mosquitoes. Today approximately 40% of the world's population mostly those living in the world's poorest countries are at risk of malaria [1]. Today malaria is found throughout the tropical and sub-tropical regions of the world and causes more than 300 million acute illnesses and at least one million deaths annually [1] [2]. Pregnant women and their unborn children are also particularly vulnerable to malaria, which is a major cause of perinatal mortality, low birth weight and maternal anaemia [2]. Although adult living in endemic areas acquires a protective immunity against developing severe malaria, women are susceptible to malaria pathogenesis when they become pregnant, especially in the first pregnancy. The clinical symptoms (syndrome) of what is termed maternal or Placental Malaria may include premature delivery, intrauterine growth restriction, stillbirth, abortions, maternal anaemia and death of the mother and the newborn [3] [4] [5]. The reason for the severe pathology associated with maternal malaria is the massive infestation of the placenta with *Plasmodium falciparum* Erythrocytes. The parasitized erythrocytes sequester in the placenta capillaries, which results in hypoxia, inflammatory reactions and chronic intervillositis.

While the placenta of infected women may be infested with parasitized erythrocytes, with parasite densities sometimes exceeding 50% of the total placenta erythrocyte count, the peripheral blood may remain free of parasites [3] [4]. This implies that the absence of peripheral malaria parasitaemia may not mean the absence of malaria Placenta infection. Sequestration of infected erythrocytes in the placenta is a virulence factor exclusively displayed by *Plasmodium falciparum*, and not observed for other human malaria parasites [6]. Malaria is the most frequent in first pregnancy [7], peaking between 13 and 16 weeks, and declining toward term.

Pre-eclampsia is another problem that is common in Sub-Saharan African and causes many deaths during pregnancy. It is defined as high blood pressure (hypertension) and protein loss in the urine. Preeclampsia is a disorder of widespread vascular endothelial malfunction and vasospasm with clinical manifestation after 20 weeks' gestation and can present as late as 4 - 6 weeks postpartum.

In developing nations, the incidence of the disease is reported to be 4% - 18% [8] [9], with hypertensive disorders being the second most common obstetric cause of stillbirths and early neonatal deaths in these countries [10]. It is also a major cause of maternal mortality and morbidity. The causes of pre-eclampsia are unclear, but many factors are probably involved. Among the theories that have been proposed is that of the inflammation of the placenta that might play a part and that this effect may affect both the mother and the fetus. Seasonal changes in the incidence of pre-eclampsia have been described in tropics, which are consistent with malaria transmission periods [11].

While some of these studies have reported the association between malaria and pre-eclampsia and malaria and hypertension during pregnancy [12] [13], other studies failed to find a significant association between malaria and pre-eclampsia [14] [15]. Furthermore, some of these studies did not differentiate between pre-eclampsia and other types of hypertension.

In tropical countries, malaria and hypertension are common diseases of pregnancy. They have physiopathologic similarities such as placenta ischemia, endothelial dysfunction, and production of proinflammatory cytokines. Recent findings suggested their possible link [16].

Placental histology is considered the "gold standard" for malaria diagnosis in pregnancy for epidemiological or biological study purposes because it can show signs of active, chronic and past infections [17] [18].

However, due to limited technical expertise, such testing is rarely available in holoendemic areas like ours. Most studies in Sub-Saharan Africa have relied on the results of the placental smear, the sensitivity of which is low compared with the placental histopathology.

We have therefore conducted this study to assess the relationship between placental malaria infection and preeclampsia in our environment where the two conditions occur commonly.

2. Materials and Methods

2.1. Study Site

This is a case control prospective, study carried out at the Obstetrics and Gynaecology Department of Lagos State University Teaching Hospital (LASUTH), using its two Maternal and Child Care units of Isolo General Hospital, and Ifako-Ijaiye General Hospital, January to December 2017. Both serve as tertiary referral centres. They were either in labour or having Caesarean section.

Ethical clearance was obtained for this study from the ethical clearance committee of Lagos State University Teaching Hospital Ikeja. All participants were fully informed about the study. They were told clearly about their right to withdraw from the study for whatever reasons at any stage of the study without penalty.

2.2. Sample Size Determination

The sample size was determined by applying the formula for comparison of two

proportions: [19]

$$n = \frac{(u + v)^2 \{p_1(100 - p_{11}) + p_2(100 - p_2)\}}{(p_1 - p_2)^2}$$

where n = the desired minimum sample size for each group.

u = One-sided percentage point of the normal distribution, corresponding to 1—the power.

v = Percentage point of the normal distribution, corresponding to the (two-sided) significance level.

p_1 = the estimated percentage of an attribute that is present in population 1.

p_2 = the estimated percentage of an attribute that is present in population 2.

At 95% confidence level, with 80% power, v = 1.96 and u = 0.84.

p_1 = 19.6% and p_2 = 7.7% (Percentage of pregnant women with Placental Malaria among those with pre-eclampsia and those without pre-eclampsia respectively in previous study) [20] [21].

$$n = \frac{(0.84 + 1.96)^2 \{19.6(100 - 19.6) + 7.7(100 - 7.7)\}}{(19.6 - 7.7)^2} = 126.59 \approx 127$$

The calculate minimum sample size for each group was 127.

2.3. Study Participants

The study comprised of 127 asymptomatic pre-eclamptic patients and a control group of 127 asymptomatic normotensive patients. Some patients were excluded from the study once they denied consent, had history of fever in the last two weeks, currently on anti-malarial treatment, had a known medical disorder such as sickle cell anaemia or infection like Human Immunodeficiency virus. Pre-eclampsia was diagnosed if the patient had a systolic blood pressure of ≥ 140 mmHg and or a diastolic blood pressure of ≥ 90 mmHg with the presence of proteinuria (≥ +1) at gestational age more than 20 weeks. Recruitment of participants was done consecutively for those that fulfill the criteria for inclusion in the study as preeclamptic while controls were those that were normotensive admitted for delivery about the same period and consent to the study.

2.4. Histopathology

At delivery, within 30 minutes, either spontaneous vaginal delivery or by caesarean section, a 2.0 cm × 2.0 cm × 2.0 placenta tissue including the placental membrane was cut with scalpel and fixed in 10% buffered formaldehyde in a specimen bottle and sent to the pathologist. They were processed and embedded in paraffin wax and sectioned onto slides by standard techniques. The placental biopsy samples were then processed and were embedded in paraffin wax. In every case, paraffin sections 4 mm thick were stained with hematoxylin-eosin and Giemsa stain. Because the samples were fixed in buffered formalin, formalin pigment formation, which has similar optical characteristics and polarized light activity to malaria pigment was not detected. Placental malaria infections were

characterized based on the classification of Bulmer *et al.* [22]; uninfected (no parasites or pigment), acute (parasites in intervillous spaces), chronic (parasites in maternal erythrocytes and pigment in fibrin or cells within fibrin and/or chorionic villous syncytiotrophoblast or stroma), past (no parasites and pigment confined to fibrin or cells within fibrin.

2.5. Laboratory Procedure

2.5 mls of the maternal venous blood was taken into separate EDTA bottles properly labelled at delivery, samples were sent to the haematology laboratory immediately for peripheral thick film smear for malaria parasite. In case of delivery in the night, the samples were preserved in the refrigerator till the following morning when they were sent to the laboratory. Microscopic examination of blood smears was done under oil immersion for parasite detection and 200 high power fields were used for the examination before the smear is considered negative. Parasites were counted against 200 leucocytes assuming an average leucocyte count of 8000 per microlitre of blood.

The data obtained were analysed using SPSS, version 17.0; a statistical computer program. Independent Students T-test was used to analyze continuous variables while Chi-square was used for categorical data. Binary Logistic Regression was used to test the independent risk factor for preeclampsia. The level of significance was set at 0.05.

3. Results

The demographic and other continuous characteristics are shown in Table 1. There were statistically significant differences between the two groups regarding maternal age, gravidity, $p < 0.05$ but not in birth weight, $p > 0.05$. There was no significant difference with regards to history of smoking between the two groups, $p > 0.05$. Table 2 showed that there were statistically significant differences between the two groups with regards to histological diagnosis of acute malarial infection and chronic infection, $p < 0.05$, but not in past infection, $p > 0.05$. Parasites and haemozoin pigments were seen in 35 (27%) in the pre-eclampsia group while it was seen in 2 (1.5%) of the normotensive group with a p-value < 0.05. This was statistically significant. Similarly, active parasites were seen in 9 pre-eclamptic patients while absence in the control group. This was also statistically significant ($p < 0.05$).

Binary logistic regression showed that only chronic placental malaria infection was an independent risk factor for placental malaria, $p < 0.05$ (Table 3).

4. Discussion

The major findings of this study were that placental malaria infection was significantly associated with and was an independent risk factor for preeclampsia in holoendemic region for malaria like ours. We also showed that chronic and active malaria infections were significantly more in patients with preeclampsia (27.5% vs. 1.5% and 7% vs. 0.0%) respectively. These values are higher than those

Table 1. Demographic and other characteristics between the two groups.

Characteristic Mean ± SD	Group 1 N = 127	Group 2 N = 127	Significance
Maternal age (years)	31.25 ± 5.79	33.02 ± 6.33	$p < 0.05$*
Gravidity	2.05 ± 1.29	2.89 ± 1.42	$p < 0.05$*
Miscarriages	1.50 ± 0.57	1.33 ± 0.51	$p > 0.05$
Gestational age at delivery (weeks)	39.38 ± 1.25	39.28 ± 1.42	$p > 0.05$
Birth weight (grams)	3175 ± 0.54	3288 ± 0.41	$p > 0.05$
Level of education			
None	8 (6.6)	0 (0)	$p < 0.05$*
1˚	28 (21.7)	11 (8.8)	
2˚	64 (50)	45 (35.4)	
3˚	28 (21.7)	71 (33.8)	
Consumed alcohol	3 (2.3)	12 (9.4)	$p < 0.05$*
Ever smoked	6 (4.9)	12 (9.8)	$p > 0.05$
Maternal venous blood positive for malaria parasites	60 (47.5)	3 (2.4)	$p < 0.05$*

SD = Standard deviation, * = significant statistically.

Table 2. Histopathological diagnosis of placental malaria between the two groups.

Characteristic.n (%)	**Group 1 N = 127**	**Group 2 N = 127**	**Significance**
Acute infection (active)	9 (7.0)	0 (0)	$p < 0.05$*
Haemozin (past)	50 (39.3)	50 (39.3)	$p > 0.05$
Thickening of basement membrane	13 (10.2)	35 (27.5)	$p < 0.05$)*
Calcification	69 (54.3)	64 (50.3)	$p < 0.05$*
Prominent synchytial knots	94 (74)	92 (72.4)	$p > 0.05$
Parasites/pigments and fibolin (chronic)	35 (27.5)	2 (1.5)	$p < 0.05$*

* = significant statistically.

Table 3. Logistic regression identifying the risk factors for preeclampsia.

	B	SE	Wald	df	Sig	Exp (B)
Age	0.028	0.022	1.600	1	0.206	1.029
Ever consumed alcohol	−1.030	0.665	2.398	1	0.121	0.357
Acute malaria infection	6.247	4.462	0.000	1	0.999	516.37
*Chronic malaria infection	1.060	0.276	14.752	1	0.000	2.887
Constant	−27.174	1.785	0.000	1	0.999	0.000

* = significant statistically.

of Adam *et al.* [16] from an area of unstable malaria transmission in Sudan. However, the rates of past infection between the two groups (39.3%) were similar. This is plausible, given the environment from where the study was underta-

ken. The results of Sartlet *et al.* [12] are in concordance with ours. Nonetheless, some studies found an association between placental malaria infection and gestational hypertension, but not preeclampsia or eclampsia [13]. It is possible for placental malaria to be associated with preeclampsia given the similar pathophysiology of the two entities namely; placental ischemia, endothelial dysfunction and production of inflammatory cytokines.

Our study also revealed that more patients with preeclampsia had significantly higher malaria parasites in the maternal venous and cord blood than normotensive controls. The implication is that these may be used as a possible screening for placental malaria infection. However, placental parasitaemia without peripheral parasitaemia may occur in women who have previously been treated with clearance of peripheral parasites. On the other hand, peripheral parasitemia without placental infection may occur in early malaria infection, especially if parasitemia is low. Nonetheless, other studies found no correlation between placental and peripheral venous parasitemia [20].

We also found in our study that some socio-demographics like young age, primiparity, low level of education were more common in patients with preeclampsia. These are very well established associations [21]. Interestingly, our result may not support the concept that smoking is negatively associated with preeclampsia.

The limitations of this study were that the patients were not matched and the fact that we did not find out whether the patients used insecticide treated nets. We also do not know how long these patients have been living in Nigeria. There could be a possibility that some of them have not been in malarial endemic region for years and subsequently could not have developed the malaria immunity expected in holo-endemic region.

5. Conclusion

In conclusion, chronic placental malaria infection was shown to be an independent risk factor for preeclampsia in our environment with stable malaria transmission. We, therefore, advocate that more efforts at prevention through health information dissemination should be intensified and at the same time, prompt diagnosis and treatment of malaria, especially in the first half of pregnancy should be institutionalized.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Hepatitis B Reactivation in Patients with Hematological and Solid Malignancies: A Retrospective Analysis of Single Center's Experience

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Abstract

Background: Hepatitis B reactivation might occur in patients with hematological and solid organ malignancies due to immunosuppressive effect of chemotherapy. **Methods:** Fourteen patients were evaluated retrospectively from their files to discuss the clinical manifestations, management, and avoiding of Hepatitis B reactivation within patients who receive immunosuppressive treatment. **Results:** These 14 HbsAg positive patients were being followed up and treated via oncological immunosuppressive chemotherapy. The ages of the patients were between 25 and 72. Seven of the patients were male, and the average follow up period for the patients was between 10 and 74 months. TV 0, 5 mg was started for seven of the patients before the chemotherapy and TFV 245 mg to one of the patients. LAM 100 was started for three patients whose basal HBV DNA was low. It has been analyzed that HBV DNA was negative in further observations. In follow up controls, we noticed HBV reactivation at two patients, LAM was given one of them and TFV was given the other one. One patient was applied allogeneic transplantation whose basal liver tests were normal and Hbsag was negative. Hepatitis B reactivation was detected after the first week of therapy. **Conclusions:** We offer testing in all patients undergoing cancer therapy for hepatitis B, HBsAg, core antibody (anti-HBc total), and anti-HBs before to start cancer therapy. Patients with higher risk of HBV reactivation require antiviral prophylaxis.

Keywords

Hepatitis B, Malignancies, Immunosuppression

1. Introduction

Hepatitis B reactivation might occur in patients with hematological and solid organ malignancies due to immunosuppressive effect of chemotherapy. Patients with a history of Hepatitis B who treated with immunosuppressive treatment are at risk for Hepatitis B reactivation and a serious hepatic attack, fulminant liver failure. This adverse condition can cause an interruption of chemotherapy, and can affect the success of primary solid cancer therapy. Several trials related to patients with solid tumors have suggested the efficacy of preventive anti-viral therapy. Many authors recommend testing all patients undergoing cancer treatment for hepatitis B in details such as hepatitis B surface antigen, hepatitis B core antibody, and hepatitis B surface antibody previous cancer therapy. Many authors recommend tenofovir or entecavir as preventive therapy, rather than lamivudine [1] [2] [3] [4].

HBV reactivations risk depends upon the kind of immunosuppressive drugs used. The risk of hepatitis B reactivation is at a great high with the use of protocols that contain anti-CD20 monoclonal antibodies and high dose glucocorticoids. And also hematopoietic cell transplantation has a great high risk of hepatitis B reactivation [1] [2] [3].

This study was performed in patients who underwent chemotherapy in South East Turkey where is an endemic location for hepatitis B virus, with an HBsAg prevalence of about 4% - 6% [2]. Our article retrospectively analyzed to discuss the clinical manifestations, management, and avoiding of hepatitis B reactivation within patients who receive immunosuppressive treatment.

2. Material Methods

14 patients were evaluated retrospectively from their files in Diyarbakır Memorial Hospital Clinic of Gastroenterohepatology between September 2013 and September 2019. Oncological or hematological cancer patients with HbsAg positive and were exposed to immunsuppressive chemotherapy were selected for analysis. These 14 HbsAg positive patients were being followed up and treated via oncological immunosuppressive chemotherapy.

3. Results

The ages of the patients were between 25 and 72, the average age was 51.5. Seven of the patients were male and the other 7 were female. The average follow up period for the patients were between 10 and 74 months.

HbsAg was positive in all of the patients. HbeAg and Anti-delta anticore were negative in all of the patients. Demographic and laboratory information of the patients are shown in **Table 1** and **Table 2**. Three of the patients were being followed up previously as inactive carriers. Other patients were newly diagnosed; their HbsAg tests were appeared out to be positive in studies before chemotherapy. None of the patients had liver cirrhosis in clinic, laboratory and imaging studies and none of them had antiviral treatment history. Prophylactic antiviral

Table 1. Patienst clinical and treatment characteristics.

	Age	Sex	Liver Cirrhosis	Malignancy	Chemotherapy	Antiviral Therapy	Follow up (Month)
1. patient	59	f	no	Breast	TRANSTUZUMAB-PERTUZUMAB	ETV 0.5	16
2. patient	70	m	no	Gall Bladder	Gemcitabine + cddp	ETV 0.5	30
3. patient	44	f	no	Breast	AC	ETV 0.5	39
4. patient	60	f	no	Periton	Pacl + Carbo	ETV 0.5	27 (ex)
5. patient	60	m	no	Prostate	Zoladex + docetaxel + enzalutamid +zometa	ETV 0.5	
6. patient	55	m	no	Rectum	5 FU, folfox-4	ETV 0.5	39
7. patient	66	m	no	Lung	Gemcitabine	Lam 100 mg + TFV 245 mg	41 (ex)
8. patient	72	f	no	NHL (Large cell)	5 years before, 6 cure chop Now R-ICE	TFV 245 mg + Lam 100 mg	72
9. patient	25	f	no	Giant cell tm of bone	Proliakordexa	ETV 0.5 mg	40
10. patient	44	f	no	NHL	BMT	ETV 1 mg	10
11. patient	46	f	no	Breast	AC-Gemcitabine-Carboplatin-Doxataksel	TFV 245 mg	50
12. patient	70	m	no	Laryngeal-Lung	Gemcitabine-Daksotaksel-cisplatin	Lam 100 mg	48
13. patient	49	m	no	Testicular	CDDp-Carboplatin	Lam 100 mg	74
14. patient	61	m	no	Prostate		Lam 100 mg	72

Table 2. Patients baseline laboratory results.

	HBV DNA (IU/mL)	HBsAg	HBeAg	Anti-delta	PLT	INR	AST (IU/L)	ALT (IU/L)	TBİL (mg/dL)
1. patient	189.746	positive	negative	negative	220,000	1.1	28	38	0.11
2. patient	2539	positive	negative	negative	187,000	1.0	11	12	0.34
3. patient	0	positive	negative	negative	340,000	1.2	26	28	0.28
4. patient	1220	positive	negative	negative	365,000	1.0	33	55	0.33
5. patient	12	positive	negative	negative	293,000	1.0	31	42	0.18
6. patient	0	positive	negative	negative	420,000	0.9	17	3	0.24
7. patient	184,000	positive	negative	negative	178,000	1.2	269	289	0.89
8. patient	59,051.199	positive	negative	negative	365,000	1.6	1350	1700	8.45
9. patient	246	positive	negative	negative	312,000	1.1	18	21	0.13
10. patient	1223.000	positive	negative	negative	229,000	1.7	2200	2120	11.2
11. patient	84	positive	negative	negative	397,000	1.1	11	11	0.64
12. patient	34	positive	negative	negative	178,000	1.2	23	27	0.21
13. patient	0	positive	negative	negative	196,000	0.9	34	29	0.44
14. patiant	0	positive	negative	negative	21,000	1.0	15	14	0.13

treatment started before chemotherapy and continued until the sixth month after the end of the chemotherapy. The use of drugs was ended if liver tests were normal and HBV DNA was negative in the tests of the sixth months.

ETV 0.5 mg was started for seven of the patients before the chemotherapy and TFV 245 mg to one of the patients. Apart from the first patient, HBV DNA values of these eight patients were negative or were less than 2000 IU. Basal HBV DNA value of the first patient was 189,746 IU. Liver tests of these eight patients were in normal values and HBV DNA values were negative. LAM 100 was started for three patients whose basal HBV DNA was low. It has been analyzed that HBV DNA was negative in 48, 72 and 74 month observations (**Table 2**).

Based on the normal liver tests LAM 100 mg was started for patient number 7 whose previous HBV DNA was 200 IU. It has been observed that liver tests were elevated in seventeenth month. HBV DNA was 184,000 IU. TFV 245 mg was added to the treatment. HBV DNA became negative in the following period.

Patient number eight had 6 doses of CHOP with the diagnosis of NHL five years ago. In that period, TFV 245 mg was started. In January 2019, R-ICE treatment was applied because of nux. ALT: 700 Tbil 8.45 HBV DNA 59.051.199 IU values were detected at the third week of the treatment. 100 mg LAM was added to TFV 245 mg treatment. ALT Tbil values of the patient became normal. HBV DNA became negative in the second month.

Allogeneic transplantation was applied to patient number 10 because of Non-Hodgkin Lymphoma (NHL). Basal liver tests were normal and HbsAg were negative. However, Anti-HBc-IgG was not tested at the basal evaluation. The patient came to us with icteric sclera and skin after the first week of allogeneic transplantation therapy. The values of the patient were: Anti-HBc-IgG positive HBV DNA 1223.000 IU AST 2200 ALT 2120 Tbil 11.2. 1 mg ETV was started for the patient. Tbil was elevated to 21 and INR was elevated to 3, 2 in the following period. Patient was sent to liver transplantation center for close follow up. However, liver tests and bilirubin became normal with medical treatment. HBV DNA became negative.

4. Discussion

This study performed in South East Turkey where is an endemic location for hepatitis B virus, with an HBsAg prevalence of about 4% - 6% [2], Hepatitis B reactivation might occur in patients with malignancies because of immunosuppressive effect of chemotherapy. So that patients with a story of Hepatitis B who treated with immunosuppressive treatment are at risk for Hepatitis B reactivation and a severe attack hepatitis B disease. This situation can conclude with elevated liver enzymes, fulminant liver failure [1] [4]. Furthermore, this negative situation (reactivation of hepatitis B) can cause an interruption of chemotherapy, delaying therapy of patient primary solid cancer. Although prophylactic antiviral therapy usage before chemotherapy has been recommended for patients with solid and hematological malignancies [5]-[9], many clinical studies related to patients with solid tumors have suggested the efficacy of preventive anti-viral therapy [10] [11]. In this article, we retrospectively analyzed naive 14 non-cirrhotic HBV positive patients with solid tumors. Our article review will discuss the clin-

ical manifestations, management, and avoiding of Hepatitis B reactivation within patients who receive immunosuppressive treatment.

In one study, where hepatitis B prevalence similar to our region, Kim *et al.* examined on 178 patients with breast cancer while chemotherapy performed. 97% of them were HBsAg negative, 35% had abnormal hepatic function. Yet, only in 1% of patients acute hepatitis has been developed during chemotherapy [3] [12]. In Kim study, 60% of the HBsAg positive patients developed liver abnormalities, and also 33% of them had a progression to acute hepatitis. Furthermore, the incidence of hepatitis because of Hepatitis B reactivation was 21% of all cases. In this study they advocated that those findings are similar with other studies which documented a 24% ~ 28% incidence of Hepatitis B reactivation; even if the patients and chemotherapeutic protocols were different [3] [11] [13]. In another study that Kim *et al.* researched, lamivudine treatment was performed the patients when Hepatitis B reactivation was found. But, Lamivudine treatment didn't affect fast enough, indeed, chemotherapy treatment had to be delayed in 78% of these patients that was 16% of all 111 patients. They retrospectively analyzed of 2431 patients with early breast cancer. Within these patients, 111 HBsAg positive female patients were accepted in their study. Thirty-seven patients (33.3%) cultivated acute hepatitis, of that 23 (20.7%) were associated with Hepatitis B reactivation. Those patients who diagnosed with hepatitis B reactivation were administered lamivudine at that case of hepatitis B reactivation [3] [14] [15] [16]. However, opposite of Kim et al., some researchers have suggested prophylactic therapy via lamivudine in patients who had solid tumors [10] [11]. In one essay on breast cancer, it was found that the patients in a prophylactic lamivudine group had a lesser incidence of hepatitis (12.9% vs. 59.0%), a decreased hepatitis B reactivation (6.5% vs. 31.1%) and decreased cessation of chemotherapy (16.1% vs. 45.9%) according to a control group [17]. In our study, ETV 0, 5 mg was started for seven of the patients before the chemotherapy and TFV 245 mg to one of the patients. Almost all these 8 patients' HBV DNA level was less than 2000 IU. We obtained good results in follow up. LAM 100 mg was started for three patients whose basal HBV DNA was low. It has been analyzed that HBV DNA was negative in follow-up results. In one patient who has normal basal liver tests, LAM 100 mg was started whose previous HBV DNA was 200 IU. It has been observed that liver tests were elevated in seventeenth month. HBV DNA was 184,000 IU. TFV 245 mg was added. HBV DNA became negative in the following period. On the other hand, another patient had 6 doses of CHOP with the diagnosis of NHL five years ago. In that period TFV 245 mg was started. In the fifth year of TFV treatment, because of NHL nux, R-ICE treatment was applied. In this period due to hepatitis B flare, 100 mg LAM was added to TFV 245 mg. HBV DNA became negative in the second month of the combination treatment.

Patients who receive anti-CD20 therapy and hematopoietic cell transplantation have a great high risk of hepatitis B reactivation, up to 20% [1]. In patients who are performed hematopoietic stem cell or solid organ transplantation are

under the risk even in the patients who are HBsAg-negative. In some studies reported that HBsAg negative patients who are treated with allogeneic transplant have risk of hepatitis B reactivation [1] [18]-[28] allogeneic transplantation was applied to our one patient because of NHL. This patient's basal liver tests were normal and HbsAg were negative. However, Anti-HBcIgG was not evaluated at the basal evaluation. The patient came to us with hepatic flare in the first week after allogeneic transplantation. One mg ETV was started and at follow up, liver tests and bilirubin became normal range with medical treatment and HBV DNA became negative.

In conclusion, we offer testing in all patients undergoing cancer therapy for hepatitis B, HBsAg, core antibody (anti-HBc total), and anti-HBs before to start cancer therapy. Patients with higher risk of HBV reactivation require antiviral prophylaxis.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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