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The New Approach to the Diagnostics and Treatment of Endogenous Intoxication in Patients with Burn Injury

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Abstract

Background: The main causes of mortality in patients with burn injury are the development of systemic inflammatory process, multiple organ failure and septic complications. **The aim of the research:** Improvement of diagnostic and therapeutic approaches to the detection and elimination of endogenous intoxication in patients with burn injury. **Materials and methods:** The main study group consisted of 19 patients and the comparison group—of 10 patients with burn injury. 92 blood serum (BS) samples of the patients of the main group were tested, using the method of fluorescence spectroscopy (MFS). The advanced therapeutic tactics were proposed for the patients of both groups. The control group consisted of 40 healthy individuals (donors). BS of these patients was also tested using MFS. **Results:** Patients with burn injury have endogenous intoxication in their blood. The effective concentration of albumin is reduced in patients with burn injury due to the blockage of albumin binding centers by bacterial metabolism products. Fluorescence spectra (FS) of BS in patients with burn trauma and donors were obtained and investigated. Based on MFS results, an improved treatment regimen using infusion of albumin solution was proposed. **Conclusions:** An improved technique for the management of patients with burn injury is based on the use of MFS for the diagnostic evaluation of endogenous intoxication in them. The idea of pathological changes in albumin molecules in patients with burn injury is pathogenetically substantiated by the successful use of infusion of albumin solution in these patients on the basis of the MFS.

Keywords

Burn Injury, Method of Fluorescence Spectroscopy, Endogenous Intoxication, Albumin

1. Introduction

According to WHO, the problem of burn injury is currently one of the most global in the field of health care. It is estimated, that up to 180,000 burn deaths occur annually in the world, most of which occur in low- and middle-income countries, including Africa, South and East Asia. The mortality rate of infant patients with burn injuries is over 7 times higher in low-income countries than in highly developed countries. Burn injury is one of the main causes of morbidity, leading to prolonged hospitalization, distortion and disability, and is often accompanied by stigma and rejection. This is especially true for patients with head and neck burns [1] [2]. Therefore, the problem of burn injury causes a number of serious economic, social and psychological problems and requires the development of effective methods of medical and social rehabilitation of patients.

Despite the introduction into medical practice the modern achievements of resuscitation, the latest methods of intensive care, the incidence of multiple organ failure, septic complications and mortality among patients with common burns remain quite high [3]. The main factors of mortality are the development of systemic inflammatory process, multiple organ failure and infectious complications [3]. The fraction of deaths from burn disease in the stage of burn shock is 23% - 39%, in the stage of acute burn toxemia—35% - 42%, and in the stage of septicotoxemia—25% - 30%.

At the same time, a number of important theoretical and practical problems remain studied insufficiently. Also, the controversial are the issues about the radicality of early surgical interventions in patients with head and face burns, the extent and time of their performance, the means of plastic wound closure and the correction of general homeostasis disorders. The role of local and general disorders, characterizing the severity of traumatic injury, is also described insufficiently.

Therefore, the problem of recovery and survival of patients with burn injury is currently very relevant, important and not enough resolved. Therefore, many scientific researchers are devoted to this problem. However, insufficient attention was focused on assessing the prognosis for the development of purulent-septic complications in patients with burn injury and for their early diagnosis capabilities, especially monitoring and treatment.

In order to develop the pathogenetic approach of diagnosis, monitoring, management of the treatment process and prognosis, it is promising to use physical research methods, in particular MFS. Its high diagnostic value, accuracy and sensitivity makes it possible to build the concept of diagnostics, monitoring and elimination of endogenous intoxication in patients with burn trauma, which

will significantly improve the survival and recovery of patients with burn injury.

2. Literature Review

The immediate cause of lethality in patients with severe burns is purulent-septic complications, which appear from damage of many organs and systems during the development of severe burn disease and septicotoxemia. Fatal complications are caused not by immediate burn injury, but by the body's reactive response to a thermal stimulus. It is based on the implementation of the local and then a generalized inflammatory response, mediated by the number of proinflammatory cytokines. Delay in the provision of intensive care in the stage of burn shock, delay in surgical repair of the skin, failure to identify and to neutralize microbial agents with the use of antimicrobial agents without local action also play a significant role in this process.

Burn necrotic scab is a source of infection and intoxication, so it should be removed as soon as possible, before the development of severe endogenous intoxication [3]. Therefore, the concept of early surgical necrectomies of burn wounds with their primary plasticity is rational, as well as the development of means for the prevention and treatment of wound infection, the restoration of anatomical structures and non-surgical correction in the postoperative period [1] [2]. However, the mechanism of the formation of endogenous intoxication in patients with burn injury was not fully established yet. There is no thorough understanding of the pathogenetic changes, that occur in burn injury, which does not allow to form an effective treatment strategy.

It should be noted, that because of presence of endogenous intoxication, conformational changes of the albumin BS molecules occur due to their interaction with toxins [4] [5]. Within the MFS, the excitation of BS was performed at a wavelength of 280 nm, which corresponds to the excitation region of human serum albumin.

Pathologically altered albumin causes changes in the fluorescence spectrum of the BS, which we detect within our research. This method allows to record these changes 24 - 48 hours before the onset of pronounced clinical manifestations [6]. It was successfully used for the early diagnosis of sepsis (patent of Ukraine N˚76953) [7] and postpartum purulent-inflammatory diseases (patent of Ukraine N˚33472) [8]. In scientific publications [9] [10], we tested the use of MFS for the diagnosis of endogenous intoxication in patients with burn injury, taking into account similar mechanisms of its formation in sepsis and burn injury, despite various etiological factors.

The aim of the research is to improve the diagnostic and therapeutic approach to the detection and elimination of endogenous intoxication in patients with burn injury.

3. Data and Methodology

The clinical base of the research was the burn department of Lviv's Communal

Clinical Hospital No. 8, and the experimental base—the laboratory of luminescence of the Department of Experimental Physics, Ivan Franko National University of Lviv. The term of the research was 2015-2020 years. Three groups of patients were formed. The main study group consisted of 19 patients with burn injury, for whom 92 BS samples were examined within the MFS. Inclusion criteria—patients with flame burns and burns with boiling of first- and second-degree (type A and B), with a total area of 18% to 45% of the body surface, including the head and neck. 11 patients (60%) of the main group were in serious condition and 8 (40%) were patients of moderate severity. Object of study—BS of patients with burn injury. The standard treatment algorithm for these patients was supplemented with infusion of albumin solution. The comparison group consisted of 10 patients, whose BS were not tested using MFS. 6 patients (60%) of the comparison group were in serious condition and 4 (40%) were patients of moderate severity. But therapeutic tactics with albumin solution was also used for these patients. The control group of the research consisted of 40 healthy individuals (donors) without chronic diseases, for whom BS samples were tested within the MFS.

Research methods: clinical, general blood test, biochemical, microbiological, morphological (structure of the areas of lesions, scars), immunological (immunohistochemistry of the skin), cytology of the wound, encephalography, ultrasound, doppler ultrasound, examination of microenvironment, computed tomography, densitometry, rheovasography, MFS.

3.1. Data Source

In the framework of this research, we investigated and analyzed the main factors, including clinical data, classification of burns, depending on the etiological factor, area and depth of lesion, localization, laboratory examination data (general blood test, general analysis of urine, biochemical blood test, bacterioscopic examination), ultrasonographic examination, MFS.

3.2. Research Results

During our research, we analyzed clinical data, results of laboratory, instrumental examinations and spectral-fluorescence characteristics of patients of the main group, group of comparison and spectral-fluorescence parameters of healthy controls. The main indicators that were used for the analysis of FS of BS were the fluorescence intensity (I_F) and the position of the maximum fluorescence band (λ_{max}). All patients underwent surgical treatment of the affected burn surfaces with subsequent wound closure by lyophilized xenografts in the hospital. The wounds were epithelized partly under dry skin, partly under dry necrosis and applicators. The residual wounds were epithelialized under dry applicators. Patients also received anti-inflammatory treatment, antibiotic therapy, infusion therapy, including using albumin solution and desensitizing therapy. After successful completion of treatment, all patients were discharged from the hospital in

satisfactory condition under the supervision of the surgeon at the place of residence. Now let's focus on some of the results obtained for patients of the main group in serious condition. To compare the spectral-fluorescence characteristics of BS of patients with burn injury, we shall also present in the relevant figures the results of the spectral-fluorescence characteristics of a patient with sepsis [6], who recovered after successful treatment.

The results of studies in the dynamics FS of BS and data for the spectral-fluorescence characteristics of the BS of patient with burn injury are depicted on **Figure 1** and **Table 1**. He was admitted to the hospital on the 27th of June, 2015 with the area of the burn surface 38%. *Staphyloccus aureus* 10^5 and *Pseudomonas aeruginosa* 10^6 were verified in this patient on the basis of the microbiological study. He was immediately prescribed appropriate treatment, including antibiotic therapy and infusion therapy with a volume of 2 - 3 liters daily and 20% albumin solution (100 ml 8 times in different days). Due to the infusion therapy, the intensity of FS of BS compared with the fluorescence intensity of albumin (I_F = 1.00) did not decrease significantly for several days (I_F = 0.88), which correlates with the results of in vitro studies [11]. At the same time, no significant shift of the FS of BS into the longwave region was recorded, despite the verification of several pathogens. Obviously, the intake of sufficient albumin allowed to improve significantly the work of detoxification systems of the body, which had a positive effect on the spectral-fluorescence parameters. Measurements of FS of BS after 10 days after admission to the hospital on the 13th of July, 2015 (**Figure 1**, curve 1.3), testified to a critical moment, when there was a significant decrease in I_F to 0.35 r.u. and the shift of the FS into the longwave region by 9 nm.

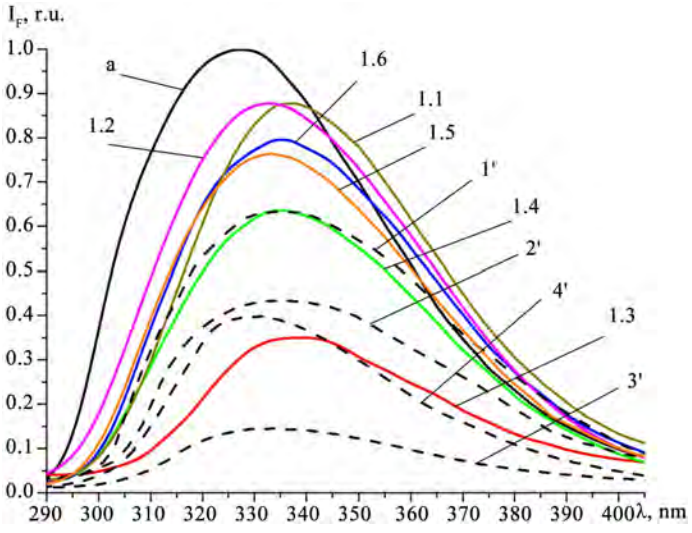

Figure 1. FS of BS of the patient 1 with burn injury, who was hospitalized at Lviv's Communal Clinical Hospital No. 8 in 2015 in dynamics during treatment (1.1—3.07, 1.2—8.07, 1.3—13.07, 1.4—17.07, 1.5—20.07, 1.6—24.07) and a patient with sepsis, who was treated in 2002 in Ambulance hospital (1'—03.06, 2'—05.06, 3'—06.06, 4'—07.06) and 20% albumin solution (a), λ_{ex} = 280 nm.

Table 1. Spectral-fluorescence parameters (fluorescence intensity (I_F) and the position of the maximum fluorescence band (λ_{max})) of blood serum of patient 1.

N	a	1.1	1.2	1.3	1.4	1.5	1.6	1'	2'	3'	4'
Date	3.07	3.07	8.07	13.07	17.07	20.07	24.07	03.06	05.06.	06.06	07.06
λ_{max} nm	327	336.1	332.2	341.1	335.1	333.1	335.1	335.2	335.2	334.1	331.6
I, r.u.	1	0.88	0.88	0.35	0.64	0.76	0.80	0.63	0.43	0.14	0.40

These parameters correlate well with the corresponding results of the study of FS of patient with sepsis, depicted in this figure by dashed lines (curves 1' – 4'), which is most likely related to the discontinuation of the albumin solution [12]. The resumption of infusion of albumin solution with subsequent complex therapy led to a gradual improvement of the spectral-fluorescence parameters of BS (approximated to the parameters of albumin fluorescence) at the subsequent blood samples during 17th-24th of July, 2015. They correlated well with the clinical parameters and laboratory test results of the patient. Therefore, he was discharged from the hospital in satisfactory condition on the 24th of July 2015.

In **Figure 2**, there are depicted the results of studies in the dynamics of fluorescence spectra, and in **Table 2**—data for the spectral-fluorescence characteristics of the BS of another patient with burn injury, who was admitted to the hospital on the 27th of June, 2015.

The area of the burn surface of this patient was 31%. In this case, the patient had no bacteremia. This led to a different character of the changes in the spectral-fluorescence characteristics of BS. No significant decrease in the fluorescence intensity of the BS was observed and no significant long-wave shift was recorded. After two infusions of 20% solution of albumin (28th of June—400 ml and 29th of June—200 ml) on the 3rd of July the primary measurement of his spectral-fluorescence characteristics was done. Thus, it was obtained I_F = 0.66 r.u. and shift in the longwave region to 339 nm (**Table 2**).

During the continuation of treatment (massive infusion therapy and 100 ml of 20% albumin solution on the 13th of July), slight changes in the spectral-fluorescence characteristics of BS were recorded. After the cancellation of treatment, the patient's condition gradually stabilized (on the 24th of July I_F = 0.87 r.u.) (**Table 2**) and he was discharged from the hospital on the 24th of July, 2015 in satisfactory condition.

In a slightly different scenario, there was a change in the spectral-fluorescence characteristics of the BS of the next patient with burn injury, with a burn surface area 40%. The results of the study of FS of this patient are depicted in **Figure 3**, and in **Table 3**—data for his spectral-fluorescence characteristics. On the basis of microbiological research, there were verified the presence of two pathogens (*Staphyloccus aureus* 5 × 10^6, *St. haemolyticus* 5 × 10^6). This patient received infusion, antibacterial therapy, as well as infusion of 20% solution of albumin (total volume 1000 ml). For this patient on the 8th of July, 2015 (curve 3.1), a marked decrease in the fluorescence intensity was recorded to 0.53 r.u.

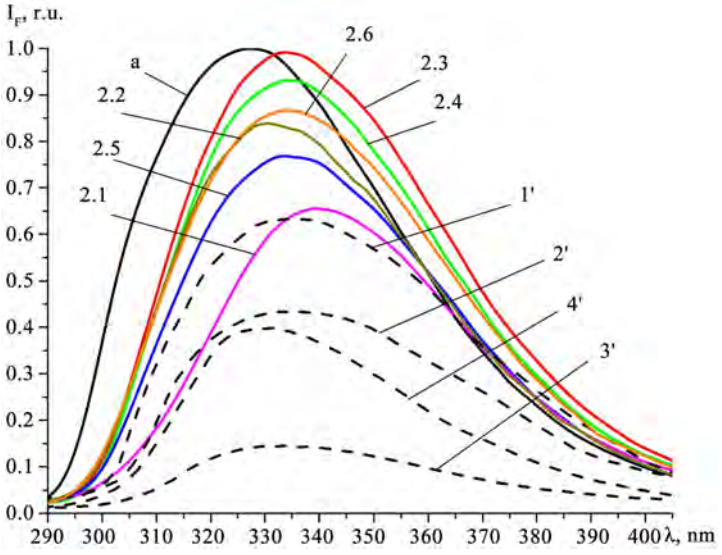

Figure 2. FS of BS of the patient 2 with burn injury, who was hospitalized at Lviv's Communal Clinical Hospital No. 8 in 2015 in dynamics during treatment (2.1—3.07, 2.2—8.07, 2.3—13.07, 2.4—17.07, 2.5—20.07, 2.6—24.07) and a patient with sepsis, who was treated in 2002 in Ambulance hospital (1'—03.06, 2'—05.06, 3'—06.06, 4'—07.06) and 20% albumin solution (a), λ_{ex} = 280 nm.

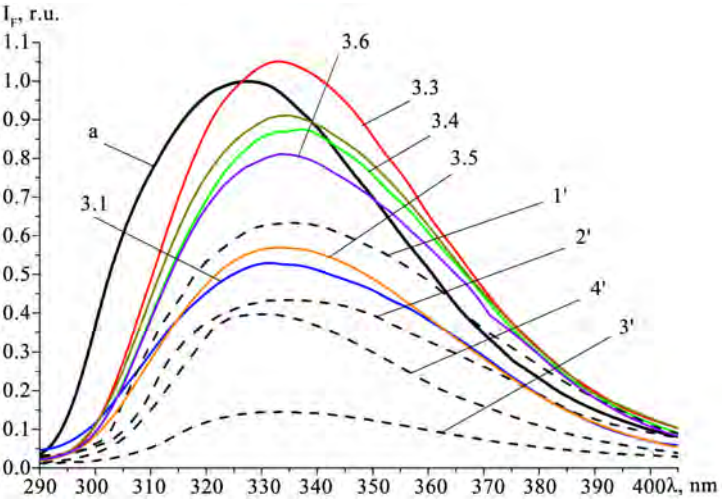

Figure 3. FS of BS of the patient 3 with burn injury, who was hospitalized at Lviv's Communal Clinical Hospital No 8 in 2015 in dynamics during treatment (3.1—8.07, 3.3—15.07, 3.4—17.07, 3.5—24.07, 3.6—28.07), and a patient with sepsis, who was treated in 2002 in Ambulance hospital (1'—03.06, 2'—05.06, 3'—06.06, 4'—07.06) and 20% albumin solution (a), λ_{ex} = 280 nm.

Table 2. Spectral-fluorescence parameters (fluorescence intensity (I_F) and the position of the maximum fluorescence band (λ_{max})) of blood serum of patient 2.

N	a	2.1	2.2	2.3	2.4	2.5	2.6	1'	2'	3'	4'
Date	3.07	3.07	8.07	13.07	17.07	20.07	24.07	03.06	05.06	06.06	07.06
λ_{max} nm	327	339	330.5	333.1	335.1	333.1	335.1	335.2	335.2	334.1	331.6
I, r.u.	1	0.66	0.84	0.99	0.93	0.77	0.87	0.63	0.43	0.14	0.40

Table 3. Spectral-fluorescence parameters (fluorescence intensity (I_F) and the position of the maximum fluorescence band (λ_{max})) of blood serum of patient 3.

N	a	3.1	3.3	3.4	3.5	3.6	1'	2'	3'	4'
Date	3.07	8.07	15.07	17.07	24.07	28.07	03.06	05.06	06.06	07.06
λ_{max} nm	327	332	333.1	337.1	333.1	333.1	335.2	335.2	334.1	331.6
I, r.u.	1	0.53	1.05	0.88	0.57	0.81	0.63	0.43	0.14	0.40

Further in dynamics on the 15th of July, 2015 there was an increase in the fluorescence band of the patient's BS (I_F = 1.05 r.u., Table 3), which cannot be interpreted as absolute hypoproteinemia, which typically causes a decrease in the fluorescence concentration quenching inherent in transient fluorescence [11]. Thereafter, there was a gradual decrease in the fluorescence intensity of the BS to I_F = 0.57 r.u. (24th of July, 2015). In the future, the patient's condition has stabilized (I_F = 0.81 r.u.) and he was discharged from the hospital.

Particularly noteworthy are those depicted in Figure 4 the results of the study in the dynamics of FS of the BS of the patient with combined body trauma, concussion, multiple laceration wounds of the frontal parietal region, chest slaughter, lung slaughter, left hemothorax, abdominal wall slaughter, traumatic detachment of the left lower third of left thigh, shock of the third-grade and sepsis.

The results of the spectral-fluorescence characteristics of her BS are presented in Table 4. It was important for us to study in dynamics the changes of FS of the BS of this patient and to compare them with the corresponding results of patients with burn injury. Based on the microbiological study, the presence of three pathogens was verified for this patient (*Ps. aeryginosa* 1×10^5, *Staphyloccus aureus* 1×10^4 and *Klebsiella pneumoniae* 1×10^4).

The effective treatment was immediately prescribed for this patient, including antibiotic therapy and infusion therapy with a volume of 2 - 3 liters every day, including a 20% solution of albumin (100 ml and 260 ml for 2 days).

The effective treatment was immediately prescribed to this patient. It included antibiotic and infusion therapy with a volume of 2 - 3 liters every day, including 20% albumin solution (100 ml and 260 ml for 2 days).

Due to the large amount of infusion therapy, the fluorescence intensity of the BS was not reduced (curve 4.1), which correlates with the results of the in vitro study and the results of the BS study of the severe burn patients, described above. Subsequently, the fluorescence intensity decreased to I_F = 0.76 r.u. (curve 4.3). On the background of further treatment, there was a significant improvement in the patient's condition (I_F = 0.98 r.u., curve 4.5) and she was discharged from the hospital. It should be noted, that according to the results of our studies, the condition of this patient was much easier compared to the conditions of previous patients.

The results of FS of BS of two more patients with burn injury are depicted on Figure 5 and Figure 6. The corresponding results for the spectral-fluorescence characteristics for their BS are presented in Table 5 and Table 6. They were

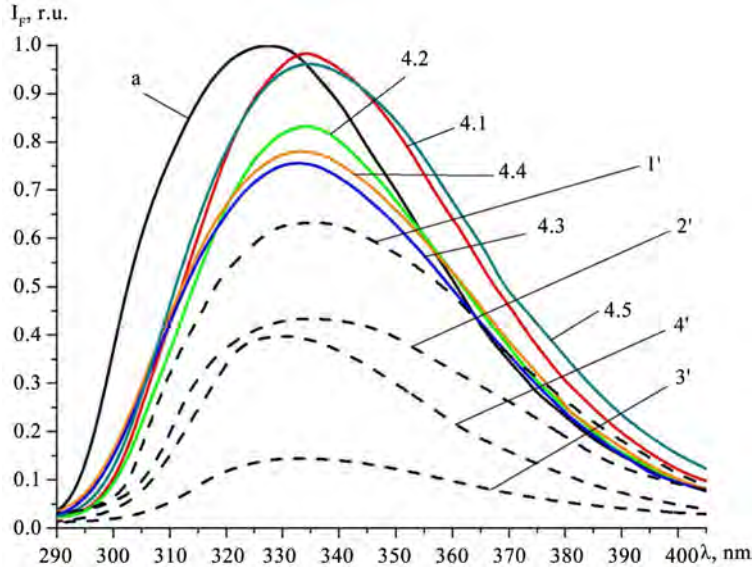

Figure 4. FS of BS of the patient 4 with combined body trauma, who was hospitalized at Lviv's Communal Clinical Hospital No 8 in 2015 in dynamics during treatment (7.1—17.07, 7.2—20.07, 7.3—24.07, 7.4—28.07, 7.5—31.07), and a patient with sepsis, who was treated in 2002 in Ambulance hospital (1'—03.06, 2'—05.06, 3'—06.06, 4'—07.06) and 20% albumin solution (a), λ_{ex} = 280 nm.

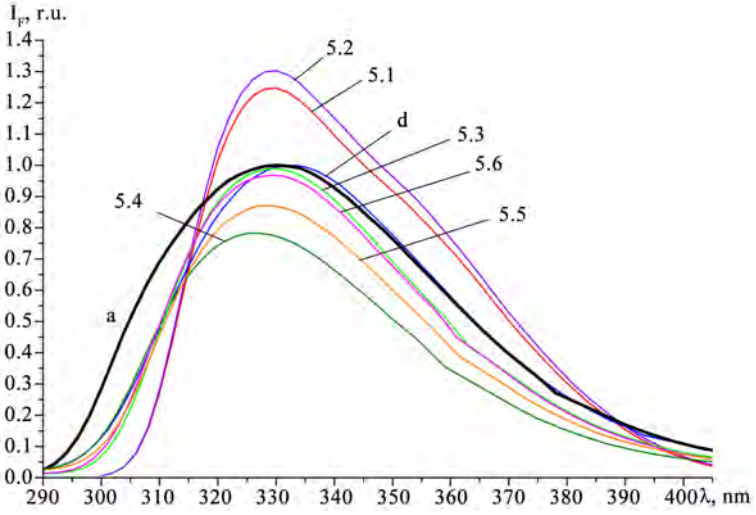

Figure 5. FS of BS of the patient 5 with burn injury, who was hospitalized at Lviv's Communal Clinical Hospital No. 8 in 2017 in dynamics during treatment (5.1—9.02, 5.2—14.02, 5.3—22.02, 5.4—03.03, 5.5—10.03, 5.6—31.03), donor (d) and 20% albumin solution (a), λ_{ex} = 280 nm.

Table 4. Spectral-fluorescence parameters (fluorescence intensity (I_F) and the position of the maximum fluorescence band (λ_{max})) of blood serum of patient 4.

N	a	4.1	4.2	4.3	4.4	4.5	1'	2'	3'	4'
Date	3.07	17.07	20.07	24.07	28.07	31.07	03.06	05.06	06.06	07.06
λ_{max} nm	327	335.1	335.1	333.1	333.1	335.1	335.2	335.2	334.1	331.6
I, r.u.	1	0.98	0.83	0.76	0.78	0.96	0.63	0.43	0.14	0.40

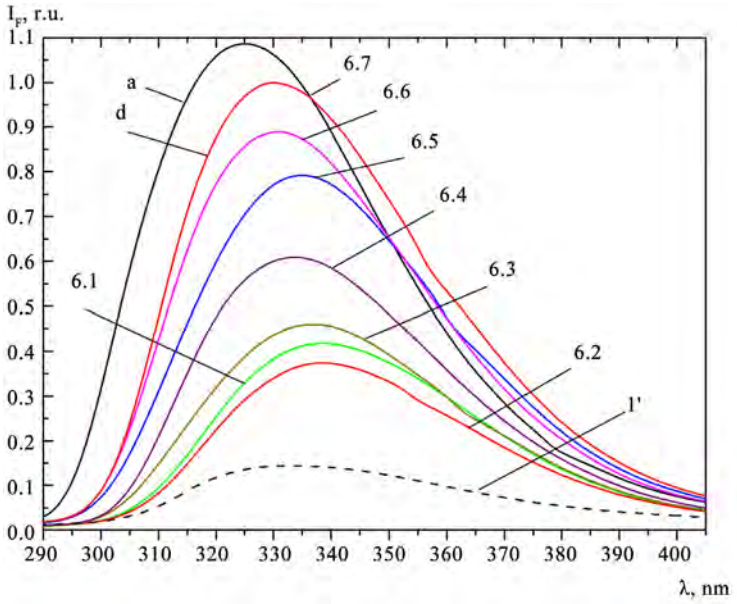

Figure 6. FS of BS of the patient 6 with burn injury, who was hospitalized at Lviv's Communal Clinical Hospital No 8 in 2017 in dynamics during treatment (6.1—9.02, 6.2—14.02, 6.3—22.02, 6.4—27.02, 6.5—03.03, 6.6—10.03, 6.7—31.03), and a patient with sepsis, who was treated in 2002 in Ambulance hospital (1'—03.06) and 20% albumin solution (a), λ_{ex} = 280 nm.

Table 5. Spectral-fluorescence parameters (fluorescence intensity (I_F) and the position of the maximum fluorescence band (λ_{max})) of blood serum of patient 5.

N	a	d	5.1	5.2	5.3	5.4	5.5	5.6
Date	3.07	9.02	9.02	14.02	22.02	03.03	10.03	31.03
λ_{max} nm	330.1	333.1	330	330	329.1	327.1	329.1	329.1
I, r.u.	1	1	1.25	1.30	0.99	0.78	0.87	0.97

Table 6. Spectral-fluorescence parameters (fluorescence intensity (I_F) and the position of the maximum fluorescence band (λ_{max})) of blood serum of patient 6.

N	a	d	1'	6.1	6.2	6.3	6.4	6.5	6.6	6.7
Date	06.06	06.06	06.06	9.02	14.02	22.02	27.02	03.03	10.03	31.03
λ_{max} nm	330.1	333.1	333	335.1	339.1	337	334	335.1	331.1	332.0
I, r.u.	1	1	0.16	0.41	0.37	0.46	0.61	0.79	0.89	0.95

hospitalized in Lviv's Communal Clinical Hospital No 8 in 2017. For the patient with burn area 32% there was a significant volume of infusion therapy (more than 2 liters daily), so the fluorescence intensity was higher than 1 (curves 5.1 and 5.2). This is consistent with the results of the in vitro study [11]. As the volume of infusion therapy decreased, the fluorescence intensity began to decrease (curve 5.3), which was caused by the leveling off of the effect of concentration quenching. But this decrease was not very noticeable due to the infusion of 10% albumin solution (200 ml once and 100 ml four times), which made it possible to

replenish the complete albumin in the patient's body, capable of performing its functions [12].

After the cancellation of the infusion of 10% albumin solution, the fluorescence intensity continued to decrease to I_F = 0.78 r.u. (curve 5.4), despite continued antibiotic therapy and antibiotic replacement. Against the background of continued treatment, the following improvement of the patient's condition was noted (curves 5.5 and 5.6), and the fluorescence intensity after completion of the treatment at the time of discharge from the hospital was I_F = 0.97 r.u.

FS of BS of the next patient is depicted on **Figure 6**. The area of the burn surface of this patient was 28%. The volume of infusion therapy of this patient did not differ significantly from the corresponding volume of the previous patient, but the fluorescence intensity of his BS was low (curve 6.1 I_F = 0.41 r.u., curve 6.2 I_F = 0.37 r.u.). His condition was much more severe, than the condition of the previous patient. During further treatment, including effective antibiotic therapy, as well as infusion of 10% albumin solution (6^{th}, 10^{th}, 15^{th}, 18^{th} of July, 2017), the fluorescence intensity began to increase from 0.46 r.u. (curve 6.3) up to 0.95 r.u. (curve 6.7). After that, the patient was discharged from the hospital in satisfactory condition.

Thus, we successfully used MFS for patients of the main group to diagnose endogenous intoxication and monitor their condition. The behavior of spectral-fluorescent characteristics of the BS of patients of different severity was under study. Standard treatment regimens were improved. It is noteworthy, that infusions of albumin solution were provided in case the patients felt worse. This ensured a successful treatment process and proper control. We took into account the treatment process under the control of MFS and formed a comparison group of 10 patients, who were treated without supervision within the MFS. But in case of the negative clinical dynamics of the patient's condition, we adjusted the treatment process by including infusions of albumin solution. In all cases, a positive effect was observed due to the changes of treatment tactics. All the patients, 60% of whom were in serious condition, were discharged from the hospital in satisfactory condition after the successful completion of their treatment.

The comparison group consisted of patients with burn injuries of first-and second-degree burns (type A and B), who was hospitalized at the stage of burn shock in the burn department of Lviv's Communal Clinical Hospital No 8 in 2019-2020. The area of burnt surfaces of patients in the comparison group ranged from 10% to 35%. 60% of the patients in the comparison group were admitted to the hospital in serious condition, and 40% of the patients were in moderate condition. Now we can focus on a few clinical cases. A 38-year-old patient's occupational injury was treated in the hospital from the 30^{th} of August to the 13^{th} of November, 2019. At the time of admission, the patient's condition was serious. The main diagnosis was second-degree (type A and B) flame burn of 35% of the head, neck, back and both upper limbs, second-degree burn shock. The patient had a fever and endogenous intoxication. The general blood test revealed leukocytosis with the increased number of rod granulocytes and the in-

creased rate of erythrocyte sedimentation. The patient underwent a successful surgical treatment. He received an anti-inflammatory, antibacterial, anticoagulant, antifungal and hormonal therapy, infusions of albumin solution (total amount of albumin solution is 700 ml). The patient also received erythromass (4 times) and native plasma (5 times). The daily infusion volume was more than 3000 ml. Considering the successful experience of using infusions albumin solution for treating patients with burns in the main group, we applied this experience to the comparison group. The patient's condition was under reliable monitoring. Infusions of albumin solution were provided in the most critical periods of the patient's condition. They made it possible to balance the amount of complete albumin in the BS and improve the patient's condition. After successful completion of the treatment process (75 bed days), the patient was discharged from the hospital in satisfactory condition.

Also notable is the clinical case of another patient, a 46-year-old man, who stayed in the hospital from the 19th of October till the 19th of December, 2019 with a 30%-surface burn injury. The patient's diagnosis was hot steam burn second-degree burns (type A and B) of up to 30% of the torso and both upper limbs. The patient also suffered from a first-degree burn shock.

The patient was hospitalized with acute intense throbbing pain in the affected areas, chills. There was a severing clinical picture of the disease. The patient had endogenous intoxication. He received an appropriate treatment, including surgery (autodermoplasty). He also received anti-inflammatory, antibacterial, infusion therapy with saline and non-saline solutions as well as 20% albumin solution. The treatment process was accompanied by the positive dynamics of changes in the patient's condition. After 61 bed days, he was discharged from the hospital in satisfactory condition.

Noteworthy is the clinical case of the burn injury of a 51-year-old man, who was hospitalized on the 1th of January, 2020 in serious condition. The diagnosis during hospitalization was second-degree (type A and B) flame burn of 25% of the head, chest, back, both forearms and hands, and first- and second-degree burn shock. The injury was received at home due to the explosion of a blowtorch. The patient underwent 4 surgeries (autodermoplasties and appendectomy). He also received massive infusion therapy with colloidal, saline and non-saline solutions. He received erythromass 5 times (213 - 319 ml) and blood plasma 4 times (180 - 260 ml). The patient also received infusions of 20% albumin solution 100 ml twice a day 5 times (total amount is 1000 ml). This contributed greatly to the improvement of his condition. Upon the successful completion of the treatment 76 days later, the patient was discharged home in satisfactory condition to the supervision of a local surgeon.

All patients were observed by us during the entire period of inpatient treatment. After discharge from the hospital, they were under the supervision of a local surgeon.

So, in our research, we proved the successful experience of using MFS to diagnose, control and improve the treatment process for patients with burn inju-

ries. The experience and skills, gained by using this method, have contributed greatly to the improvement of treatment tactics for severe patients with burn injuries, whose treatment was carried out without the use of MFS. At the same time, further thorough research is very important to improve the diagnosis and treatment tactics, especially during severe purulent-inflammatory diseases, like sepsis.

4. Conclusions

Using the method of fluorescence spectroscopy, at the first time, spectral-fluorescence characteristics of blood serum were obtained for the patients with burn injury. They have been found to be the effective markers of the severity of this disease. Their research in dynamics allows to monitor their behavior and to manage effectively the process of treatment. This makes it possible to assess quickly and qualitatively the threat of critical purulent-septic complications in order to adjust treatment and to prevent the development of septic conditions in patients.

It has been justified pathogenetically the positive effect of infusion therapy with albumin solution in the treatment of burn injury. Probable scenarios of behavior of spectral-fluorescence characteristics of BS of patients with burn trauma, depending on the severity of the disease, have been established. Patients with burn injury in serious condition can be used as the model objects for the study of sepsis, including the improvement of the therapeutic tactics of this disease.

Conflicts of Interest

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

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Parametrization of Survival Measures (Part III) Clinical Evidences in Single Arm Studies with Endpoint of Overall Survival

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Abstract

Many clinical trials have prospective or retrospective data-sets without comparison to the control-group formed by the same cohort as the active one. The measured single arm naturally contains the relevant information, however, in most of the cases, it is impossible to obtain it from the complex survival curve without a reference. In our previous articles [1] [2], we had shown that the self-similar Weibull distribution fits the self-organized biological mechanisms well, and so it is the best option to study the single-arm survival curves, where self-organizing process is actively present. With the Weibull decomposition of the survival curve, we can fit at least two subgroups of patients. The weighted sum of the decomposed fractions could be optimized analytically and determining the best parameters of the components and the best composition ratio of the weighted sum is also possible. In this part of our series of articles, we will show how the method works in a real clinical environment through modulated electro-hyperthermia (mEHT) as a complementary method, applied curatively when no other conventional curative therapies are available. The decomposed function of the non-responding group provides an excellent agreement with the historical controls in pancreatic cancer and non-small-cell-lung-cancer studies. In the case of glioblastoma multiform, the historical missing control from the institute where the treatment was made does not allow a comparison. We used a modified Hardin-Jones-Pauling statistical estimation and had shown in single arm clinical trials for advanced pancreas, non-small cell lung cancer and glioblastoma multiforme, that this estimation is applicable, and it is corresponding with the historical arm and with the non-responding group where this comparison was available.

Keywords

Single-Arm-Study, Weibull-Decomposition, Hardin-Jones-Pauling-Estimation, Modulated Electro-Hyperthermia (mEHT), Glioblastoma Multiform, Pancreatic Carcinoma, Non-Small-Cell Lung Cancer

1. Introduction

Overall survival (OS) is the most reliable parameter which characterizes the efficacy of a clinical trial. Evidence-based medicine (EBM) needs statistical evidences by clinical trials [3]. The clinical evidences are categorized into phases from basic preclinical (Phase 0) to the postmarket surveillance (Phase IV) [4]. The next steps are clinical, showing safety (Phase I study), efficacy (Phase II study), and an extensive, stable applicability (Phase III study), post-sale surveillance (Phase IV study) [5]. The usual basis of statistical evaluation is the randomized separation of a well-chosen cohort to control and active arms, while being as objective and as double-blinded as possible. Extracting strong reliable evidence from single-arm survival studies is rather challenging due to the missing control in the cohort. Due to the missing control-arm, the hypothesis check is unavailable. The information about the success of the treatment is of course somehow well-embedded in the results of the active arm, but without a reference set of values, its proper selection from the data is highly difficult and, in many cases, even impossible. Double blind categorizing is when neither the patient nor the therapist has any information about the actual treatment is impossible in cases of many medical equipment approvals, because the equipment usage cannot be hidden if no other treatment is possible.

In systemic diseases like malignancies, local response is not relevant in trials, because the local responding tumor refers to the local advantage, while no data is collected for the systematic behavior of the malignancy. Late stages probably have micro or macrometastases that essentially modify the survival. Local success does not give reliable information about the survival of the patient. The decreased overall survival among others for breast carcinoma [6] [7], for non-small-cell lung cancer [8] [9], for uterine cervix [10] [11], and even for the easily "heatable" surface tumors [12] were measured together with anyway significant local response (shrinking) of the tumor. Consequently, relevant information about the success of the treatment can only be obtained, if the endpoint is OS.

The effect of active therapy that changes the patient's survival is the hidden information in the measured OS. Looking for the embedded data is hard, and the success is doubtful when only a standard data-mining is used. The actually unavailable comparison to reference could lead to misinterpretations in a single-arm study [13]. Furthermore, the enormously massive bio-variability of the

participating individuals creates a stumbling-block for objective evaluation even in a well-chosen cohort; and covers the useful data. The life conditions (lifestyle, diet, social position, etc.) of the studied individuals are also very different; these may modify the results [14], which gets even worse when the patient uses additional supportive therapies like "home medicine", that can be picked up easily from the widely available uncontrolled internet sources.

Naturally, when the well-controlled single arm study offers obviously much better results than expected from the historical data, we tend to regard it as a breakthrough, however significant heterogeneity is observed in these comparisons [15]. When the survival is not obviously much better than the historical data, the evaluation of a single arm study is complicated and in most of the cases impossible.

A commonly applied possibility to evaluate single-arm therapy information is when researchers use a historical control from the same clinic/hospital, choose retrospectively the same conditions of the cohort-selection. The evidence of the retrospective data-collection from historical archives is, of course, weaker than the randomization. The propensity scores method offers an increased reliability of the obtained results [16] [17] by adding a database construction of the control arm to single-arm results [18]. Data mining in large and representative databases selects a comparative group of patients, with relevant and characteristic properties of the disease and the conditions of the patients, supposing that these (directly independent parameters from the actual therapy) do not change during the complete curative or palliative process. The method can be verified statistically if the confounding variables are chosen well [19]. Advanced cancerous cases limit the applicability of the propensity scores method, because the patients might have had a large variety of previously failed treatments and could develop various metastatic lesions.

For improving the statistical relevance, another method has been developed: the sequential trial [20]. It is a method during which we continue the study until the number of the patients reaches a level where it can be regarded as statistically significant. In such sequenced study, cumulative data is analyzed interim after the treatment of the chosen group of patients and a decision is made to continue or stop the given treatment at every step [21]. The sequenced trial is commonly applied in small studies [22], as a tool for evaluating the interim data for statistically significant values [23] [24] [25]. It is a useful tool for studies of advanced cases when other ways do not exist [8] [26]. This way, multiple survival endpoints could be evaluated [27]. Just like the propensity score method, the sequential method also has complications, for example when the patients are in late metastatic stages with multiple pretreatments and possible comorbidities (like organ failure or unsatisfactory laboratory results).

Oncological hyperthermia is one of the therapies that cannot be blinded, due to its machinery application, the sham treatment is usually well-sensed by the patient, so it is not possible to be blinded. Moreover, the medical staff who takes care of the patient, must also know that the treatment is a sham or not for safety

issues. These conditions challenge the evidence, affect the reliability of these trials and make them less comparable to the evidences of conventional applications.

The chosen end-points of oncological local/regional hyperthermia clinical studies are often connected to local responses (local remission rate, local remission free survival, local progression-free survival). This choice is a logical consequence of the local treatments—however, the problem of malignancy is far beyond the local response. Malignant diseases have the possibility of forming micro- and macro-metastases by systemic dissemination far from the original tumor. The development of metastases is more life-threatening than local tumor development [28], and the invisible micro-metastases worsen the life-prognosis further [29] significantly. Unfortunately, there are multiple studies with effective and significant local control, but at the same time a decreased OS is shown in well-conducted studies among others for breast carcinoma [6] [7], for non-small-cell lung cancer [8] [9], for uterine cervix [10] [11], and even for the easily heatable surface tumors [12]. An important fact is that the inclusion criteria was "locally advanced", so no metastases were observed at inclusion. This raises doubts [30], that could block the application of hyperthermia in oncology, [31].

One of the categories of oncological hyperthermia methods is the modulated electro-hyperthermia (mEHT, trade name: oncothermia) [32]. The mEHT method is usually applied in the stages when conventional curative methods fail, and conventionally only palliation would be applicable. The method of mEHT is able to resensitize the previous refractory treatments, and usually, it is applied for late-stage patients. In most of the cases, the quality of life (QoL) is in the focus of the trials in palliative care [33]. These studies provide evidence of the palliation being mostly irrespective of the tumor-type and the selection is usually only based on the unavailability of curative approaches [34] [35].

The direct rationale of mEHT is that it attacks the malignancy in its systemic conditions, so instead of the local responses of the actual tumor, the complex issue of the overall survival with the QoL together is the usual endpoint of its studies. The basic idea behind mEHT is the selective heating of the malignant cells in a highly heterogeneous tumor. The bioelectromagnetic interactions [36] with the physiology differences of the malignant and non-malignant cells [37], allow the attack and induce the apoptosis [38], in malignant cells, while no change has been made in healthy neighboring ones. The process produces a damage-associated molecular pattern and immunogenic cell-death [39], which has a crucial role in the abscopal effect of the mEHT method [40] [41]. The immune-effect is so strong that after the treatment the re-challenging of the same tumor was unsuccessful [39]. Significant differences can be shown in a comparison of mEHT to conventional water-bath heating [42] or with other bioelectromagnetic heating methods [43].

Considering the possible controversial endpoint response-related parameters of clinical studies, the appropriately combined endpoint with QoL should be the

overall survival (OS). The complete mEHT method was developed to solve this problem, ensuring the significant improvement of local response and the OS together [44] [45], which is viewed as the future of hyperthermia in oncology [46]. Clinical results prove that the improvement of the survival is induced by mEHT [47]. There are studies for multiple localizations, like pancreas carcinoma [48] [49] [50]; small-cell [51] and non-small-cell lung cancer [52] [53] [54]; brain gliomas [55]-[61]; uterine cervix carcinoma [62] [63]; hepatocellular carcinomas [64] [65]; sarcomas [66] [67]; biliary cancer [68], malignant ascites [69], and liver metastases [70] [71].

Our objective in this present study is to evaluate mEHT results using the single arm studies with the calculated parametric fitting to the non-parametric Kaplan-Meier (KM) estimates.

2. Method

First, we define the inclusion criteria for unifying the mEHT cohort. Selecting late-stage patients for mEHT in curative approach, when conventionally only palliation is available makes mEHT studies complex, and obtaining evidence difficult. The before-mentioned problems have aroused because the actual cohort contains only those late-stage patients, for whom conventional therapies are unavailable due to their refractory cases, organ failure, inadequate hematology measures, multiple relapses, or simply, there are no curative possibilities in that concrete stage of the disease. In this meaning, mEHT starts as a definitive palliation, but its intent is curative. Specialized medical facilities like hospitals, university clinics, and private services use mEHT treatment for a broadly heterogeneous group of patients who are not treatable by conventional therapies anymore. The long years of mEHT usage in oncological practice shows that the actual stage of the patient determines the time of the first, so the point of the inclusion of the patients to mEHT process is based on identical criteria: conventional curative possibilities (chemotherapy, radiotherapy, gene therapy, etc.) no longer available for this group of patients.

The blind process in a clinical study is obviously impossible in the case of mEHT. In many mEHT clinical studies, even the simple, non-blinded randomization is impossible because late-stage patients need the only applicable curative possibility, therefore, the option of exclusion from the mEHT by randomization would be unethical.

The point, when the patient leaves conventional therapy to start complementary mEHT can be regarded as the end of an independent trial. This stage is usually grouped by late palliative intent, and the aim is to provide the best supportive care. The time when previous treatments fail forms a reference point for a cohort of patients, for whom conventional curative protocols alone do not work anymore. At this point, mEHT treatment can be started and/or promoted to a complementary, but curative therapy in order to be able to use conventional approaches again. The failure of conventional therapies as the only inclusion criteria of the study unifies the mEHT cohort. In consequence, the starting point

of mEHT is defined by the cohort-forming condition, therefore, the time between the diagnosis and the start of mEHT treatment (T_s) has importance.

All the information about the efficacy of the mEHT treatment is included (but hidden) in the single arm process as well. The information describes the obtained OS, however without the reference arm, information cannot be seen. By adding quasi control-arms, the accuracy of the estimation can be improved, and the double-checking of the subgroup division becomes available, that can be compared to the historical control arm of the group with the same (but retrospective) inclusion criteria. The simplest way to create the control arm in late-stage treatments is by choosing the patients for whom conventional treatment was ineffective, or those, who were censored or deceased earlier than the end of the protocol. Note, that local response is not relevant information in trials with OS as an endpoint, because the locally responding tumor excludes the systematic behavior of the malignancy. Late-stages probably involve micro or macrometastases, which essentially modify the survival. Local success does not give reliable information about the survival of the patient.

As it was shown earlier [59] [60], the survival is expected to fulfill some universal rules originated from the self-organizing and self-similarity of the bio-structures. In consequence, the parametric Weibull function (WF) fits to the non-parametric KM plot with high accuracy. The regression curve has simple information, considering, that all the individuals in the cohort have identical fate because of the development of the malignant disease. This universality gives the possibility to extract the outliner changes from the data-coherency in the parametric curve. So, when the observed KM survival plot does not fit with appropriate accuracy by WF, the weighted sum of two or more WFs with different parameters gives a satisfactory solution [59]:

$$W^{(KM)}(t)=\frac{k_1}{N}\mathrm{e}^{-\left(\frac{t}{t_0^{(1)}}\right)^{n^{(1)}}}+\frac{k_2}{N}\mathrm{e}^{-\left(\frac{t}{t_0^{(2)}}\right)^{n^{(2)}}}+\cdots+\frac{k_M}{N}\mathrm{e}^{-\left(\frac{t}{t_0^{(M)}}\right)^{n^{(M)}}}$$

$$\text{or } W^{(KM)}(t)=\sum_{i=1}^{M}\frac{k_i}{N}\mathrm{e}^{-\left(\frac{t}{t_0^{(i)}}\right)^{n^{(i)}}} \quad \text{and} \quad \sum_{i=1}^{M}k_i=N \tag{1}$$

where M subgroups exist in the complete cohort of N patients, and in every group, we have $k_1,k_2,\cdots,k_M$ patients, we introduce the WFs for every subgroup with $n^{(i)}$ and $t_0^{(i)}$ parameters to fit the actually measured non-parametric KM.

Other reference groups may be compared to the historical arm or make a decomposition of KM with the process of WF-fit [59]. For the usual facilities of the trial, we may group the patients roughly into two groups: responding (r) and non-responding (nr). In this grouping only two subgroups of KM in (1):

$$W^{(KM)}(t)=c_r\mathrm{e}^{-\left(\frac{t}{t_0^{(r)}}\right)^{n^{(r)}}}+c_{nr}\mathrm{e}^{-\left(\frac{t}{t_0^{(nr)}}\right)^{n^{(nr)}}} \tag{2}$$

Due to the complete set of patients, $c_r+c_{nr}=1$, so (2) looks like this:

$$W^{(KM)}(t) = c_r \mathrm{e}^{-\left(\frac{t}{t_0^{(r)}}\right)^{n^{(r)}}} + (1-c_r)\mathrm{e}^{-\left(\frac{t}{t_0^{(nr)}}\right)^{n^{(nr)}}} \quad (3)$$

This bi-grouping is not always possible. The measured accuracy of the obtained $W^{(KM)}(t)$ decides the necessity of further subgroups. For detailed investigation we, had chosen two single arm trials performed by mEHT: inoperable, advanced pancreas [36] and advanced non-small-cell lung cancer (NSCLC) [40], as well as for glioblastoma multiform (GBM) [42].

3. Results

3.1. Inoperable Pancreas Carcinoma, a Palliative Stage with Curative Intent

A study for the mEHT treatment of inoperable advanced pancreas carcinoma [36] involves 99 patients in the active arm from two centers (73 and 26 patients) and a historical control with 34 patients. The overall survival is shown in **Figure 1**.

The measured KM of historical control compared to the KM of OS of mEHT treatment is shown in **Figure 2**. WF can be well fitted to the historical control, but to the OS plot it is far from accurate.

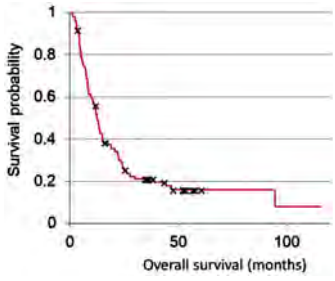


Figure 1. KM plot of OS of pancreatic cancer treated by mEHT (solid line, n = 99, median = 12.6 m, mean = 28.1 m) with censored patients (crosses).

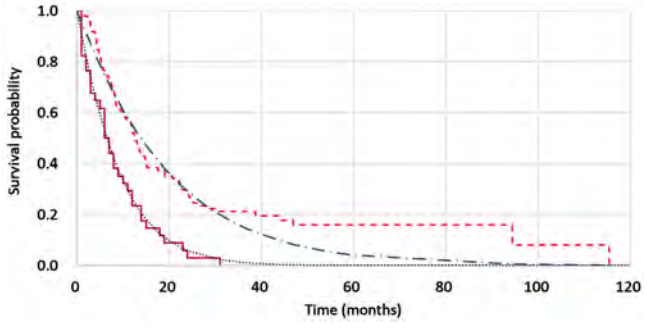


Figure 2. The KM plots of OS of pancreatic cancer treated by mEHT (dashed line) and the historical control (solid line, n = 34, median = 6 m, mean = 8.6 m). The WF fits the parameters for control (dotted line): $n^{(ctr)} = 1.08$; $t_0^{(ctr)} = 9.17$; $SE = 0.05$, $r^2 = 0.984$. The single WF does not fit the KM of mEHT (dash-ditted line, $n^{(OS)} = 1.05$; $t_0^{(OS)} = 19.7$; $SE = 0.4$, $r^2 = 0.967$), a decomposition of responding and non-responding group of patients has to be applied.

The WF decomposition fits significantly well to the OS (regression by minimizing the sum of deviations points by points), which is shown in Figure 3.

The comparison of the historical control and the non-responding subgroup obtained from the WF decomposition of OS in Figure 3 shows that mEHT has slightly effected even the non-responding group, but its statistical difference from the historical control is not significant ($p = 0.23$) (Figure 4). The information contents, that are measurable by the Shannon entropy of the Weibull probability distribution [72]; are remarkably equal in this case: $S^{(nr)} = 3.15$ and

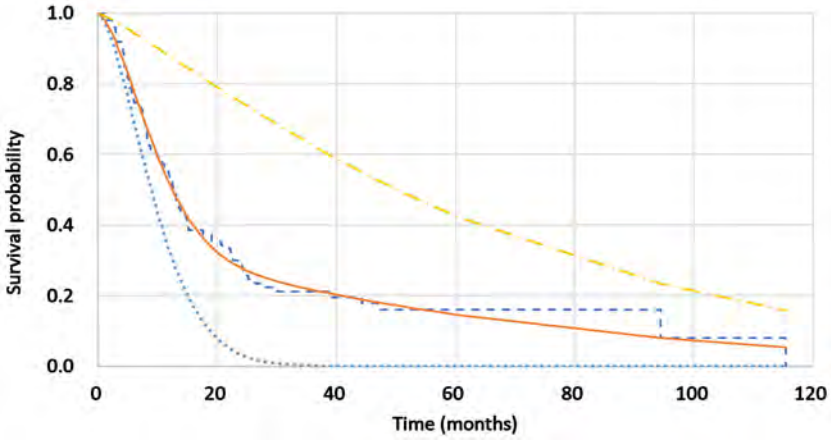


Figure 3. The Weibull decomposition fits to the OS (solid line) of pancreatic carcinoma of the advanced inoperable pancreatic cohort of patients. The Weibull parameters of "responders" (r), the dot-dashed line, and "non-responders" (nr), the dotted line are $n^{(r)} = 1.18$; $t_0^{(r)} = 68.58$; $n^{(nr)} = 1.62$; $t_0^{(nr)} = 11.19$; the percentage of the "responders" is 34.4%. The sum of the two decomposed parts (dashed line) well fits to the KM. The deviation of the weighted sum of WFs from the KM estimates remains under 0.002 until $t = 60$, and remains under 0.006 afterward. $SE = 0.1204$, $r^2 = 0.995$.

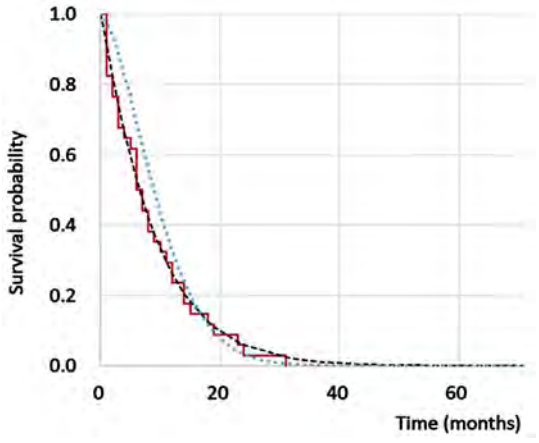


Figure 4. The non-responding component of OS of pancreatic carcinoma from Figure 3. (dotted line, $n^{(nr)} = 1.62$; $t_0^{(nr)} = 11.19$; $S^{(nr)} = 3.16$) compared to the historical control (solid line). The parameters of the WF fit to the historical control are: $n^{(ctr)} = 1.08$; $t_0^{(ctr)} = 9.17$, $S^{(ctr)} = 3.18$, (dashed line). No significant difference is observed (p = 0.23), and the Shannon entropies show the equivalence.

$S^{(ctr)} = 3.18$, which supports the statistical equivalence of the non-responding group from single non-parametric Kaplan-Meier with the historical control. This equivalence well verificates the decomposition concept by identifying the responding and non-responding patients, and so forming references to the single-arm study. This is not only a simple reference, but at the same time, it shows the percentages of the patients, whom the active treatment helps.

Despite the late stages and the conventionally palliative phase of the inoperable pancreatic patients, mEHT had shown curative features. The survival time from the first mEHT application has 6.1 m median (Figure 5).

Studying the KM of the time from the first mEHT treatment gives another opportunity for controlling the WF approach. Decomposing the KM by WFs, the sum properly fits the measurement (Figure 6).

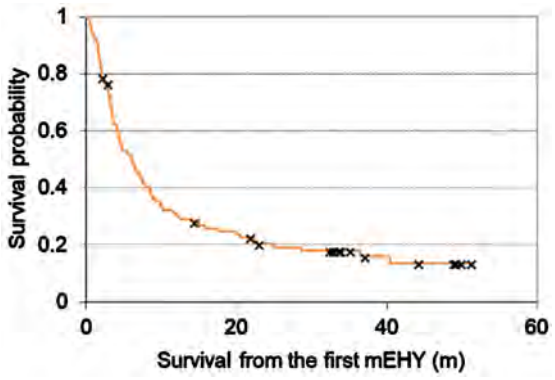


Figure 5. Survival probabilities of inoperable pancreatic carcinoma treated by mEHT (n = 99, median = 6.1 m, mean = 14.1 m). The survival is measured from the first mEHT treatment, practically when the patient loses the possibility of curative intent by conventional therapies. The censored patients are denoted by a cross.

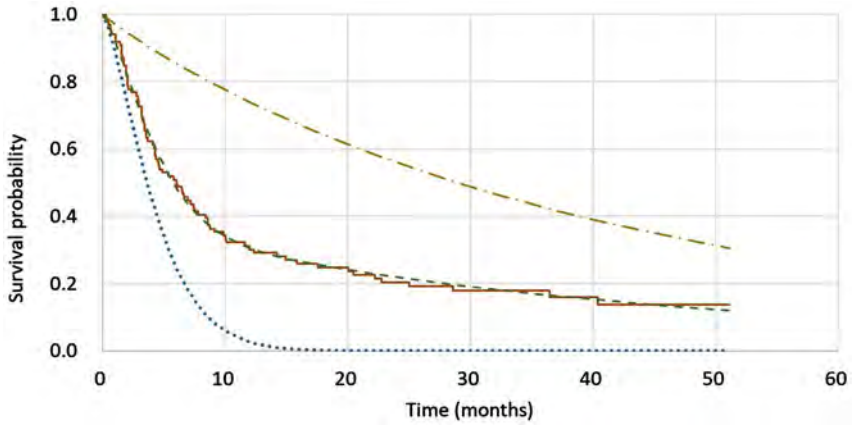
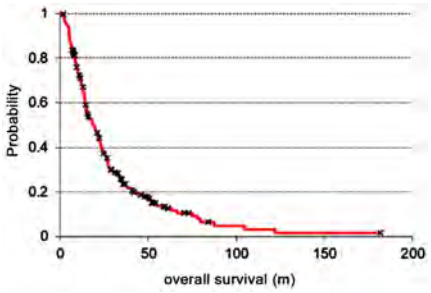


Figure 6. The KM of the survival distribution of pancreatic carcinoma by the time from the first mEHT treatment (solid line); and its best WF fit (dashed line). The accuracy of the regression is: $r^2 = 0.9966$, $SE = 0.0367$. The WF decomposition has a responding (dot-dashed line, $n^{(mEHT\_r)} = 0.94$; $t_0^{(mEHT\_r)} = 42.67$) and a non-responding group (dotted line, ($n^{(mEHT\_nr)} = 1.39$; $t_0^{(mEHT\_nr)} = 4.74$). The percentage of the responding patients is $c^{(r)} = 39.2\%$.

The decomposition percentage (39.2%) for the responding subgroup of the mEHT period is higher by 4.8% than the percentage of the same group in complete OS. Similarly to the results of the OS's decomposition number in Figure 3, it is over 30%, support further the previously observed accuracy of the WF decomposing fit.

3.2. Non-Small-Cell Lung Cancer (NSCLC) Palliative Phase Curative Intent

Another clinical trial was conducted for the advanced NSCLC by mEHT treatment [40], where patients were selected based on their finished conventional therapies without curative possibilities. The study involves 258 patients from two centers (197 and 61 patients, respectively) and a historical control from another hospital including 53 patients. Figure 7 shows the overall survivals for the two centers and the completely unified cohort.



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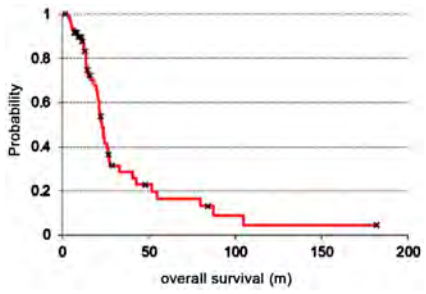

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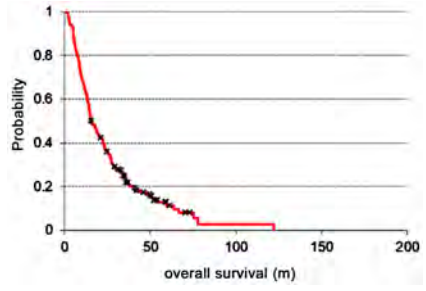


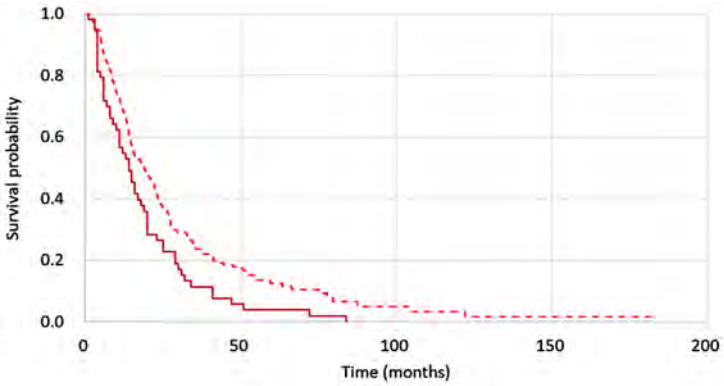
(c)

Figure 7. KM plot of OS of NSCLC treated by mEHT with censored patients (crosses). (a) all mEHT treated patients from the two centers (n = 258, median = 18.97 m, mean = 29.59 m), (b) center A, governmental hospital (n = 61, median = 23.03 m, mean = 37.88 m), (c) center B, private hospital (n = 197, median = 15.8 m, mean = 26.2 m).

The measured KM of the historical control (in the case of patients who were treated with only palliative treatments, due to failed curative possibilities) compared to the KM of the OS of mEHT treatment is shown in Figure 8. WF can be well fitted to the historical control, but fitting to the OS plot it is far no accurate.

The WF decomposition, a regression by minimizing the sum of deviations data by data, fits to the OS of NSCLC is shown in Figure 9 significantly well.

The comparison of the historical control and the non-responding subgroup obtained from WF decomposition of OS in Figure 8 shows that mEHT has slightly affected even the non-responding group, but its statistical difference from the historical control is not significant (Figure 10). The information coincidences well: $S^{(nr)} = 3.56$ and $S^{(ctr)} = 3.85$, which supports the statistical equivalence of the non-responding group from the single non-parametric Kaplan-Meier with the historical control. This equivalence verifies the decomposition concept well by identifying the responding and non-responding patients,



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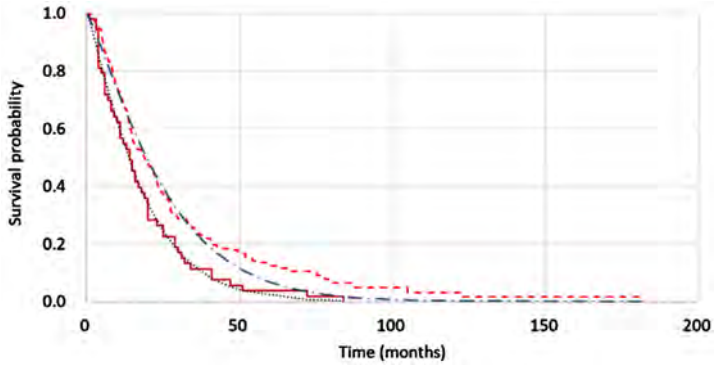


(b)

Figure 8. (a) KM plots of the OS of NSCLC treated by mEHT (dashed line, n = 258, median = 18.97 m, mean = 29.59 m), and the historical control (solid line, n = 53, median = 14.0 m, mean = 18.53 m). The difference between the OS of the mEHT arm and the control arm is strongly significant ($p < 0.0045$) (b) The WF fit parameters for control (dotted line $n^{(ctr)} = 1.19$; $t_0^{(ctr)} = 18.83$; $SE = 0.045$, $r^2 = 0.992$). Single WF does not fit the KM of mEHT (dash-dotted line, $n^{(OS)} = 1.21$; $t_0^{(OS)} = 26.56$; $SE = 0.353$, $r^2 = 0.989$), the decomposition of responding and non-responding group of patients has to be applied.

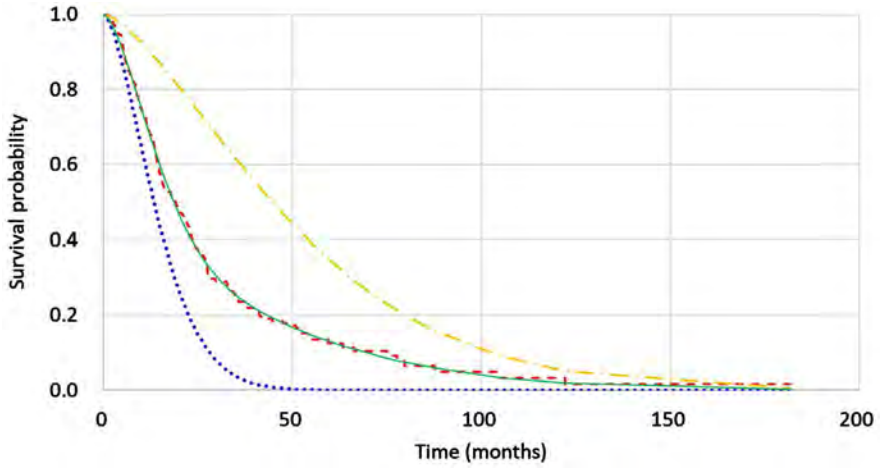


Figure 9. The Weibull decomposition fits for the OS (dashed line) of NSCLC of advanced stages of the disease. Weibull parameters of "responders" (r), dot-dashed line, and "non-responders" (nr) dotted line are $n^{(r)} = 1.45$; $t_0^{(r)} = 57.59$; $n^{(nr)} = 1.61$; $t_0^{(nr)} = 16.73$; the percentage of the "responders" is 37.4%. The sum of the two decomposed parts (solid line) fits to the KM, $SE = 0.062$, $r^2 = 0.9980$ well.

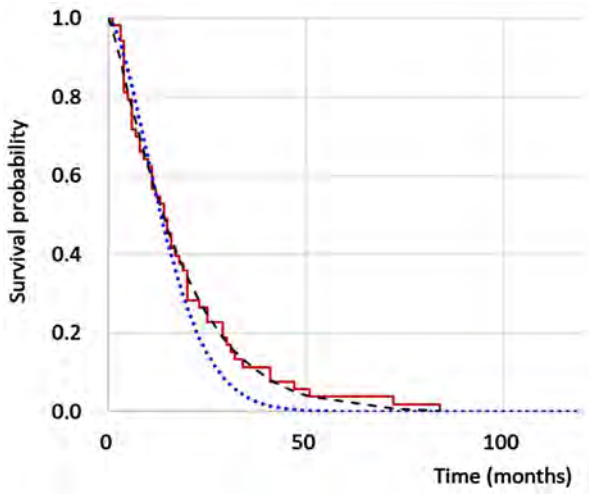
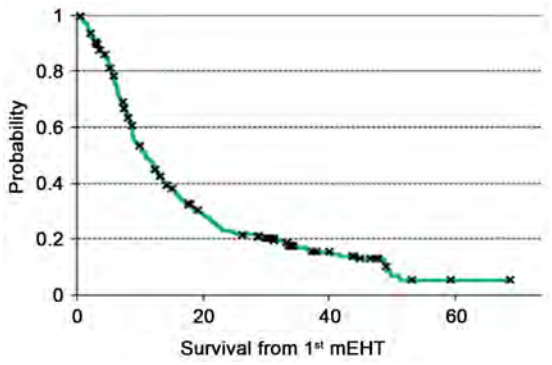


Figure 10. The non-responding component of the OS of NSCLC from **Figure 8**. (dotted line) compared to the historical control (solid line). The WF fit of the historical control (dashed line) has no significant difference from the non-responding group of mEHT treated patients.

and so forming references to the single-arm study. This is not only a simple reference, it shows the percentage of the patients, who the active treatment has helped as well.

The KM curve is approached well by the sum of two WF with decomposition sub-curves of responding and non-responding patients (**Figure 11**).

The percentage of responding patients in the decomposition of the OS of mEHT treatment time (48.1%) is better by 10.4% compared to the OS and similarly to the result with the decomposition number of OS in **Figure 9**, it is over 37%, supporting the previously observed accuracy of the WF decomposing fit.



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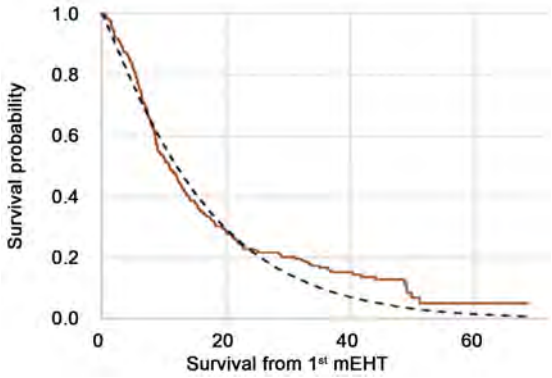

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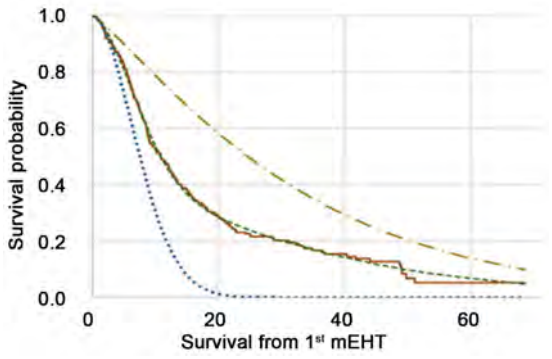
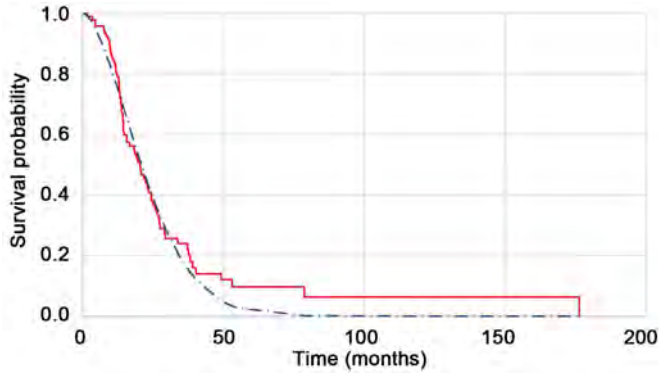


(c)

Figure 11. The elapsed time after the first mEHT treatment, when the conventional treatment has reached the palliative phase. (a) the measured KM plot from the start of the mEHT treatment periods; (b) A single WF regression (dashed line) does not fit well to the measured KM plot. (c) The WF decomposing produces perfect fit (dashed line) to the measured KM (solid line). The parameters of the responding and non-responding components: $n^{(r)} = 1.18$; $t_0^{(r)} = 33.7$; $n^{(nr)} = 1.89$; $t_0^{(nr)} = 9.2$; the percentage of the "responders" is 48.1%. The sum of the two decomposed parts (solid line) well fits to the KM, $SE = 0.057$, $r^2 = 0.998$.

3.3. Glioblastoma Multiform

A clinical trial for the advanced GBM was performed by mEHT treatment after the conventional therapies had no more curative possibilities [42]. The study involves 94 patients. The overall survival is shown in **Figure 12**.



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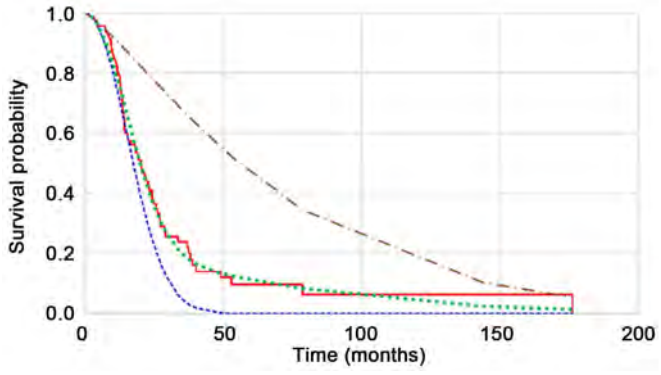

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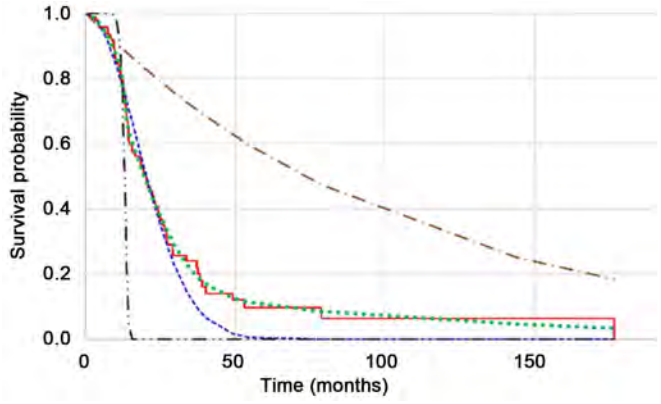


(c)

Figure 12. The overall survival including the mEHT treatment finishing, when the conventional treatment has reached the palliative phase. (a) the measured KM plot (solid line) with a single WF regression curve, (dashed-dotted line; $n^{(1)}=1.69$; $t_0^{(1)}=25.81$; $SE^{(1)}=0.295$; $r_1^2=0.975$); (b) regression with a decomposed WF. Two parts are applied, responders (dashed-dotted line, $n^{(r)}=1.25$, $t_0^{(r)}=75$, $c^{(r)}=25\%$) and non-responders (dotted-line, $n^{(nr)}=2.11$, $n^{(nr)}=2.11$, $c^{(nr)}=75\%$). The sum of the parts (dotted line; $SE=0.078$, $r^2=0.993$) fits with the error. (c) Regression with decomposition into three parts. Superior responders (dashed-dotted line, $n^{(sr)}=1.2$, $t_0^{(sr)}=124.6$, $c^{(sr)}=15.6\%$); responders (dashed line, $n^{(r)}=1.95$, $t_0^{(r)}=24.3$, $c^{(r)}=14.9\%$) and non-responders (dashed-double-dotted line, $n^{(nr)}=15.6$, $t_0^{(nr)}=13.4$, $c^{(nr)}=69.5\%$), and the sum of the parts (dotted line, $SE=0.038$, $r^2=0.997$), shows the best fit.

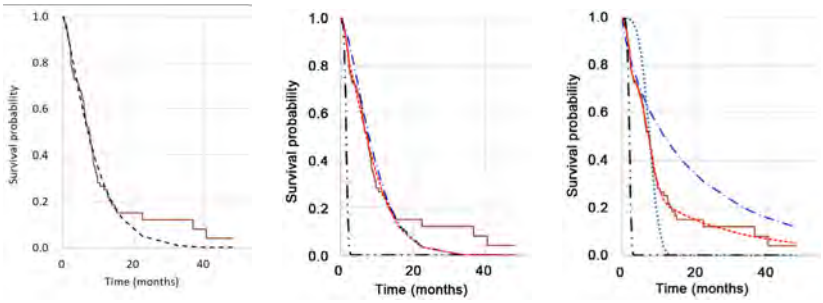
The overall survival curve in case of GBM cannot be fitted by two regression curves (responders and non-responders). The non-responders are unfortunately large (67.5%), but the responders' group has two subgroups, superior response (17.5%) and response (15%). The survival from the first mEHT treatment (finalizing the complete therapy set) shows the same behavior (Figure 13), but much fewer non-responders (14.7%) in this part of the treatment.

It is remarkable that the non-responding subgroup in the period of mEHT treatment is only 14.7% (compared to the complete OS, where it was 67.5%).

4. Discussion

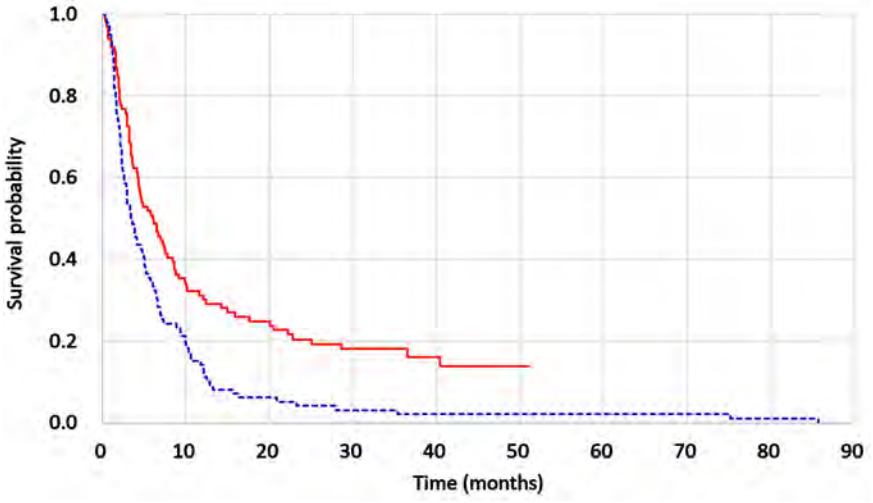
By the proper decomposition of KM to WF sub-groups, we were able to unhide the well-buried information in the single-arm study, and we were able to see the percentage of responding and non-responding patients when fitting WF-curves by best regression possibilities. The pancreas and NSCLC analyses had an accurate decomposition of KM into two parts, but GBM needed three subgroups for an accurate regression. The analysis of the elapsed time until the first mEHT treatment compared to the time when the mEHT was active shows huge differences between the groups, Figure 14. While the two KM plots are well-distinguishable in the pancreas and NSCLC cases. However, the elapsed time to the first mEHT and the survival from that have similar curves in GBM plots.

The comparison of OS KM curves to the KM of mEHT involvement (Figure 15). It is obvious (that can be seen from the Figure 14 too), that the survival



(a) (b) (c)

Figure 13. The survival from the start of the mEHT treatment, when the conventional treatment has reached the palliative phase. (a) the measured KM plot (solid line) with a single WF regression curve, (dashed line; $n^{(1)}=1.26$; $t_0^{(1)}=9.44$; $SE^{(1)}=0.175$; $r_1^2=0.985$); (b) regression with a decomposed WF. Two parts are applied, responders (dashed-dotted line, $n^{(r)}=1.51$, $t_0^{(r)}=10.1$, $c^{(r)}=91\%$) and non-responders (dashed-double-dotted-line, $n^{(nr)}=3.85$, $t_0^{(nr)}=1.76$, $c^{(nr)}=9\%$). The sum of the parts (dashed line; $SE=0.16$, $r^2=0.987$) fits with the error. (c) Regression with decomposition into three parts. Superior responders (dashed-dotted line, $n^{(sr)}=0.79$, $t_0^{(sr)}=18.47$, $c^{(sr)}=43.8\%$); responders (dotted line, $n^{(r)}=3.8$, $t_0^{(r)}=8.34$, $c^{(r)}=41.5\%$) and non-responders (dashed-double-dotted line, $n^{(nr)}=4.82$, $t_0^{(nr)}=2.17$, $c^{(nr)}=14.7\%$), and the sum of the parts (dotted line, $SE=0.034$, $r^2=0.997$), shows the best fit.



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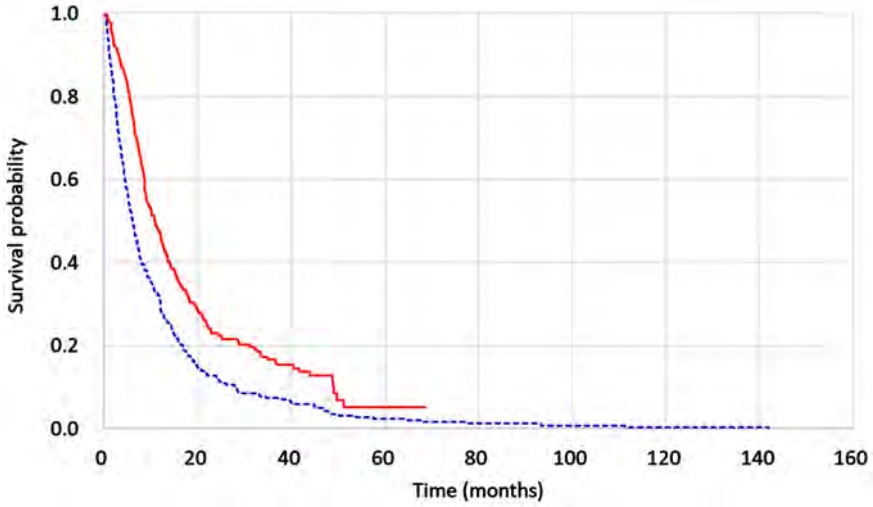

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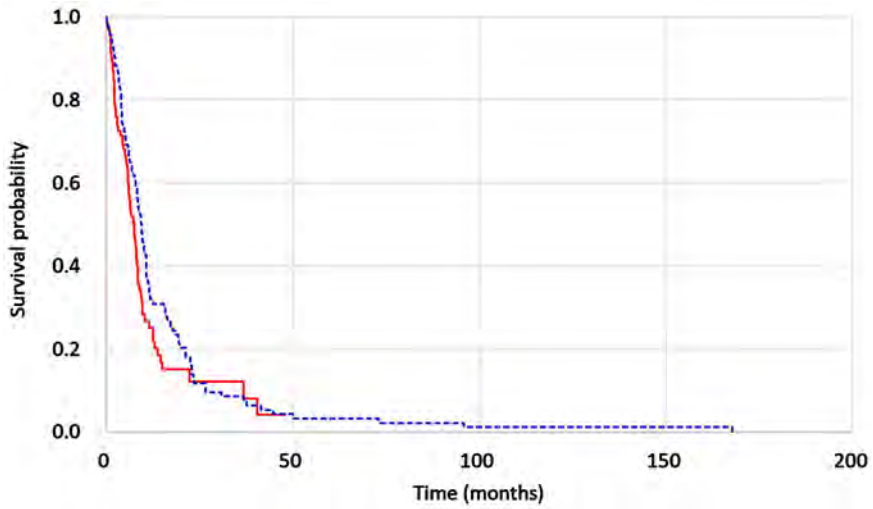
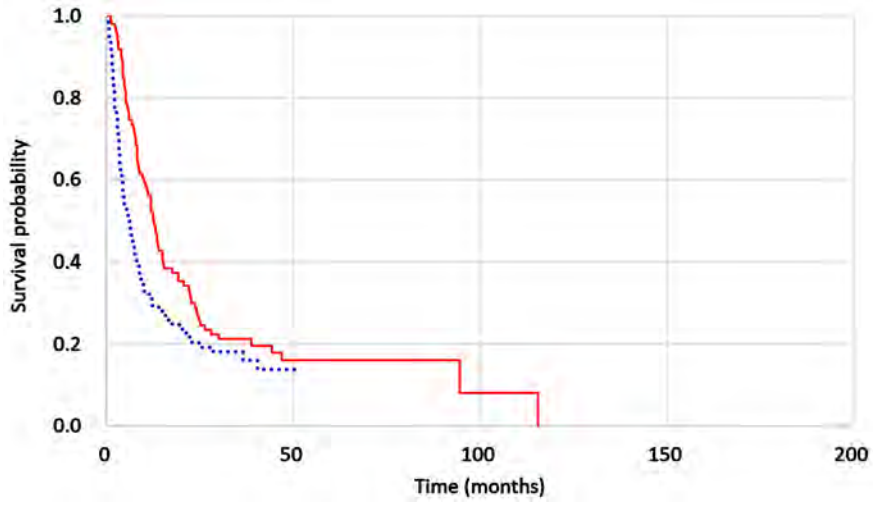


(c)

Figure 14. Comparison of the elapsed time until the mEHT process (dotted line) to the time from the first mEHT treatment (solid line), (a) pancreas; (b) NSCLC; (c) GBM.



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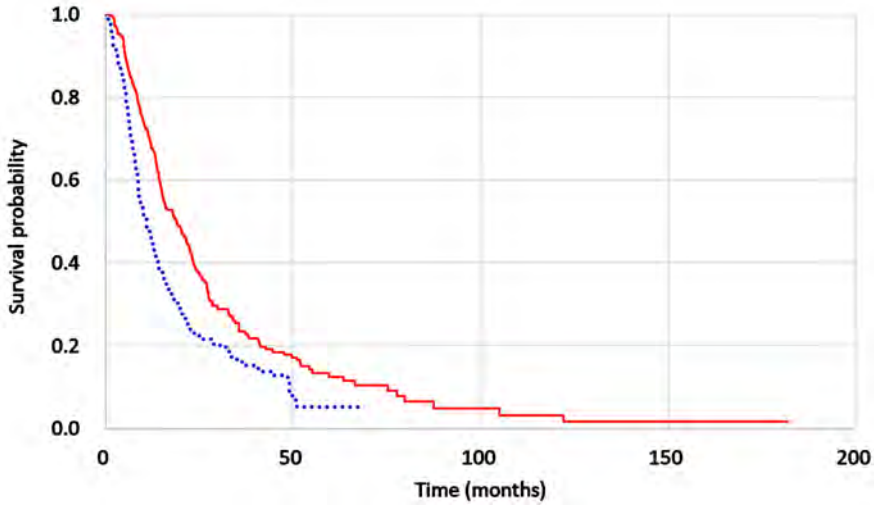

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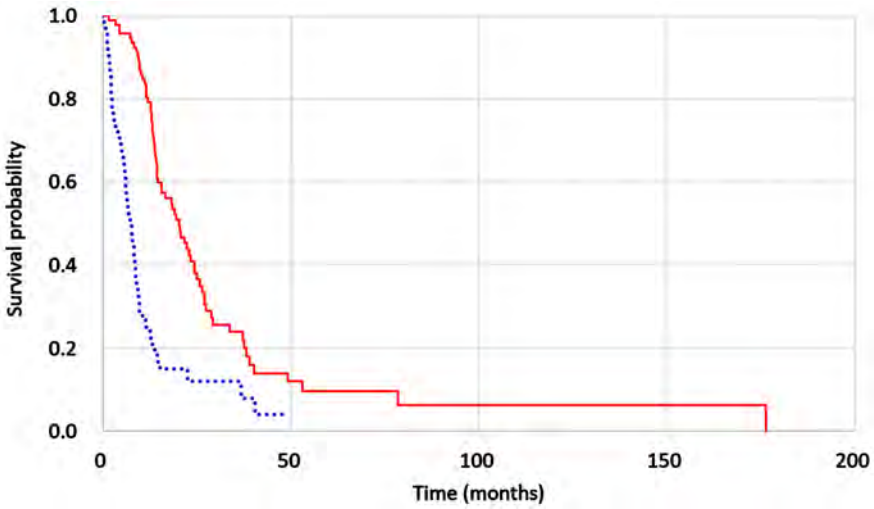


(c)

Figure 15. Comparison of the OS (solid line) and the time from the first mEHT treatment (dotted line), (a) pancreas; (b) NSCLC; (c) GBM.

time from the start of mEHT is too short in GBM cases compared to the pancreas and NSCLC studies. The reason is probably the fact, that GBM does not create metastases, in case of relapse, multiple intracranial surgeries can be done, therefore a longer time is available for conventional treatments than in other cases.

A tool was proposed to evaluate single arm data-collection [73], focusing on the survival of censored patient's after leaving the study. Knowing the possible survival of these censored patients is crucial for the evaluation, regarding them as a control group with patients whose lifetimes were not modified by the further therapy. The proposal of this method was elaborated by Pauling and was worked out theoretically later, known as the Hardin-Jones-Pauling (HJP) biostatistical theory [74] [75]. The HJP approximation calculates the event after censoring, when the patient leaves the study before its end and his/her condition is unknown afterward. The approximation is rather simple: adding the average survival of the study to the actual time when the censoring happens:

$$t_{HJP} = t_{actual} + \tau \tag{4}$$

where τ is the mean value of the survival in the last treatment-line period. This calculation gives a quasi-reference value for all the patients comparing the expectancy of the survival time to the patients who completed the therapy. The HJP approximation can be applied self consistently as a new arm [76]. An independent, but similar concept was used recently with the mean of OS, extrapolating the long-surviving "tail" in KM curve [76]. The asymptotic properties of the estimator showed a proper coverage probability.

A method to find the reference to the single arm study could be developed by the HJP biostatistical principle. Patients, who complete a given line of treatment could be newly diagnosed in a more serious stage and could continue the treatment in a higher line. We may regard, that the finished treatment line, when no conventional curative treatment is available anymore is a clinical treatment period with the endpoint determined by the patient's need for the next line of treatment. This next line is the mEHT combined curative period. The KM plot from the first diagnosis to the first mEHT treatment refers to the probability of leaving the conventional curative protocols, due to further unavailability. In this KM approach, all the patients are censored at the end, leaving the conventional protocol, and starting the mEHT. The HJP approximation from the conventional treatment period is independent from the mEHT, consequently could be used as a assumption of the overall survival, and so as a control group, derived by the HJP approximation. However, this approach has a great challenge. The threshold when the curative treatment stops could create two groups of patients.

Patients whom conventional treatments could not help, and who very quickly run out of possibilities (have no effective improvement or are blocked by hematological reasons, organ failure or comorbidities), or patients, who despite having long-term benefits from conventional treatments reach the overall limit of application when the disease becomes refractory.

Patients from both groups start the mEHT treatment with very different backgrounds and prognoses. Patients, who have been in the conventional period for a long time have already had a condition, in which the defense mechanism against the cancer was strong, while patients in the 2nd group have had a poor defense against the malignancy. The defense mechanism covers multiple factors: genetic behavior, social situation, family environment, general condition (including immune condition), comorbidities or susceptibility to comorbidities, psychological factors (including susceptibility to depression), etc. The distribution of these factors is unknown, but due to their common occurrence in a large number of participants and the central limit theorem [77], the sample means are close to a normal distribution when the sample size is over 30. According to this, the mean of all samples is approximately equal to the mean of the population, and independent from the shapes of the population distributions.

The KM plot that fits the elapsed time between the first diagnosis and the first mEHT treatment (**Figure 16**), could be the basis for the approximation of the further survival of the patients after starting the mEHT.

All of those are eligible for the new line, but everybody is censored at the end of the previous treatment protocols. The KM plot's mean (average) value is $\langle \text{pre\_mEHT} \rangle = t_0^{(0)} \Gamma\left(1+1/n^{(0)}\right) \cong 5.41$, which according to (4) is the elongation period of the expected survival time of the patients leaving the actual conventional protocol, shown in **Figure 17**.

In this approach, the HJP estimate is a simple time-shift of the distribution of elapsed time to the first mEHT treatment form the first diagnosis. This could be used as a control arm for the mEHT treatment, but it is not automatic. The situation is different, if the patient kept in the line of conventional therapies longer than the therapy is effective enough (for example after the second relapse). In this case, the long time, that elapsed until the first mEHT, will show a longer

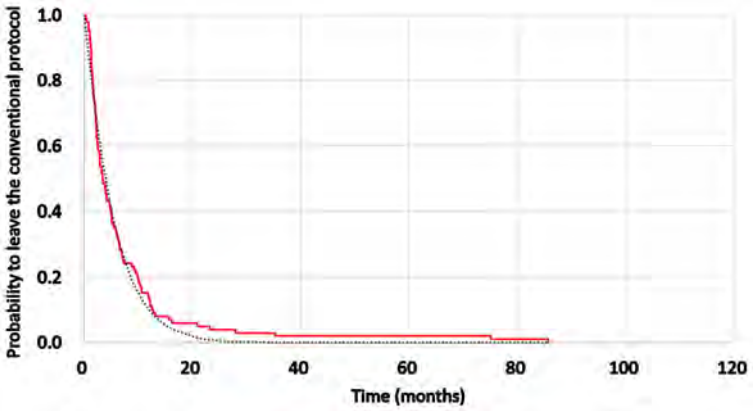


Figure 16. The time when finishing conventional lines and starting mEHT for pancreatic carcinoma from **Figure 3**. (solid line, n = 99, median = 3.4 m, mean = 7.1 m). The WF fit to it (dotted line, $n^{(0)} = 1.08$; $t_0^{(0)} = 5.57$, $r^2 = 0.982$, $SE = 0.294$; mean = 5.41, median = 3.97, $S^{(0)} = 2.68$). The WF fits, no significant difference is observed between the curves.

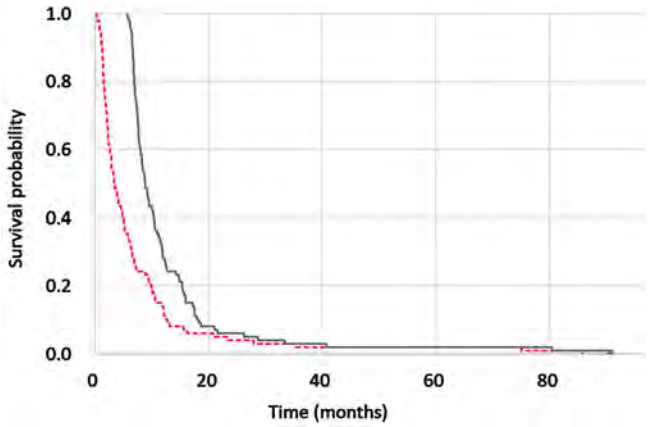


Figure 17. The HJP estimate (solid line) of pancreatic carcinoma from the survival to the first mEHT treatment. The elapsed time-distribution between the first mEHT and the first diagnosis is shown with a dashed line.

time for survival by the control arm with HJP estimates, due to the addition of the average value of the time to mEHT. To get over this complication, we can apply a normal distribution as a modifier of the simple τ average of elapsed time until the mEHT involved treatment period. So the modified KM (KMm) of the parametric estimate which time series at (4) will be rewritten like:

$$KMm\left(t_{HJP}\right) = \frac{KM\left(t_{HJP}\right)}{\alpha\sqrt{2\pi\sigma^2}}\exp\left(-\frac{\left(KM\left(t_e\right)-\mu\right)^2}{2\sigma^2}\right) \tag{5}$$

where $KM\left(t_e\right)$ is the probability of the KM-plot of elapsed time from the first diagnosis to the first mEHT, μ is the mean and σ is the standard deviation (σ^2 is the variance) of the distribution; and α is a normalizing factor. The parameters are fixed by physical assumptions (**Figure 18**):

1) The $\mu = 0$ was chosen to fix the strict monotony of the plot.

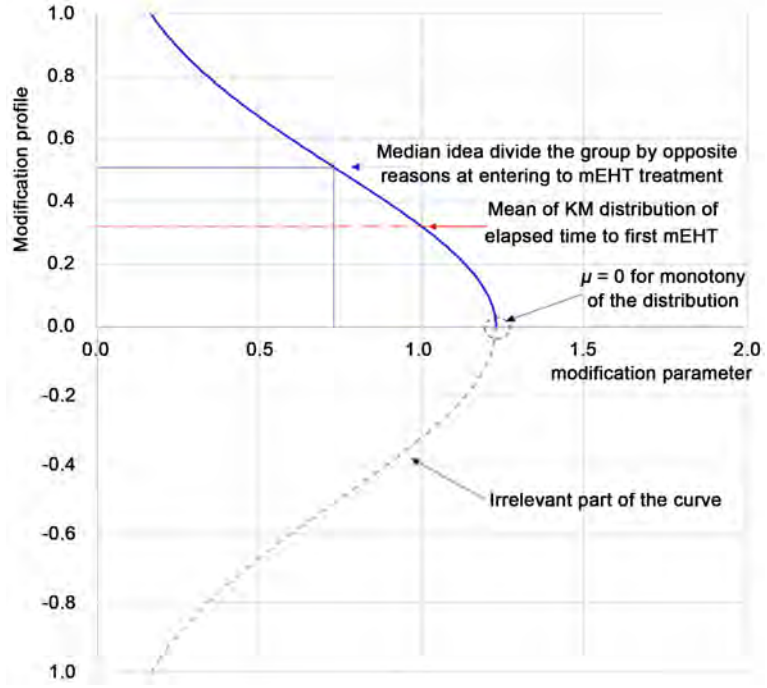
2) The α was chosen to have the function value 1 at the mean of the distribution.

3) For the σ we use the percentage of the non-responding patients, as a dividing parameter for groups of patients in weak and strong condition. The group which is higher than σ, has a lower extrapolated survival. They start the mEHT earlier than the limit made by non-responders, and other patients are late starters, due to their defense systems, that can be regarded stronger.

The modified HJP (HJPm) and the elapsed time from the first diagnosis to the first mEHT show significant differences (**Figure 19**); the elapsed time bases the approximated expected survival well after the failure of the conventional curative therapies.

The comparison of the HJPm survival curve, the historical control and the non-responding fraction from the WF decomposition, the three control arms are practically equivalent (**Figure 20**).

In the case of GMB, no historical control exists, therefore we may compare the OS and the HJPm approximation. The WF decomposition, in this case, has three



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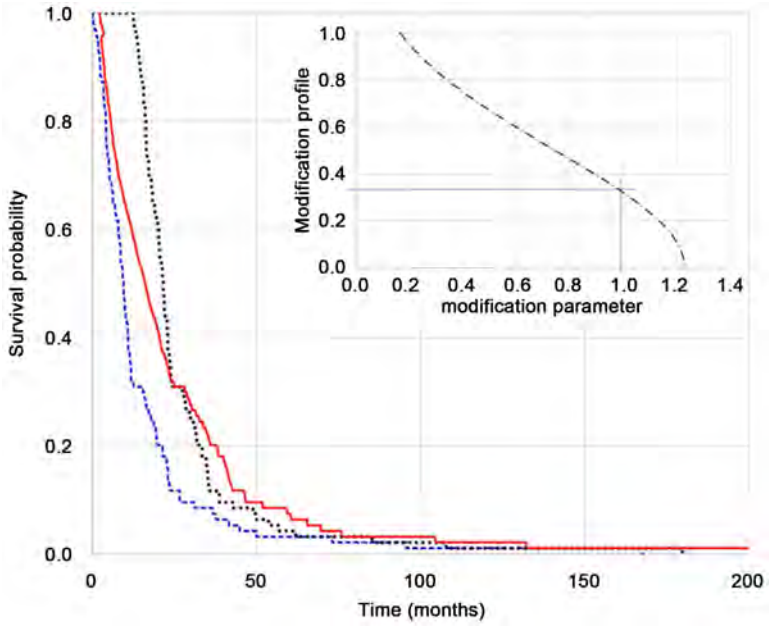
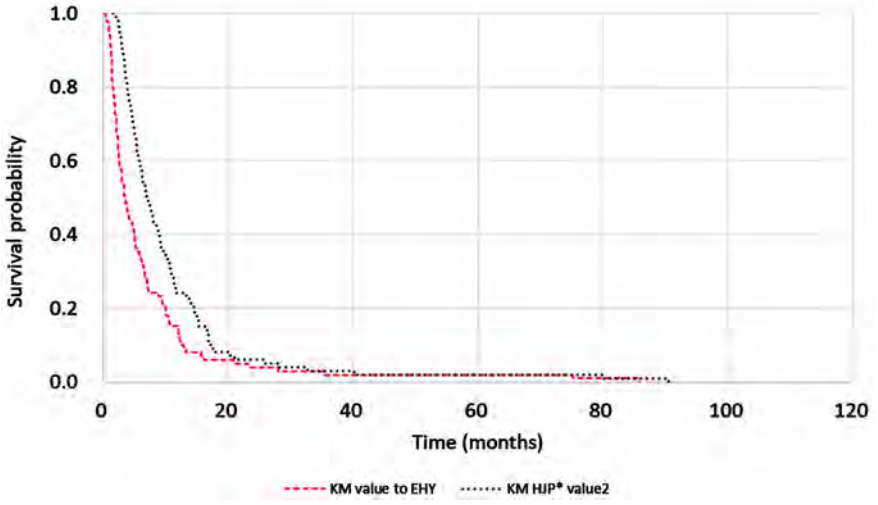
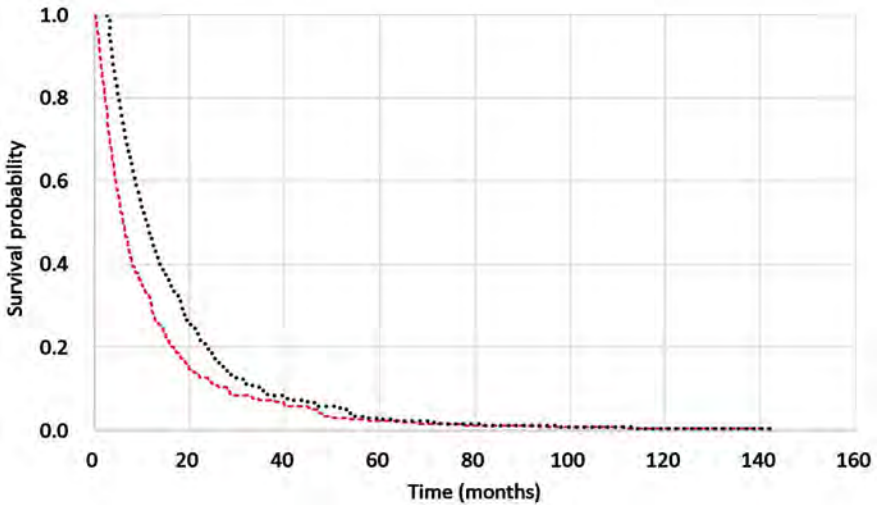


(b)

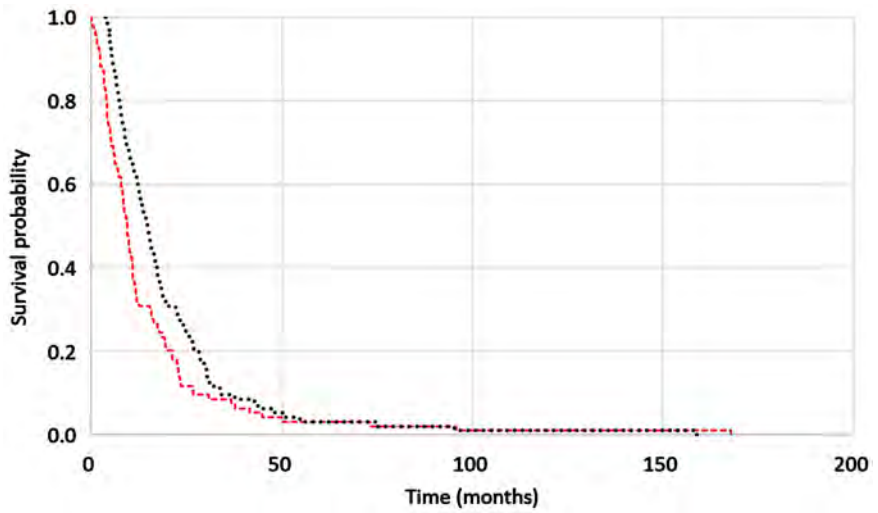
Figure 18. The HJP (HJPm) principle modified by the differences of the patients leaving the conventional curative treatment period. For simplicity, we used the median (50% - 50% of patients in weak and strong conditions). Below the median shows patients who have left early due to insufficient improvement or personal weakness; while the patients over the median have appropriate defense and/or benefited from the treatments for a long time. (a) the multiplication function. Here only the positive (solid line) part is used, the negative (dashed line) is shown only for clarity; (b) The HJPm estimation based on the elapsed time until the first mEHT treatment (for GBM) have shown the elapsed time (dashed line) and its HJP approximation, a shift by mean (dotted line) and the HJPm curve (solid line). The modification function (normal distribution) is shown in the insert.



(a)

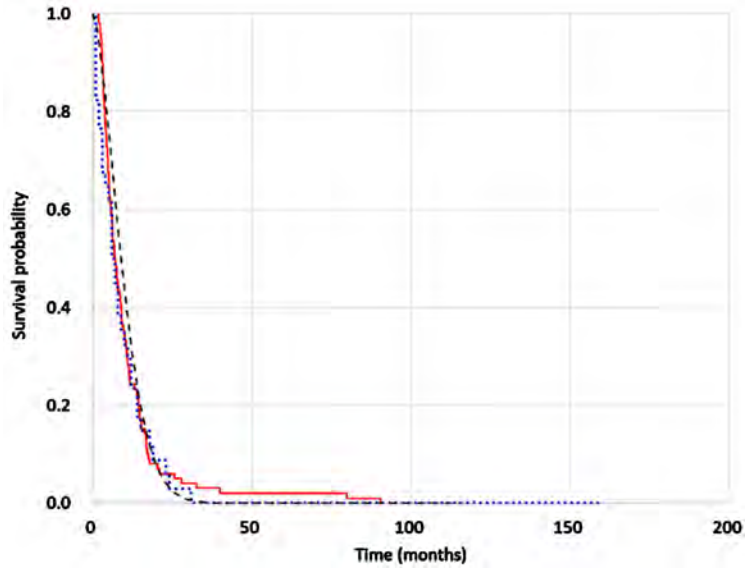


(b)

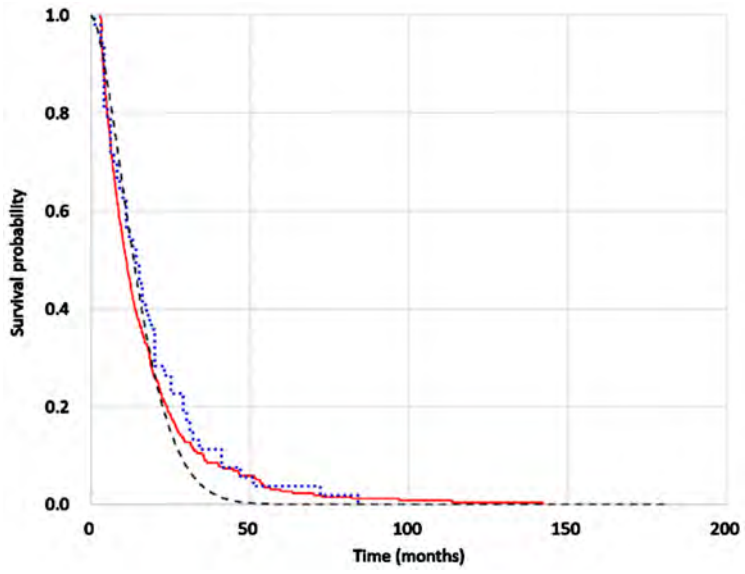


(c)

Figure 19. Comparison of HJPm curve (dotted line) and the elapsed time from the first diagnosis to the mEHT treatment (dashed line), (a) pancreas, (b) NSCLC, (c) GBM.



(a)

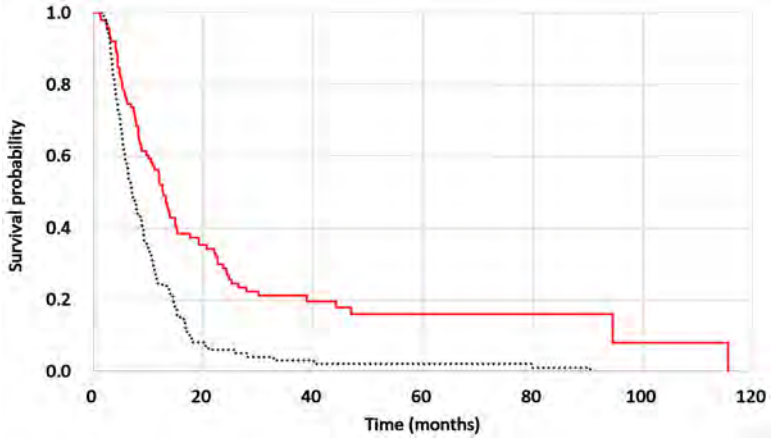


(b)

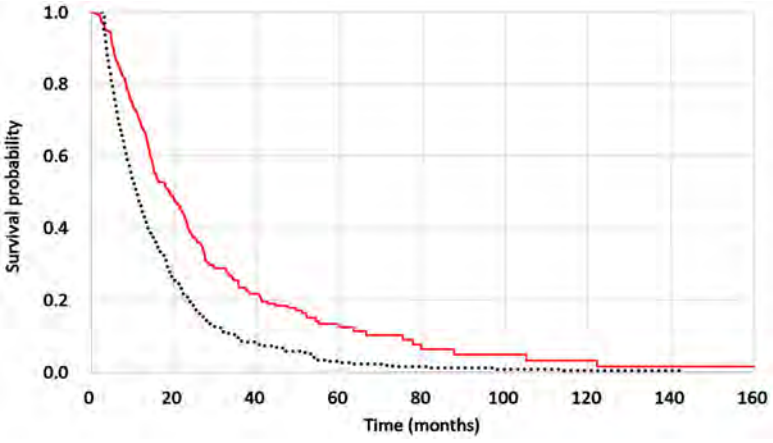
Figure 20. Comparison of the historical control (dotted line), the HJPm approximation (solid line) and the non-responding fraction from the WF decomposition (dashed line). (a) pancreas cancer, (65.6% of weak conditions); (b) NSCLC (62.7% of weak conditions).

subcomponents, so obtaining a single control arm is impossible, but the HJPm could be regarded as one of the possibilities. The relatively long time to the first mEHT treatment in the case of GBM creates longer expected survival too. Conventional curative possibilities take more time, and the patients start the mEHT mostly in terminal stages. In this case, 69.5% of the patients are grouped into the weak personal defensive conditions.

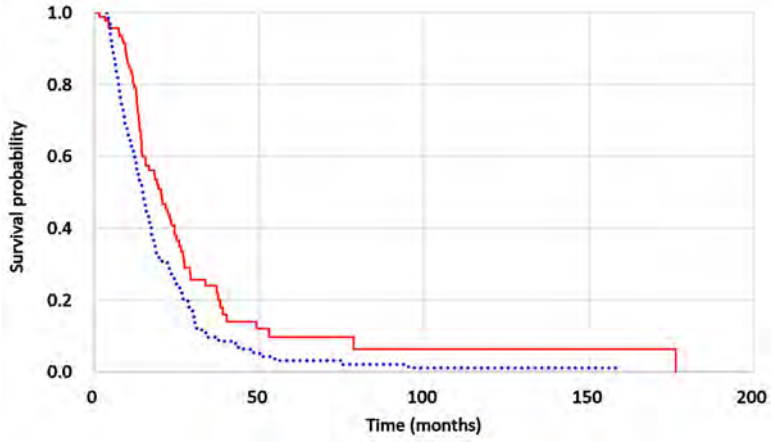
The curative benefit of mEHT complementary application is significant in comparison to the overall survival and the control-arm of the expected survival after the failure of conventional curative approaches (**Figure 21**).



(a)



(b)



(c)

Figure 21. Comparison of the HJPm approximation as control (dotted line), with the overall survival (solid line). (a) pancreas cancer; (b) NSCLC; (c) GBM.

The research could be continued for a more complex single-arm research, where the QoL is taken into consideration too. The quality-adjusted survival (QAS) [78] [79], which considers the QAS without symptoms and toxicity (Q-TWIST) [80] would be an important extension to the single-arm study.

5. Conclusion

The WF regression fit to KM non-parametric estimate works precisely in real clinical studies of advanced pancreatic cancer, NSCLC and GBM trials where the mEHT method was applied as a complementary treatment when no more conventional curative possibilities were available. The WF decomposition method creates an estimated reference-arm in a chosen homogeneous cohort. The control arm is correct, if we assume that patients start their mEHT treatment when the conventional therapies fail, so their overall status (relative to the lines of the conventional therapies) groups them into groups with similar conditions. The mEHT method has no harm for the patients (no adherent effects to make tumor-progress by the treatment alone), so the possibility of the treatment results has two categories only: effective or ineffective, which fits the decomposition concept well. Regression is accurate, and the control-arm from the decomposed WF corresponds well with the modified Hardin-Jones-Pauling statistical estimation too, when the number of patients is high enough (>30) for statistical evaluation.

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Conflicts of Interest

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

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COVID-19: Africa's Challenge and the Need for a Paradigm Shift on the Use of Ventilators

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Abstract

Background: The December 2019 Chinese epidemic of Corona Virus Disease [COVID-19], which erupted in Wuhan, South China, was declared a pandemic, by the World Health Organization [WHO], on 12th January 2020. The worldwide spread from China was rapid, but Africa was the last port-of-call. Her first diagnosed case was two months after China's, on 14th February, 2020 in Egypt. The morbidity and mortality rates have, however, remained lower in Africa than in the developed world, and analysts believe that it was more of a temporary respite, since Africa's poor health infrastructure will become her eventual albatross. **Methodology:** Data were collected on COVID-19 and records of the socio-economic capacity of Africa by accessing the relevant previous and current peer-reviewed publications from multiple search engines on internet. The data were, then, collated and comparatively analyzed. **Results:** The available data revealed that Africa had, mostly, the milder forms of COVID-19, and so, morbidity and mortality were low. Her shrinking elderly population and hot climate were believed to be contributory, but lately, as the pandemic spread, the role of these factors was not exactly predictive. Being low on healthcare infrastructure, Africa could tenaciously leverage on the supportive and preventive measures prescribed by WHO, while the world awaited a vaccine. The role of ventilators in the care of critically ill patients, also, came under scrutiny as some workers were questioning the underlying pathology, and advocating a paradigm shift from high-tech positive end expiratory pressure ventilation to plasmapheresis and packed cell transfusion. **Conclusion:** Africa faces a huge challenge with COVID-19, but the predicted heavy mortalities may be reduced by some local confounding factors, control

of spread and re-focusing of critical care away from the expensive and unavailable ventilators.

Keywords

Blood Failure, China, Confirmed Cases, Cytokine Storm, Deaths, Egypt, Interleukin-6 as Biomarker, Packed Cell Transfusion, Respiratory Failure, Plasmapheresis, SARS-CoV-2, USA

1. Introduction and Overview of COVID-19

Background

The 2019 Chinese epidemic of Corona Virus Disease [COVID-19], which erupted in a local Seafood Market in Wuhan, South China, at the end of 2019, was declared a pandemic by the World Health Organization [WHO], on 12th January 2020 [1] [2] [3]. The causative organism was identified and code-named SARS-CoV-2, by WHO [4].

Spread

The spread from China was rapid, all around the world, but Africa was the last port-of-call, recording her first confirmed case in Egypt on 14th February, followed by Nigeria 25th February, Morocco 3rd March and South Africa 5th March, 2020.

Tissue Concentration of the Virus

When the virus gains entry into the human body, it concentrates mostly in the respiratory system, and saliva. On account of this, any of four secretions are useful in screening for SARS-CoV-2: sputum, throat swab, respiratory tract secretions and saliva [5]. The focus of the treatment of COVID-19 is, logically, on the respiratory tract, where it concentrates.

Interleukin-6 as a Biomarker for Poor Prognosis

In critically ill patients, the inflammatory cytokine, interleukin-6 [Il-6], levels increase significantly, to almost 10 times the normal levels. This high rise is correlated to the detection of RNAaemia. Remarkably, also, all cases of death exhibited high levels of Il-6, suggesting that it as an important biomarker for poor prognosis [6].

Classification

There are two classes of COVID-19, based on the effects on the respiratory system, where it predominantly manifests. These are: Asymptomatic and Symptomatic, both of which are contagious and can transmit the disease. The symptomatic COVID-19 is sub-classified into: 1) Mild 2) Moderate 3) Severe 4) Critical; based on the intensity of hypoxaemia and progression to multiple organ dysfunction syndrome [MODS].

Post-mortem Findings

Sharif Sultan, recently, reported that, based on the observations from post-mortem studies done on deceased COVID-19 patients, there was a consistent

finding of pulmonary thrombosis, which was not typical of Acute Respiratory Distress Syndrome [ARDS]. Also, that the hypoxaemia found in the patients did not respond to PEEP ventilation, but to high oxygen flow [7]. And so, he advised that patients be started early on maximum oxygen flow, until ventilation becomes inevitable.

Molecular Findings, Cytokine Storm and Failure of Haemoglobin

The viral structural protein, was discovered to stick to haeme, displacing oxygen releasing iron-free ion, and leading to toxicity at the pulmonary bed with inflammation of alveolar macrophages. The virus attacks the beta chain of haemoglobin, dissociates haeme and removes the iron converting it to porphyrin, and leading to "failure of blood" to carry oxygen. The underlying pathology, therefore, is not "failure of respiration".

The oxidative iron released from the haemolysed blood cells damages the lungs, leading to an abnormal rise in levels of Il-6 which becomes the hallmark and driving force of the associated Cytokine Storm, that leads to MODS [7]. The final common pathway, therefore, is the metabolic hypoxia from blood organ failure.

The physiological implication of this is that an invasive ventilation will not be of the best benefit, rather, frequent plasmapheresis and transfusions, to replace the compromised haemoglobin and boost the oxygen-carrying capacity, will be more beneficial in ameliorating the Cytokine Storm [7].

This study evaluates the current status of COVID-19 around the world and the challenges facing the resource-poor African nations. It, then, suggests a paradigm shift from mandatory mechanical ventilation to mandatory plasmapheresis and packed cell transfusion in the management of COVID-19.

Data were collected on the available body of knowledge on COVID-19 and socio-economic capacity of African countries, from multiple search engines on internet. The results collected from all the sources were collated and presented in prose, tables and a graph and analyzed.

2. Methodology

Data were collected on COVID-19 and records of the socio-economic capacity of African countries by accessing the relevant previous and current peer-reviewed publications from multiple search engines on internet. The data were, then, collated and comparatively analyzed.

3. Results

Statistics on SARS-CoV-2 Infection around the World

Within the first 4 months of the pandemic, [30th April, 2020], some 160 [of 212] countries around the world had been infected, with a total of 3,304,309 cases confirmed COVID-19 positive. Out of those, 1,980,404 were mild [97%] and 50,950 [3%] severe/critical infections. There were 233,839 deaths, and 1,039,104 recoveries [8] [9] [10]. China, the source of the coronavirus, had 82,874 confirmed cases, 4633 deaths and 77,642 recoveries [11]. And, there were the 300

million non-infected pupils worldwide, who were taken off schools and asked to stay at home, until the pandemic came under control.

The USA topped the world list with 1,095,019 confirmed cases, 1,039,136 recoveries and 63,856 deaths; followed by Spain with 239,639 cases, 137,984 recoveries and 24,543 deaths; Italy 205,463 cases, 75,945 recoveries and 27,967 deaths; UK 171,253 cases and 26,771 deaths; France 167,178 cases, 49,476 recoveries, 24,376 deaths; and Germany 163,009 cases, 123,500 recoveries and 6623 deaths [12]. As the UK and French figures rose rapidly, the German figures rose less rapidly, just as her comparative death rates, as well. Surprisingly, China, with the largest population in the world [1.4 billion], came a distant 11th, and did not even make the Top-10; see **Table 1**.

Impact on Africa

In Africa, by the end of April, 52 out of her 54 countries were already infected, with 39,713 confirmed cases, 13,070 recoveries, and 1,638 deaths. Out of these, South Africa was the worst hit with 5647 confirmed cases, followed by Egypt with 5537 cases and Morocco 4423 cases.

But, Algeria with 4006 cases, 1779 recoveries and 450 deaths, had the worst outcome amongst the African nations. Ghana was 5th with 2074, cases; Nigeria was 6th with 1932 cases, and Cameroon 7th with 1832 cases; see **Table 2** [13].

Table 1. World's top 10 countries with COVID-19 [16] [30th April, 2020].

Country	Confirmed Cases	Recoveries	Deaths
1. USA	1,095,023	152,324	63,856
2. Spain	239,639	137,984	24,543
3. Italy	205,463	75,945	27,967
4. United Kingdom	171,253	N/A	26,771
5. France	167,178	49,476	24,376
6. Germany	163,009	123,500	6623
7. Turkey	120,204	48,886	3174
8. Iran	94,640	70,933	6028
9. Russia	106,498	11,619	1073
10. Brazil	87,187	35,935	6006
11. China	84,338	77,474	4642

Table 2. Africa's top 10 countries with COVID-19 [8] [13] [17] [18] [19] [20] [30th April, 2020].

Countries	Confirmed Cases	Recoveries	Deaths
1. South Africa	5647	2073	103
2. Egypt	5537	1381	392
3. Morocco	4423	984	170
4. Algeria	4006	1779	450
5. Ghana	2074	212	17
6. Nigeria	1932	319	58
7. Cameroon	1832	934	61
8. Cote d'Ivoire	1164	499	14
9. Guinea	1495	329	7
10. Djibouti	1089	846	2

The Nigerian Centre for Disease Control [NCDC] equally reported a total of 13,500 tests done by this time, and a plan to increase testing capacity to 3500 tests daily; while South Africa led Africa with 60,000 tests already done, and an existing capacity for 10,000 tests, daily [14] [15].

4. Discussion

Africa appeared lucky with her much lower incidence and mortality rates than the rest of the world; and the worst hit African country was South Africa with 5647 cases, though Algeria had the highest mortality rate, followed by Egypt; see **Table 2**.

The Infamous "Bleak Situation" in Our Continent

Being that massive resources are required for the diagnosis and treatment of patients, protection of the care givers and community, as well as research, with a hope to developing a cure, or, vaccine, Africa's capacity to cope with this pandemic appears to be, unarguably, sub-optimal. Observers believed that the African situation was like a ticking time-bomb, and that, it was just a matter of time before the pandemic will overrun the continent. A few disagree on account of some observed factors.

Immunity by Default?

At the outbreak of the pandemic, there appeared to be in Africa:

1) a lytic hot climate, adverse to the survival of SARS-CoV-2, which showed a predilection to the cold regions;

2) a viral strain, Type B mostly, which was less toxigenic;

3) the factor of low population of elderly persons, due to her lower life expectancy, from poverty and disease.

Perhaps, these 3 variables explained the lower morbidity and mortality rates in Africa; but, may well be confounding factors, only.

Capacity for the Care of the Severely Ill Cases in Africa

In Africa [*population* 1.2 *billion*], the total number of COVID-19 cases was 39,713 confirmed cases, which was 3.63% the figure for USA [*population* 331 *million*] [20] [21] [22]. Yet, it is noteworthy that in Africa, the volume and quality of essential expertise, equipment and infrastructure, for the intensive care of critically ill persons, are grossly inadequate.

Kenya, for example, had 200 intensive care [ICU] beds for her 50 million citizens, *i.e.* a ratio of one ICU bed to 250,000 citizens; whereas, the USA had 34 ICU Beds [*could be up to* 45] per 100,000 persons [23]. The ICU bed ratio of USA translated to 85 - 100 times disparity against Kenya.

African Initiatives

Learning from the experiences of their forebears in the COVID-19 pandemic in USA, Asia and Europe, many African states adopted some indigenous measures to contain COVID-19 [24]. Madagascar produced an organic drink from the antimalarial, artemisia, which was reported to reduce the mortality from COVID-19 [25]. Senegal, with UK government and Bill and Melinda Gates Foundation, adapted the screening kit originally used for Dengue Fever to a

cheap $1 COVID-19 quick diagnostic kit [26]. The Senegalese researchers, also, designed an affordable ventilator, costing $60 each, as against $16,000 for each imported unit in the country which had only 50 ventilators for her 16million population [27].

Abuja Declaration on Health Budgets of African Nations

At the April 2001 Abuja Declaration, African Heads of Government under the auspices of the WHO, agreed to allot, at least, 15% of total annual budgets to health [28]. After the first decade following that Declaration, only one African country met that target, and 11 actually reduced their budgets. Nigeria's health budget range, very embarrassingly, averaged at 4% - 6% since the Abuja Declaration [29].

WHO Recommendations on Healthcare Personnel and Equipment

The WHO recommends 1 doctor to 1000 persons; 1 nurse to 1 patient in ICU [1 *nurse to* 2 *or* 3 *acutely ill but stable patients*]; and 1 nurse to 500 persons; see **Table 3** and **Figure 1** [28] [29] [30]. Other WHO recommendations include: one ICU bed/10,000 persons, and a 50-bed hospital/100,000 persons. On none of these counts do the African countries meet the recommendations, whereas all the World Top-5 COVID-19 countries exceeded the WHO benchmarks.

Amongst the Top-5 African COVID-19 affected countries, only Algeria [1.8-per-1000] met the WHO recommendation of 1 doctor per 1000 persons, whereas all the World's Top-5 affected countries had more than double the recommendation. This is a further illustration of the low manpower capacity of Africa in healthcare services.

Curiously, the world's Top-5 had the highest infection and death rates globally, demonstrating the massive impact on their resources. It can best be imagined how the African countries could cope if the infection rates rise to those of the developed economies.

Table 3. Comparison of doctor-to-patient ratio [Physician Density per 1000 Persons] between Top-5 COVID-19 infected nations in the World and Top-5 of Africa [31] [32].

Country	Population [million]	Confirmed COVID-19 Cases	Doctor/1000 Pop
	Africa's Top-5		
1. South Africa	60	5647	0.9 [2017]
2. Egypt	102	5537	0.814 [2014]
3. Morocco	40	4423	0.7 [2017]
4. Algeria	44	4006	1.8 [2016]
5. Ghana	31	2074	0.2 [2017]
	World's Top-5		
6. USA	331	1,000,000	2.6 [2016]
7. Spain	47	220,000	4.1 [2016]
8. Italy	60	199,000	4.021 [2016]
9. Germany	84	158,000	4.191 [2015]
10. UK	68	153,000	2.825 [2017]

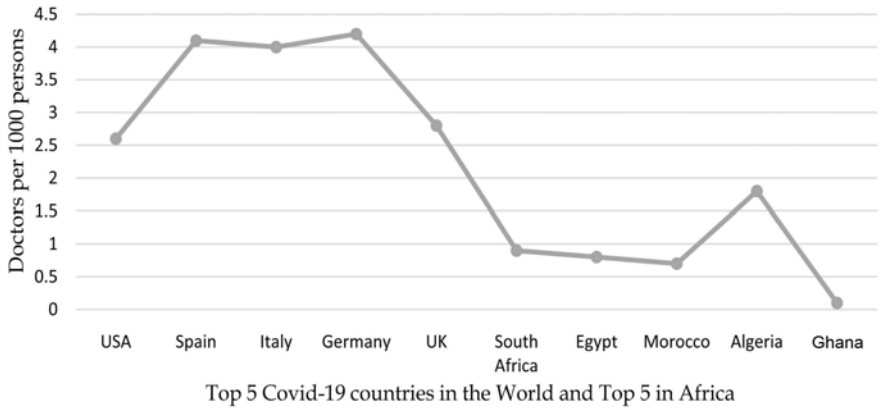

Figure 1. Graphic representation of doctors-per-1000-persons ratios in the World's top-5 and Africa's top-5 COVID-19 infected countries.

Evaluating the availability of ventilators, Nigeria had an estimated 370 units for 206 million citizens; an average of 1 to 560,000 persons, compared to USA with 150,000 ventilators for 331 million citizens, a ratio of 1 per 2200 persons [15] [33] [34] [35] [36] [37]. Meanwhile, with COVID-19, the ventilator is a major respiratory back up, in severe stages, against failing respiration and death [30] [35]. The disparity between Africa and the developed nations is very scandalous; see **Table 4**.

If the $16,000 cost per unit, of an imported ventilator in Senegal, is used as benchmark, it becomes a herculean task for any of the African Top-10 affected countries, whose highest income per capita [Algeria $15,293] is 25% of that of USA [$59,928], to procure enough ventilators to match the ratio of any of the World's Top-10 affected countries; see **Table 5**.

And so, what are the options available to Africa?

By April 2020, Senegalese researchers had begun the production of very cheap ventilators at $60 per unit [cc: $16,000/imported unit], and, if these can be mass-produced, Africa will improve on her current ventilator/100,000 persons ratios, to a good extent [27]. But those may be reserved for just the critical cases.

Sultan had in his report clearly enunciated the pathological basis for the respiratory difficulties and Il-6 Cytokine Storm in COVID-19, and gone ahead to proffer the solution of plasmapheresis and packed cell transfusion, with maximum oxygen flow, as more effective than PEEP ventilation [7].

At the average cost of $40 per unit of blood and $400 for 10units in the African countries, it appears that multiple transfusions will even be 400 times cheaper [$400 vs. $16,000] than the hardware of a mechanical ventilator. It, therefore, behooves the African nations to adopt the Sultan prescription along with existing management protocols which may be more cost-effective, pragmatic and efficient for them, even on an experimental basis, than investing their little income-per-capita on just a few ventilators at the critical stage of COVID-19.

Table 4. Comparison of ventilator-to-persons ratio between African countries and USA [38] [39].

Country	Population [millions]	Total No. of Ventilators	Ventilator Ratio/100,000
1. Senegal	16	200	1.25/100,000
2. Nigeria	206	370	0.184/100,000
3. South Africa	59	6000	10/100,000
4. Egypt	102	6000	6/100,000
5. USA	331	150,000	45/100,000

Table 5. Distribution of income per capita of the Top-10 COVID-19 affected countries in Africa and the world [40].

Country	Income Per Capita [$]	Country	Income Per Capita [$]
1. South Africa	13,526	1. USA	59,928
2. Egypt	11,608	2. Spain	39,037
3. Morocco	8225	3. Italy	40,924
4. Algeria	15,293	4. United Kingdom	44,920
5. Cameroon	3722	5. France	44,033
6. Ghana	4502	6. Germany	52,556
7. Nigeria	5887	7. Turkey	28,002
8. Cote d'Ivoire	3945	8. Iran	20,885
9. Guinea	2247	9. Russia	25,763
10. Djibouti	N/A	10. Brazil	15,553

In the long term, nevertheless, the more impacting factors like poverty, malnutrition, corruption and endemic diseases, which pre-dated COVID-19, along with the poor healthcare infrastructure, have to be resolutely addressed by all African nations, as a priority.

5. Conclusions

With COVID-19, Africa is going to face harder times ahead, because of the protracted negligence of the health infrastructure of her countries over the decades; and so, despite the initial low morbidity and mortality rates, there is a possibility that these figures may rise astronomically.

Developing countries need to adopt home-grown indigenous hygienic and health promotional measures to successfully fight COVID-19.

If, however, the lockdown remains imperative, appropriate measures should be taken to avert both food and economic crises, by ensuring that food supply lines and essential businesses are sustained.

Africa should immediately explore the prospects of plasmapheresis and packed cell transfusion as a cheaper and more efficient treatment protocol for critically

ill COVID-19 patients. The absolute dependence on mechanical ventilators, which are both expensive and in short supply, should be reserved for the critical cases.

Disclosures

I have nothing to disclose; I have no commitment whether financial, intellectual or philanthropic to any of the references or institutions or companies cited and I have no form of payment or gratification to any individual or group, whatsoever.

Conflicts of Interest

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

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Sandwich Rolling over Method in Patients with Prone Position Ventilation

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Abstract

Background: Prone positioning is nowadays considered as one of the most effective strategies for patients with severe acute respiratory distress syndrome (ARDS). Prone position ventilation can lead to some severe complications. Effectively implement prone ventilation and reduce the incidence of complications become an important problem for clinical medical staff. **Aims:** To investigate whether the Sandwich rolling over method was convenient for clinical implementation and can reduce complications. **Design:** This is a single-center, retrospective, observational study. **Results:** The mean pronation cycles per patient were 6.11 ± 4.40. The mean time spent in prone position for each cycle was 10.05 ± 4.42 hours. Two patients developed a pressure sore and the positions were cheek, auricle and chest. The mean time it took from preparation to cover the patient with the quilt was 10.56 ± 4.35 minutes. **Conclusions:** This retrospective study has shown that under the close cooperation and supervision of the team, the implementation efficiency of prone position ventilation can be improved and the occurrence of complications can be reduced.

Keywords

Prone Position Ventilation, Respiratory Distress Syndrome, Pressure Sores

1. Background Information

A recent international multicenter prospective study enrolling 29,144 patients reported that the period prevalence of acute respiratory distress syndrome (ARDS) was 10.4% of ICU admissions [1]. In recent years, the ARDS mortality rate ranged between 25% and 45% with lower survival in patients with more severe ARDS [1] [2]. Prone positioning is nowadays considered as one of the most effective strategies for patients with severe ARDS [3]. A Cochrane systematic re-

view recommends that prone ventilation for 16 or more hours per day should be actively considered in patients with severe hypoxaemia within 48 hours of mechanical ventilation [4]. An international prospective epidemiological study conducted in 459 intensive care units (ICUs) that analyzed the treatment of 2377 ARDS patients has shown that the prone position ventilation was adopted only for 16% of patients with severe ARDS [5]. Prone position ventilation can lead to complications such as displacement of indwelling catheters, pressure sores, compression of nerves and retinal vessels, vomiting, and intolerance to the maneuver [6]. Nurses have an extremely important role in the care of the prone positioned patient. In the past, studies have focused a great deal on the efficacy of prone positioning and adjuncts to prone positioning; however, limited research has been performed on the details of the procedure [7]. Effectively implement prone ventilation and reduce the incidence of complications become an important problem for clinical medical staff. Therefore, our objective was to investigate whether the Sandwich rolling over method was convenient for clinical implementation and can reduce complications.

2. Method

2.1. Study Design and Observed Variables

The study was developed from January 2017 to July 2019 in an ICU unit of a third-grade first-class hospital in China. In the study period, we enrolled all patients with ARDS undergoing invasive mechanical ventilation (both with endotracheal tube or tracheostomy) who were treated with prone position. The criteria for prone position were as follows: fulfilled the diagnostic criteria of ARDS [8] and age of patients ≥ 18 years; Patients with contraindications to prone position were excluded. The observed variables were as follows: pressure sores (face, thorax, abdomen, knees, other sites), unplanned extubations (central venous, arterial, thoracic drainages, endotracheal tube or tracheostomy), airway obstruction. Another observation variable was the amount of time it took to rolling over. All patients routinely applied an antidecubitus mattress with alternate pressure.

2.2. The Sandwich Rolling over Method

2.2.1. Equipment

Airbed, Airway trolley, Endotracheal tube tapes, Eye ointment, 2 * 120 cm * 160 cm clean bedsheets, 4 * 40 cm * 40 cm square pillows, ECG electrodes, 6 * Foam dressings.

2.2.2. Patients Preparation

Patient should be receiving adequate sedation and analgesia. Deep sedation was usual, ensure RASS score −3 - −4. Endotracheal intubation was fixed with both bandage and adhesive tape. Airway secretions should be suction out. Suspend enteral nutrition for at least one hour. Ensure all lines were sutured and secured. Placed the patient's drainage bottle and drainage bag were beside the thigh, and

placed precise urine bag in the middle of both legs. Patient should be pre-oxygenated with 100% O_2 two mintues.

2.2.3. Medical Staff Preparation

1 airway doctor, 4 nurses including the senior nurse were needed. Airway doctor positioned at head end and give orders. Four nurses stand over the patient. For patients with large body weight or patients using ECMO, 2 more medical staff should be added. All staff received unified training on operating procedures and theoretical knowledge.

2.2.4. Supine to Prone

The airway doctor was responsible for fixing the endotracheal tube and ensures appropriate ventilator settings. Two nurses located on either side of the patient's upper body were responsible for fixing the deep venous tube, the gastric tube and remove the electrodes from the patient. Posted two foam dressings to the patient's chest to protect the skin. And then placed the two square pillows separately above the clavicle to reduce the pressure placed upon the chest. Arm was tucked underneath the buttock. Two nurses stood on the left and right sides of the patient's lower body were responsible for fixing the patient's tube and placing the bag and drainage bottle on the patient's side. Posted two foam dressings to the patient's iliac spine and the soft pillow was placed above. A clean bed sheet should be placed on top of the patient leaving only the head and neck exposed to make patient appear Sandwich shape (**Figure 1**). The edges from the top and bottom bed sheets were rolled tightly together thereby encasing the patient between the two. The airway doctor gave the first command to move the patient horizontally to lie on the edge of the bed meanwhile keeping the bed sheets pulled taught and the edges rolled tight. The direction of the horizontal move should toward any central venous devices in the opposite direction to which the patient will be turned. The airway doctor gave the second command to move the patient horizontally to 15 cm away from the bedside. The airway doctor gave the third command, whilst maintaining a tight grip on the rolled up sheets the patient was rotated 90˚ to lie on their side (**Figure 2**). Staff on either side should then adjust their hand positions on the rolled up sheets. The rolled up sheet was pulled up from beneath the patient whilst the patient was carefully turned into the prone position.

Figure 1. Sandwich shape.

Figure 2. Rolling up the sheets.

2.2.5. Positioning

Reattached the ECG electrodes, arterial blood pressure monitoring and re-established all monitoring. Placed a soft pillow under the patient's lower leg to suspend the knee joint. The patient's head was cushioned with a C-letter-shaped gel pressure relief pad and the endotracheal tube was placed on the gap. Observed the situation of blood pressure, adjust the infusion speed of vasoactive drugs. Raised one arm on the same side to which the head was facing whilst placed the other arm by the patient's side. Covered the patient with the quilt again. The patient was turned to the right and left with a triangle pillow under the single side every two hours. The position of both the head and arms should be alternated every two hours.

All of the complications were reported as recorded in the medical and nursing record sheet. Braden score for predicting pressure sore risk was performed before each prone position [9]. The charge nurse was responsible for recording the time of each prone position operation.

This study was reviewed by the institutional review board (IRB) and deemed to be exempt from IRB oversight.

2.2.6. Statistical Analysis

The primary analysis compared the cases of adverse events which include unplanned extubation and pressure sores; the secondary predictor variables compared rolling over time (The time from preparing to roll over to cover the patient with the quilt again) and the average duration of each prone position. After data collection, the data were checked for accuracy and analysis using SPSS software. The data were described as the mean ± standard deviation for continuous variables and as frequency percentage for categorical variables.

3. Result

A total of 28 patients were included in the study. The mean age was 62.35 ± 12.22 years; 15 patients underwent prone position with an endotracheal tube, whereas 13 patients had a tracheostomy. Prone position was adopted in 2 patients while connected to ECMO.

The mean pronation cycles per patient were 6.11 ± 4.40, range from 2 to 18. The total pronation cycles for all patients were 171. The mean time spent in

prone position for each cycle was 10.05 ± 4.42 hours. The mean time it took from preparation to cover the patient with the quilt was 10.56 ± 4.35 minutes. Three patients developed a pressure sore and the positions were cheek, auricle and chest. According to the European Pressure Ulcer Advisory Panel (EPUAP) pressure sores classification, 1pressure sores were at stage I, 2 were at stage II. No stage III and IV pressure sores were recorded [10]. There was no displacement of unplanned extubations drainages was observed in the study.

4. Discussion

Prone position ventilation can significantly improve PaO_2/FiO_2 ratios and reduce mortality in ARDS patients [11]. We performed the Sandwich rolling method, which only required 5 medical staff to participate. This method makes detailed requirements on the staff, so that the rolling over process can be carried out in a more orderly manner. The time spent in each rolling over operation can be effectively shortened.

Previous studies have shown that the ventilation time in prone position over 12 hours, and the longer time in prone position, the better the treatment effect [12]. In this study, the mean time spent in prone position for each cycle was 10.05 ± 4.42 hours, which was lower to previous research results [4]. In this study, the prone flip was only performed during the day. More effective measures are needed in the future to extend the prone position.

Pressure sores were reported as the main complication reported in the literature and the incidence rate was 43.4% [13]. The rate of pressure sores in this study was only 1.76%, which was obviously lower than the reported. Before the Sandwich rolling method was adopted, the chest, iliac crests and knees of the patient was protected by foam dressing. The square pillow of the shoulder and hip was station keeping shift during the rolling process, which make the patient's abdomen, breast and other positions hanging in the air and not easy to be compressed. The triangle pillow exchanged direction every 2 hours could transform the compression site, promote the local blood circulation and reduce the occurrence of pressure sores.

Endotracheal intubation, nasointestinal tube, central venous lines and other important tubes may escape during the rolling over process, thus increasing the incidence of unplanned extubation [12]. Medical staff were worried about the unplanned extubation during the rolling over process, which cause accidental injury to patients. This study showed that no unplanned extubation occurred. The Sandwich rolling over method could effectively reduce the incidence of unplanned extubation. To analyze the reasons, the drainage tube was placed on the side of the patient or between the legs, and the position of the patients and tubes were relatively fixed between the bed sheet. Double fixation of endotracheal intubation and other important pipes. The airway doctor should ensure the stability and patency of the endotracheal tube during the rolling over process to prevent the tube from falling off.

5. Conclusion

This retrospective study has shown that under the close cooperation and supervision of the team, the implementation efficiency of prone position ventilation can be improved and the occurrence of complications can be reduced. The Sandwich rolling over method was easy to implement.

6. Limitations

The data collection took two years, so factors such as personnel structure and equipment technology may have an impact on the observed variables. This study is a single-center study, further study is still needed because of the limited cases. Multi-center studies are still needed to reduce the incidence of complications in the future.

Conflicts of Interest

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

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