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Evaluation of the Validity of SARS-CoV-2 Infection Control Measures through Antibody Testing for Employees of a University and Hospital

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Abstract

Introduction: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is spread through person-to-person transmission and has become a global pandemic. At Saitama Medical University Hospital, many medical staff members have been involved in treating patients with COVID-19. The Care Task Force was established in collaboration with physicians, medical staff, and clerical staff in the various hospital departments to strengthen infection control measures based on standard precautions. **Methods:** To determine the outcome of infection control measures, we administered anti-SARS-CoV-2 antibody tests and questionnaires to all 2461 employees including nonhospital workers, as a local standard, between June 29 and July 10, 2020. **Results:** Among the hospital workers, 698 (33.99%) had contact with patients with COVID-19 and 325 healthcare workers worked in specialized wards for the COVID-19, intensive care unit, and high-fever outpatient clinics. Positive for the anti-SARS-CoV-2 antibody were only 4 (0.16%) employees. Among them, the past histories of two employees were unknown, while the other two had a history of COVID-19 before the test and were not involved in the medical care of COVID-19 patients at our hospital. **Conclusion:** It is the first study assessing the seropositive rate in Saitama-prefecture, a bed-town of Tokyo. Compared with the local standard, we found that health care workers are not at risk for viral droplet transmission, especially with SARS-CoV-2 and even with the

current pandemic, with infection control measures based on standard precautions. Based on our findings and with no clusters formed in our university and hospital, we continued current infection control measures.

Keywords

COVID-19, Infection Control, Health Care Workers, Standard Precautions

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in December 2019 and has since become a global pandemic [1]. COVID-19 spreads through person-to-person transmission, primarily through respiratory droplets produced during talking, coughing, or sneezing, and approximately half of transmissions may occur via asymptomatic carriers [2] [3]. Therefore, as the primary sector in contact with COVID-19 patients, all healthcare workers (HCWs) should adhere to standard precautions, including simple ventilation, universal masking of all patients and hospital staff, and sufficient physical distances to control hospital COVID-19 infections.

Saitama Medical University Hospital, located in western Saitama Prefecture, has been providing medical care to patients with COVID-19 since March 2020, before the declaration of the first state of emergency in Japan. The COVID-19 Care Task Force was established in response to the initial COVID-19 outbreak in Japan, on March 10, 2020, and in collaboration with physicians, medical staff, and clerical staff in various hospital departments. The Care Task Force aimed to raise awareness regarding universal masking; social distancing throughout university facilities, including hospital areas; monitoring febrile patients at hospital entrances; and early isolation. The Care Task Force, which is led by infectious disease specialists, received medical treatment requests from febrile patients and immediately provided consistent COVID-19 treatment in the infectious disease ward and dedicated outpatient booths. Symptomatic patients or patients with a history of contact with COVID-19 underwent in-hospital reverse transcriptase-polymerase chain reaction (RT-PCR) tests using nasopharyngeal swab specimens. Moreover, the Care Task Force members underwent RT-PCR screening tests.

This study aimed to determine the outcomes of infection control measures based on standard precautions against viral pathogens in the early stage of the pandemic, when the virological characteristics of SARS-CoV-2 were still unclear. All employees, including nonhealthcare workers, underwent assessments of the prevalence of specific IgM and IgG antibodies that target the nucleocapsid protein (N) of SARS-CoV-2. Testing was done using commercially available automated high-throughput immunoassays and questionnaires were administered.

2. Methods

Between June 29 and July 10, 2020, all university staff, including physicians, nurses, radiologists, pharmacists, clinical laboratory technicians, and clerical staff were invited to voluntarily participate in testing for IgG antibodies against the N protein of SARS-CoV-2, which indicated exposure (Figure 1). All employees were aged ≥18 years. Though we excluded staff who declined consent, there were no specific inclusion or exclusion criteria. Antibody quantification was performed using a residual serum specimen collected during a periodic health checkup. Anti-SARS-CoV-2 antibody testing was done using Roche's Elecsys® Anti-SARS-CoV-2 and the electrochemiluminescence method (ECLIA) for IgM and IgG for N protein (Roche Diagnostic Scandinavia AB, Solna, Sweden) on a Cobas 8000 e801 (Roche Diagnostics, Mannheim, Germany), following the manufacturer's instructions. The results were reported as signal sample/cutoff (cutoff index [COI]) values and qualitative results indicating nonreactive (COI < 1.0; negative) or reactive (COI ≥ 1.0; positive). Additionally, the participants were asked to fill out a questionnaire that assessed type of work, work area, contact history with patients with COVID-19, and history of symptoms associated with COVID-19 from January 2020 to June 2020. This study was approved by the ethics committee of Saitama Medical University (Approval No. 944).

Serum samples were collected from 2461 employees for antibody testing. We counted the number of respondents to each questionnaire item and the number of respondents who were anti-SARS-CoV-2 antibody positive and compared the results with those of the questionnaire items.

3. Results

Table 1 shows the background characteristics of the employees. The numbers of hospital and nonhospital staff who completed the questionnaire were 2054 and

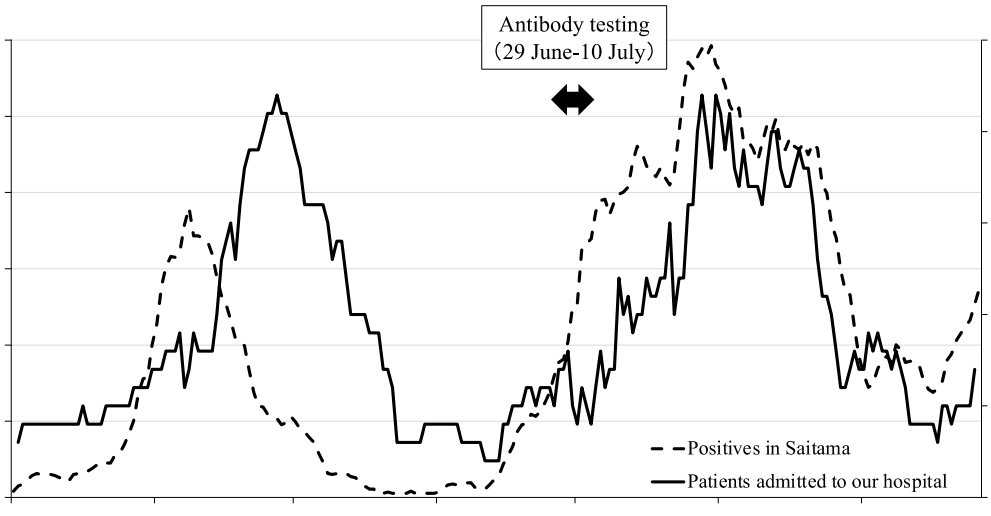

Figure 1. Time of antibody test implementation, number of new patient outbreaks in Saitama Prefecture, and number of patients admitted to our hospital.

330, respectively, while 77 staff members did not respond. Among the hospital workers, 449 (18.24%), 834 (33.89%), 395 (16.05%), and 200 (8.13%) were doctors, nurses, other medical staff, and clerical staff, respectively. Furthermore, 698 (33.99%) HCWs had contact with patients with COVID-19 while 325 HCWs belonged to specialized wards for COVID-19, intensive care unit, or febrile out-patient clinics as members of the COVID-19 Care Task Force.

Table 2 shows an overview of the anti-SARS-CoV-2 antibody-positive employees. Four (0.16 %) employees tested positive for anti-SARS-CoV-2 antibodies.

Table 1. Background characteristics of the employees.

		Number	Ratio (%)
Type of work (n = 2461)			
Hospital workers		2054	83.46
	Doctor	449	18.24
	Nurse	834	33.89
	Other medical staff	395	16.05
	Clerical staff	200	8.13
	Others	173	7.03
	N.A.	3	0.12
Nonhospital workers	Clerks, teaching staff and basic scientists	330	13.40
N.A.[a]		77	3.13
Contact history with COVID-19 among the hospital workers (n = 2054)			
Yes		698	33.99
No		1344	65.43
N.A.[a]		12	0.58

a. N.A.; not available; Two of antibody positive employees did not respond to the questionnaire.

Table 2. Overview of employees positive for anti-SARS-CoV-2 antibody.

Age	History of COVID-19 pneumonia	Antibody titer (U/mL)	Occupation	Medical services for patients with fever or COVID-19	History of contact with COVID-19 outside the hospital
50s	Yes	34.1	Administrative staff	No	Yes
40s	Yes	72.0	Nurse	No	Yes
N.A.[a]	N.A.[a]	109.5	N.A.[a]	N.A.[a]	N.A.[a]
N.A.[a]	N.A.[a]	127.0	N.A.[a]	N.A.[a]	N.A.[a]

a. N.A.; not available; Two of antibody positive employees did not respond to the questionnaire.

Among them, two (one nurse and one nonhospital worker) had a history of hospitalization for COVID-19 before the antibody test, while the past histories for the other two employees were unknown, as they had not completed the questionnaire. The two antibody-positive employees had an established history of out-of-hospital contact with individuals with COVID-19 at the time of COVID-19 onset. The antibody-positive nurse was not involved in the medical care of and did not have direct contact with COVID-19 patients or those with fever. Thus, at least these two seemed to be a local background. No evidence of high-risk SARS-CoV-2 transmission during worktime was noted at our hospital.

4. Discussion

It is the first study assessing the seropositive rate in Saitama-prefecture, a bed-town of Tokyo. In this study we assessed the risk of SARS-CoV-2 infection among hospital workers compared with nonhospital workers. It is particularly important to study the antibody positivity of the hospital workers compared with nonhospital ones at the same time in the same area as a fair control. To do so, we can show the medical workers are not high risk at our hospital compared with the local control. Our findings suggest that infection control based on standard precautions practiced in our university and hospital with periodic health checkups effectively controlled COVID-19 infections among the employees. However, since both antibody-positive cases were due to out-of-hospital contacts, infection and the spread of pathogens should be prevented not only in the hospital care of patients, but also in the daily life of the staff, especially during the pandemic. Several large-scale antibody tests conducted in Japan in early June 2020 revealed an estimated antibody positive rate of 0.03% - 0.17% [4], which is consistent with our findings. Additionally, from July to August 2020, medical staff at the Juntendo University Hospital in Japan were tested for antibodies against SARS-CoV-2. The antibody positivity rate was 0.34%, which was consistent with findings among Tokyo citizens, as reported by the Japanese government [5]. Most of these studies were conducted in big cities, like Tokyo and Osaka, that were different from ours. In other countries, HCWs do not necessarily have high antibody-positive rates [6] [7] [8] [9]. University and hospital staff are considered to be at high risk of infection because the "three Cs (closed spaces, crowds, and close contact)" can easily be formed through contact with many people and meetings in the workplace. These results suggest that adherence to standard precautions, including simple ventilation, universal masking, and sufficient physical distancing, is effective in hospital settings.

This study has several limitations. First, this was a single-center study. There is a need for large-scale, multi-center studies to elucidate the adequacy of infection control measures. Second, antibody tests can yield false-negative results. Early cases of SARS-CoV-2 infections may have been missed due to the low antibody positivity rate within 7 days of infection [10]. Third, the background characteristics of the staff might not be accurate because we relied on self-reported

questionnaires. Finally, we lacked information on employees who did not fill out the questionnaire. For example, in this study, two antibody-positive cases did not fill out the questionnaire so that we could not assess their transmission route.

5. Conclusion

The described infection control strategies were continued based on our findings and no clusters of SARS-CoV-2 infections have occurred among employees in our university and hospital. Our findings demonstrate that with infection control measures based on standard precautions, HCWs are not at risk of viral transmission, especially with SARS-CoV-2 and even in the current pandemic.

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Conflicts of Interest

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

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A New Type of Flat Vehicle for Emergency Patient Transfer

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Abstract

The utility model discloses a new type of flat vehicle for emergency patient transfer, comprising a support frame, a bed board, an infusion stand and a transfer assembly; the transfer assembly comprises a trapezoidal base fixed on the upper part of the support frame, and a trapezoid mounted on the bottom or side of the bed board. A sliding sleeve, a limit pin, a fixing cylinder and a spring; the trapezoidal sliding sleeve is matched on the trapezoidal base, a pin shaft hole is arranged on the trapezoidal base, the fixing cylinder is fixed on the trapezoidal sliding sleeve, and the limit pin is sleeved in the fixing cylinder, The bottom of the limit pin protrudes from the trapezoidal sliding sleeve, and the upper part is provided with a traction rod; the spring is sleeved on the traction rod, and a limiting plate is arranged at intervals on both sides of the trapezoidal base, and the limiting plate is wrapped in the trapezoidal sliding sleeve. The outer end: by setting the transfer component, the bed board is allowed to be fixed, slid and completely disengaged from the support frame, which is convenient for transferring the bed board together with the patient on it during the patient transfer process. It provides convenience for medical staff.

Keywords

Medical Equipment, Transportation, Emergency, Flat Vehicle

1. Introduction

Technical Field: The utility model belongs to the technical field of medical equipment; it is particularly related to a new type of flat vehicle for emergency patient transfer.

*The authors have the same contribution.
#Corresponding author.

Background Technology: The emergency transfer vehicle is a kind of equipment used in the first aid in the hospital, and it is a common equipment in the hospital [1]. In daily use, after receiving the first aid, the patient is usually transported to the emergency room by an ambulance. During the rescue process, it is often necessary to transport the patient at least one or more times. However, in the existing transfer method, since the bed board and the support frame are an integral structure, many people are often required to lift the patient's body, which is difficult and time-consuming to operate [2] [3]. For seriously ill patients, it is easy to cause the deterioration of the condition during the lifting process.

In view of the above problems, there is also a transfer flat car in which the bed board is separated from the support frame. The bed board is directly fixed on the support frame, and the bed board needs to be lifted upward to separate the connection structure, and then the bed board and the support frame can be separated [4]. During the whole transfer process, many people are required to lift the bed board, which is laborious to operate, especially the separation of the bed board and the support frame from the ambulance, the operation space is small, and most of the nurses are women, so the operation is difficult and brings inconvenience to people. Therefore, it is necessary to study a new type of flat vehicle for emergency patient transfer [5] [6].

2. Summary of the Invention

Aiming at the defects and problems existing in the existing equipment, the utility model provides a new type of flat vehicle for emergency patient transfer. It effectively solves the problem that the bed board and the support frame are difficult to separate in the existing equipment, and the bed board needs to be lifted, which is time-consuming and labor-intensive.

The scheme adopted by the utility model to solve its technical problem is: a new type of flat vehicle for emergency patient transfer, including a support frame, a bed board, an infusion pole and a transfer assembly. The bed plate is provided with a guard plate and an infusion stand, and the transfer assembly includes a trapezoidal base fixed on the upper part of the support frame, a trapezoidal sliding sleeve installed on the bottom or side of the bed plate, a limit pin, a fixed cylinder and a spring. The trapezoidal sliding sleeve is matched on the trapezoidal base and can slide along the trapezoidal base, and a pin shaft hole is arranged on the trapezoidal base. The fixing cylinder is fixed on the trapezoidal sliding sleeve, the limit pin is sleeved in the fixing cylinder, the bottom of the limiting pin passes through the trapezoidal sliding sleeve, and the upper part is provided with a traction rod, and the traction rod is led out from the upper part of the fixing cylinder, and is placed in the upper part of the fixing cylinder. The lead-out section is provided with a baffle. The spring is sleeved on the traction rod and is located between the fixing cylinder and the limit pin. When the limit pin is sleeved in the pin shaft hole, the trapezoidal sliding sleeve cannot slide along the trapezoidal base, and is arranged at intervals on both sides of the tra-

pezoidal base. The limit board is wrapped around the outer end of the trapezoidal sliding sleeve, and the bed board is fixed on the support frame.

Further, the drawbar includes a rectangular section of the upper section and a cylindrical section of the lower section; the upper part of the fixing cylinder is provided with a rectangular through hole, and the rectangular section is matched and sleeved in the through hole. When the rectangular section is pulled out of the through hole, the position of the drawbar can be maintained by turning the drawbar. The short side of the rectangular segment is equal to the diameter of the circular segment. The end of the drawbar is provided with a pull ring. The infusion frame is a retractable support frame, the bottom of the support frame is provided with a universal wheel, and the middle part of the support frame is provided with a placement plate.

The beneficial effects of the utility model: The utility model provides a flat car that is convenient for transferring a patient, which connects the bed board and the support frame through the transfer assembly, so that the bed board and the support frame can be fixed together and maintain a stable connection relationship. The concrete realization mode is, utilize the limit pin and the pin shaft hole to realize the fixation of the two lateral positions, utilize the limit plate that is arranged at the end of the trapezoidal base to limit the side of the trapezoidal sliding sleeve from the side, Fix the trapezoidal sliding sleeve on the trapezoidal base vertically, and the limit relationship disappears when the trapezoidal sliding sleeve is separated from the limit plate. At the same time, the bed board is allowed to slide relative to the support frame. The specific implementation method is as follows: Remove the limit pin from the pin hole, the lateral restraint disappears, push the guard board from the side, the bed board can slide along the trapezoidal base, and the bed board can be transported out of the ambulance by pushing. During the whole process, the position of the bed board is basically unchanged, and the bumps are small, and after a certain distance of lateral sliding, the trapezoidal sliding sleeve is released from the limitation of the limit plate, and the vertical restraint also disappears, thus allowing the bed board to be directly separated from the support frame. Due to the docking of the trapezoidal structure, it is convenient to dock when it is placed again.

At the same time, the present utility model sets the limit pin as the rectangular section of the upper section and the cylindrical section of the lower section, and its setting purpose is: Pull the limit pin upward to make the rectangular section come out of the trapezoidal sliding sleeve, rotate the limit pin to make the rectangular section touch the trapezoidal sliding sleeve, so that the limit pin is separated from the pin shaft hole and is in a fixed state, avoiding the sliding process of the bed board, the limit pin scratches the trapezoidal base.

Thus, the utility model has a novel structure, and by setting the transfer assembly, the bed board is allowed to be fixed, slid and completely disengaged from the support frame, so that the bed board and the patient on it are transported together during the patient transfer process. The sliding method is used

to move, which saves manpower, is easy to operate, and provides convenience for medical staff.

3. Discussion

The present utility model will be further described below in conjunction with the accompanying drawings and embodiments.

Embodiment 1: The present embodiment aims to provide a new type of flat vehicle for emergency patient transfer, mainly used for the transfer of patients during emergency. In view of the existing structure, the bed board must be lifted for transferring the patient [7]. During the lifting process, it is easy to cause bumps, and the operation process is laborious and troublesome to use. This embodiment provides a patient transfer cart that is lightweight and easy to use [8] [9] [10].

This embodiment is shown in **Figure 1**: a new type of flat vehicle for emergency patient transfer includes a support frame 1, a bed board 2, an infusion frame 23 and a transfer assembly (**Figure 2**). Wherein, a guard plate 22 and an infusion stand 23 are provided on the bed board 2, a lifter 21 is provided at both ends of the bed board, the guard board 22 is used to protect the patient, and the infusion stand 23 is used for hanging infusion bottles. During the transfer process, the infusion stand 23 and the guard plate 22 are connected and the bed board is transported together, and the structure is reasonable. In addition, in the present embodiment, the infusion stand 23 can be telescopic and can specifically include a sleeve rod and a sleeve, and a lock wire is provided between the sleeve rod and the sleeve. The telescopic structure here can be adjusted as needed, and in the retracted state, it takes up little space. The bottom of the support frame 1 is provided with a universal wheel 11, and a placement plate 12 is provided in the middle of the support frame 1, and the placement plate 12 is used for placing articles.

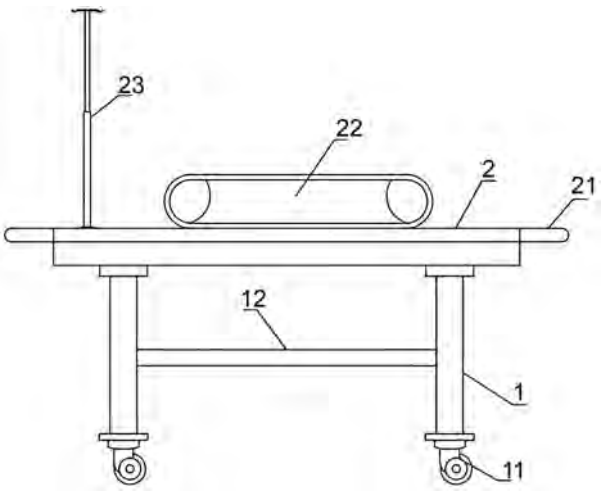

Figure 1. Schematic diagram of the structure of the present utility model. 1. Support frame, 2. Bed board. 11. Universal wheel. 12. Place the board. 21. Lifter. 22. Guard plate 23. Infusion stand.

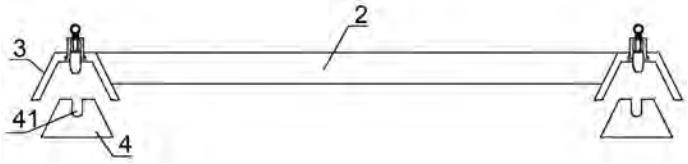

Figure 2. Schematic diagram of the structure of the transport assembly. 3. Trapezoidal slide sleeve. 4. Trapezoidal base. 41. Pin shaft hole.

The transfer assembly includes a trapezoidal base 4 fixed on the upper part of the support frame 1, a trapezoidal sliding sleeve 3 mounted on the bottom or side of the bed board 2, a limit pin 6, a fixed cylinder 5 and a spring 8. The trapezoidal sliding sleeve 3 is matched and sleeved on the trapezoidal base 4, and can slide along the trapezoidal base 4, and a pin shaft hole 41 is arranged on the trapezoidal base 4. In this embodiment, only one pin shaft hole 41 is provided. In order to facilitate the butt joint between the limit pin and the pin shaft hole, the bottom of the limit pin 6 may be provided with a butt joint smaller than that of the pin shaft hole 41.

In this embodiment, the fixing cylinder 5 is a hollow structure, the fixing cylinder 5 is fixed on the trapezoidal sliding sleeve 3, and the limit pin 6 is sleeved in the fixing cylinder 5. The bottom of the limit pin 6 protrudes from the trapezoidal sliding sleeve 3, and the upper part of the limit pin 6 is provided with a traction rod 7 (**Figure 3**), and the traction rod 7 is drawn out from the upper part of the fixed cylinder 5, and a baffle plate is provided in the lead-out section. The baffle plate is used to overcome the elastic force of the spring, as the limit position of the limit pin 6 extending downward (**Figure 4**).

The spring 8 is sleeved on the traction rod 7 and is located between the fixing cylinder 5 and the limit pin 6. When the limiting pin 6 is sheathed in the pin shaft hole 41, the trapezoidal sliding sleeve 3 cannot slide along the trapezoidal base 4, and limiting plate 9 is arranged at intervals on both sides of the trapezoidal base 4. The limiting plate 9 is wrapped around the outer end of the trapezoidal sliding sleeve 3 to fix the bed plate 2 on the support frame 1. In this embodiment, in order to conveniently locate the position of the limiting pin 6 and the pin shaft hole 41, a positioning plate can also be provided on the trapezoidal sliding sleeve. When the positioning plate touches the limit plate, the limit pin just corresponds to the pin shaft hole.

In this embodiment, the bed board 2 and the support frame 1 are connected together through the transfer assembly, and are in three states.

First, the bed board 1 and the support frame 2 can be fixed together and maintain a stable connection relationship. The specific implementation method is to use the limit pin 6 and the pin shaft hole 41 to realize the fixation of the lateral positions of the two. The side of the trapezoidal sliding sleeve is limited from the side by the limiting plate 9 arranged at the end of the trapezoidal base, and the trapezoidal sliding sleeve is fixed on the trapezoidal base from the vertical direction, and the limiting relationship disappears when the trapezoidal sliding sleeve is separated from the limiting plate.

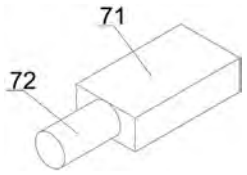

Figure 3. Schematic diagram of the structure of the traction rod. 71. Rectangular segment. 72. Cylindrical segment.

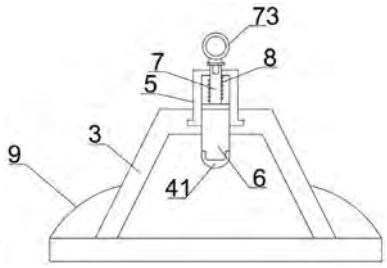

Figure 4. Schematic diagram of the structure of the limit plate. 5. Fixed cylinder. 6. Limit pin. 7. Traction rod. 8. Spring. 9. Limiting plate. 73. Pull ring.

Second, the bed board 2 slides relative to the support frame 1. The specific implementation method is to disengage the limit pin from the pin shaft hole, the lateral restraint disappears, push the guard plate 22 or lift the hand 21 from the side, and the bed plate (trapezoidal sliding sleeve) can slide along the trapezoidal base 4. The bed board was transported from the ambulance. During the whole process, the position of the bed board is basically unchanged, the bumps are small, and labor is saved. For further labor saving, rollers or rollers can be arranged between the trapezoidal sliding sleeve and the trapezoidal base.

Third, the bed board and the support frame are completely separated. After the trapezoidal sliding sleeve slides laterally relative to the trapezoidal base for a certain distance, the trapezoidal sliding sleeve escapes the restriction of the limit plate, and the vertical restraint also disappears, allowing the bed board to be directly separated from the support frame. Due to the butt joint of the trapezoidal structure (the trapezoidal sliding sleeve and the trapezoidal base), when the trapezoidal sliding sleeve is placed again, the docking is convenient.

Therefore, the novel structure of this embodiment is novel. By setting the transfer assembly, the bed board is allowed to be fixed, slid and completely disengaged from the support frame, so that the bed board and the patient on it can be transferred together during the patient transfer process [11]. It is moved by sliding, which saves manpower and is easy to operate, which provides convenience for medical staff [12] [13].

Embodiment 2: This embodiment is basically the same as Embodiment 1, and the difference lies in: the structure of the traction rod 7 is further described in this embodiment. In this embodiment, the end of the traction rod 7 is provided with a pull ring 73, and the traction rod 7 includes a rectangular section 71 of the upper section and a cylindrical section 72 of the lower section. The short side of the rectangular segment is equal to the diameter of the circular segment, the up-

per part of the fixing cylinder 5 is provided with a rectangular through hole, and the rectangular segment is matched and sleeved in the through hole. When the rectangular section 71 is pulled out of the through hole, the position of the traction rod can be maintained by rotating the traction rod, and the spring is sleeved on the cylindrical section and abuts against the bottom of the rectangular section. The diameter of the spring is larger than the short side of the through hole so that it does not come out of the through hole. During the specific operation, due to the elasticity of the spring, a downward pressure is applied to the limit pin, so that the limit pin protrudes from the trapezoidal sliding sleeve. Then manually overcome the elastic force, so that the spring continues to be compressed, and the rectangular section comes out of the through hole. Then turn the pull ring so that the long side of the rectangular segment corresponds to the short side of the through hole. In this way, the traction rod can be in a fixed state, and the limit pin can be retracted into the trapezoidal sliding sleeve, so as to prevent the limit pin from scratching the trapezoidal base during the sliding process of the bed board.

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Conflicts of Interest

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

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Characteristics and Social Support Needs Predicting Anticipatory Grief in the Spouses of Patients with Cancer at the End of Life

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Abstract

Background: Medical staff provide care to spouses of terminal cancer patients through trial and error by meeting their various support needs and spousal factors regarding their anticipatory grief. Studies on the association between spousal characteristics and anticipatory grief have been inconclusive; additionally, there has been insufficient research on support needs for anticipatory grief of spouses. This study aimed to explore the spousal characteristics and social support needs predicting anticipatory grief in spouses of patients with cancer at the end of life. **Methods:** This was a cross-sectional study. Eligible spouses (n = 102) completed a self-report questionnaire in two hospitals with palliative care units in Japan. The questionnaire included demographic information, a tool assessing social support needs of spouses, and the Anticipatory Grief Scale for Family Caregivers. **Results:** Simple regression analyses indicated that patient age, chemotherapy, no treatment, ECOG PS3, children aged under 20 years, total score of "social support needs regarding the disease and treatment of the patients" and subscale scores ("medical condition and cure," "daily life and social support," and "intimacy and employment"), and total score of "social support needs of the spouses" and subscale

scores ("family psychological issues and social support" and "intimacy, employment, and society") were significant variables (all $p < 0.05$) for the multiple regression analysis. Multiple regression analyses revealed that "chemotherapy" and "social support needs of the spouses" in Model 1, and "family psychological issues and social support" in Model 2 significantly predicted anticipatory grief (all $p < 0.05$). **Conclusions:** Patients having no experience of "chemotherapy" and higher "social support needs of the spouses" in Model 1, and greater spousal needs of "family psychological issues and social support" in Model 2 were significant predictors of severe anticipatory grief. Medical staff should pay attention to these risk factors that predict anticipatory grief among spouses.

Keywords

Cancer, Spouse, Spousal Characteristics, Social Support Needs, Anticipatory Grief

1. Introduction

The loss of a loved one is an extremely tragic experience for a family; specifically, the death of a spouse ranks as the most stressful life event [1]. In the field of psycho-oncology, it is well-known that spouses' demise is a predictor of being at a higher risk for developing complicated grief [2] [3] [4] and a greater level of depressive symptoms after bereavement [5].

Psychological distress and a comprehensive response before patients' death experienced by their spouses is referred to as "anticipatory grief." Lindemann (1944) first coined this term to explain the grief responses he observed in people who were not bereaved [6] [7]. He explained that anticipatory grief might work as a safeguard against the impact of a sudden death notice, using an instance where a soldier had just returned from the battlefront and complained that his wife did not love him anymore and demanded immediate divorce as grief work [6]. Lebow (1976) defined "anticipatory mourning" as "the total set of cognitive, affective, cultural, and social reactions to expected death felt by the patient and family" [8]; moreover, he designated "anticipatory grieving" as "that portion of anticipatory mourning involving the affective responses" [8]. While all emotions in response to the threat of losing a loved one are an aspect of anticipatory grief, the main ones are sorrow, depression, and anxiety [9]. Anticipatory grief has been found to be significantly correlated with depression (history of/current depression) [10] [11] and subjective stress [10]; furthermore, it may be a risk factor for poor early bereavement adjustment [10].

Additionally, anticipatory grief measured at the point of time of a patient's admission to palliative care was a highly, statistically significant predictor of prolonged grief disorder in the long-term [12]; its symptoms appeared to persist for at least three years after bereavement for almost 20% of caregivers [12]. This situation indicated that an intervention for anticipatory grief might be an effec-

tive prevention against prolonged grief disorder for the bereaved. However, medical staff provide care to spouses by trial and error in clinical settings because there are many spousal support needs and various spousal-related factors of their anticipatory grief.

Studies on the association between spousal characteristics and anticipatory grief have been inconclusive. For example, a study demonstrated that caregivers aged below 60 years of terminally ill cancer patients, had higher levels of complicated grief pre-death than did those aged 60 years and above [11]; however, another study found that being 61 years or above was a predictor of an increased risk of complicated grief among the bereaved [4]. Additionally, each person's grief reaction would be idiosyncratic, determined by a unique combination of psychological, social, and physiological factors [9]. In addition to assessing the variables of individual family members, we must analyze those describing the family constellation, the family system's functioning, and the impact of the dying patient and his terminal illness on the family [9]. There are various spousal-related factors affecting anticipatory grief. Thus, it is important to understand the aspects of the spousal characteristics that predict anticipatory grief for evidence-based, appropriate assessments and interventions.

Perceived social support significantly correlates with complicated grief pre-death [11]. In addition, the assistance of a family member in differentiating his own needs from those of the patient is a treatment goal of remaining psychologically separate from the patient [8]; additionally, the assessment of the family's needs is an important first step in supporting their anticipatory grief [7] [9]. However, there are limited studies on the spouse's social support needs regarding anticipatory grief. Therefore, we considered it is necessary to explore the spousal characteristics and social support needs predicting anticipatory grief among spouses to provide appropriate care formulated for anticipatory grief and prevent complicated and prolonged grief after the patients' loss.

In a preliminary survey [13], we developed an original tool to assess social support needs of Japanese spouses based on the Social Problem Checklist (SPC) for Japanese patients with cancer [14] [15] to provide specific care related to individual spousal needs. In this study, we employed a novel measure to assess social support needs of spouses. Furthermore, we explored the spousal characteristics and social support needs predicting anticipatory grief in spouses of patients with cancer at the end of life.

2. Methods

2.1. Participants

We administered a self-report questionnaire to 138 spouses of cancer patients between September 6, 2017, and August 7, 2020, at the palliative care and general wards (the department of palliative care) of the Heiwa Hospital and the palliative care ward of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (JFCR). The former is a community-based hospital since 1946 and the latter is Japan's first specialized hospital for cancer. There were no sig-

nificant differences in anticipatory grief among spouses of patients in the two hospitals.

The inclusion criteria were as follows: spouses of cancer patients, prognosis within 6 months until the patients' death as assessed by their doctor, aged 20 to 79 years, able to cooperate with this study as determined by their doctor, capable of completing a questionnaire in Japanese, Japanese, and provided informed consent. The exclusion criteria were as follows: unable to cooperate with this research as determined by their doctor, incapable of filling out a questionnaire in Japanese, not Japanese, having a severe mental illness, and inability to provide informed consent.

Of 138 eligible participants, 111 returned the questionnaire (initial response rate = 80.4%). Of these, 102 spouses were included in the analyses (final response rate = 73.9%) after excluding those who had over 50% missing data on either of the two psychological scales following the recommendation [16]. Subsequently, the mean values of the subscale items that were available were substituted for the remaining missing items [16].

2.2. Procedures

This was a cross-sectional survey. The palliative care doctors (HS/RY/ST/YS/KK/OT) informed the appropriate spouses about this research and inquired if they would be willing to be approached by the first author, who is a researcher, and a clinical psychologist (KA). Subsequently, the first author approached these identified spouses to explain this study's purpose and procedures using verbal and written explanations and obtained their permission to partake using an informed consent form. Furthermore, the first author explained that they could discontinue answering the survey form if they wished.

We designed the survey as "the questionnaire for the spouses' stress and support." Participants were asked to complete a 10- to 30-min anonymous questionnaire at the hospital or their home. They either submitted their answered questionnaires to hospital staff or mailed them to the laboratory of the Liaison Psychiatry and Psycho-oncology Unit of the Tokyo Medical and Dental University.

This study was approved by the Medical Research Ethics Committee of the Tokyo Medical and Dental University (M2017-013), the Heiwa Hospital (20170801), and the Cancer Institute Hospital of the JFCR (0137).

2.3. Measured Items

2.3.1. Demographic and Medical Information (22 Items)

Demographic data (12 items) included the following: hospital ID; spouse's sex; patient's age; spouse's age; relationship with the patient; spousal occupation; spousal educational background; living separately or jointly with the patient; presence or absence of a housemate/housemates other than the patient; familial situation of a housemate/housemates other than the patient; presence or absence of a child/children; and the number and age of children. These data were collected from the questionnaires and patients' case records.

Additional medical information (10 items) comprising the following: primary site of cancer; multiple primary cancers (two cancer sites); previous cancer; previous treatment; treatment status; recurrence/metastasis; ECOG performance status (ECOG: Eastern Cooperative Oncology Group, see Table 1); period between cancer's occurrence and the present time; disclosed prognosis to the spouse; and duration between prognostic disclosure to the spouse and the present time. These data were collected from patients' case records.

2.3.2. Tool to Assess Social Support Needs of Spouses of Patients with Cancer (73 Items)

In our preliminary survey, the tool to examine social support needs of spouses of patients with cancer was a 73-item self-rating scale [13]. This original assessment tool was based on the SPC for Japanese patients with cancer [14] [15].

This measure uses a six-point Likert scale ranging from zero (inapplicable) to one (extremely satisfied), two (solved by myself), three (a little), four (quite a lot), or five (very much); we modified these scores based on our preliminary survey's questionnaire [13] to those corresponding to their word meanings because it was easy for participants to answer in clinical settings. We scored each response category as follows: four (very much), three (quite a lot), two (a little), one (solved by myself, extremely satisfied), or zero (inapplicable).

This scale comprises two domains and five factors: (1) Social support needs regarding the disease and treatment of the patients (54 items): "Medical Condition and Cure" (22 items); "Daily Life and Social Support" (25 items); and "Intimacy and Employment" (7 items). The total score of "social support needs regarding the disease and treatment of the patients" can range from 0 - 216. (2) Social support needs of the spouses (19 items): "Family Psychological Issues and Social Support" (14 items); and "Intimacy, Employment, and Society" (5 items). The total score of "social support needs of the spouses" ranges from 0 - 76. "Social support needs regarding the disease and treatment of the patients" entails spousal social support requirements regarding the patients' illness and treatment. In contrast, "social support needs of the spouses" denotes spouses' social support necessities.

In the present study, Cronbach's alpha coefficients for social support needs regarding the disease and treatment of the patients and social support needs of the spouses were 0.96 (0.89 - 0.96 for the subscales) and 0.88 (0.70 - 0.90 for the subscales), respectively.

2.3.3. Anticipatory Grief Scale for Family Caregivers (19 Items)

We used the 19-item Anticipatory Grief Scale for Family Caregivers (AGSFC) [17] to assess participants' anticipatory grief. We chose this scale because it is useful for Japanese families of terminally ill cancer patients; furthermore, the small number of items is less demanding for participants. Additionally, its reliability (Cronbach's alpha: 0.87 (0.70 - 0.85 for the subscales)) as well as the criterion-related and construct validity were confirmed.

The AGSFC has four factors: spiritual pain in preparing for a loss (6 items),

physical and mental fatigability in daily life (6 items), precedent anxiety regarding bereavement (4 items), and exhaustion (3 items). Subscale items are rated on four-point Likert scales, ranging from zero (not at all) to one (a little), two (quite a lot), or three (very much); the total score ranges from 0 to 57. Higher scores indicate more severe levels of anticipatory grief. Cutoff points were as follows: below 25 (not severe), 25 to 34 (somewhat severe), and 35 and above (severe). In a previous study, these cutoff points were based on the distribution curve of the scores by comparing families of patients with terminal and non-terminal diseases [17]. In the present study, Cronbach's alpha coefficient was 0.90 (0.76 - 0.81 for the subscales).

2.4. Statistical Analysis

The demographic and clinical characteristics of participants and the study variables were summarized using descriptive statistics (**Table 1** and **Table 2**, respectively). The characteristics and social support needs predicting anticipatory grief were assessed using simple and multiple regression analyses (**Table 3** and **Table 4**, respectively).

In these analyses, the following variables were represented by dummy-coded variables: hospital ID (the Heiwa Hospital = 1, the Cancer Institute Hospital of the JFCR = 0); spousal sex (male = 1, female = 0); primary site of cancer (e.g., having gastrointestinal cancer = 1, not having gastrointestinal cancer = 0); multiple primary cancers (yes = 1, no = 0); having had a previous cancer/cancers (yes = 1, no = 0); the content of previous cancer (e.g., having gastrointestinal cancer = 1, not having gastrointestinal cancer = 0); previous treatment (e.g., receiving chemotherapy = 1, not receiving chemotherapy[1] = 0); treatment status (e.g., being under treatment = 1, not being under treatment = 0); recurrence/metastasis (yes = 1, no = 0); ECOG performance status (PS) (see **Table 1**) (e.g., being PS 1 and 2 = 1, not being PS 1 and 2 = 0); period between cancer's occurrence and the present time (e.g., under three years = 1, three years and more = 0); disclosed prognosis to the spouse (e.g., two weeks or less = 1, over two weeks and uninformed = 0); period between prognostic disclosure to the spouse and the present time (e.g., under two weeks = 1, two weeks or more and uninformed = 0); having a child/children (yes = 1, no = 0); the number of children (e.g., having only one child = 1, having two or three children and not having any children = 0); children's age (e.g., aged under 20 s = 1, aged 20 years or more = 0); having a housemate/housemates other than the patient (yes = 1, no = 0); familial situation of a housemate/housemates other than the patient (e.g., living with a child/children = 1, not living with a child/children = 0); spousal occupation (e.g., having a full-time job = 1, not having a full-time job = 0); and spousal education (e.g., junior high school graduate = 1, not a junior high school graduate = 0).

All the data were statistically analyzed using SPSS version 23.0 (IBM, Armonk, NY, USA).

[1]Not receiving chemotherapy: Patients who have not received chemotherapy have received other treatments (surgery, radiation, and other pharmacotherapies) or have not received any treatment (no treatment).

3. Results

3.1. Demographic and Medical Information of Participants

We distributed the questionnaires to 138 participants and analyzed 102 that were answered and returned (valid response rate = 73.9%). Table 1 shows their demographic and clinical characteristics.

There were 58 (56.9%) and 44 (43.1%) spouses in the Heiwa Hospital and the Cancer Institute Hospital of the JFCR, respectively. About one-quarter of them were males (n = 26, 25.5%). The mean ages of patients and spouses were 68.3 years (range 40 - 83) and 66.3 years (range 40 - 79), respectively. Patients were divided into the following age groups: 40 s and 50 s (n = 17, 16.7%), 60 s (n = 30, 29.4%), 70 s (n = 48, 47.1%), and 80 s (n = 7, 6.9%). Furthermore, spouses were divided into the following age groups: 40 s and 50 s (n = 18, 17.6%), 60 s (n = 45, 44.1%), and 70 s (n = 39, 38.2%).

Current cancers were divided into primary site of cancer (n = 96, 94.1%) and multiple primary cancers (two cancer sites) (n = 6, 5.9%). The former comprised gastrointestinal (n = 27, 26.5%), hepatobiliary and pancreatic (n = 21, 20.6%), thoracic (n = 17, 16.7%), female-specific (n = 15, 14.7%), head and neck (n = 6, 5.9%), and other cancers (n = 10, 9.8%).

Only 17 (16.7%) of spouses whose patients had previous cancers, divided into gastrointestinal (n = 12, 11.8%) and other cancers (n = 9, 8.8%).

Previous treatments included surgery (n = 59, 57.8%), chemotherapy (n = 90, 88.2%), radiation (n = 40, 39.2%), and other pharmacotherapies including hormone therapy and immunotherapy (n = 16, 15.7%). There were some untreated cases (n = 3, 2.9%). The treatment status of nearly all patients was completed and discontinued (n = 100, 98.0%), except for those who were under treatment (n = 2, 2.0%).

Overall, 92.2% of patients (n = 94) had recurrence/metastasis and 85.3% (n = 87) were PS3 and over on ECOG performance status (PS, see Table 1). Moreover, for approximately 60% of patients, the period between cancer's occurrence and the present time was under 3 years (n = 62, 60.8%).

During this survey, the disclosed prognosis to 83.3% of the spouses divided into 2 weeks or under (n = 36, 35.3%) and 1 - 3 months (n = 49, 48.0%); only 11 (10.8%) were uninformed. For over 60% of participants, the period between prognostic disclosure to the spouse and the present time was under 2 weeks (n = 63, 61.8%).

Furthermore, 88.2% of spouses (n = 90) had a child or children, while 56.9% (n = 58) had two. Children were divided into the following age groups: below 20 years (n = 7, 6.9%); 20 s and 30 s (n = 56, 54.9%); 40 s and 50 s (n = 52, 51.0%), and no answer (n = 1, 1.0%). All participants lived together with the patients (n = 102, 100.0%) and 42.2% (n = 43) had a housemate or housemates other than the patient. Additionally, 37.3% (n = 38) resided with their child or children; 34.3% (n = 35) and 38.2% (n = 39) were full- or part-time employees and homemakers, respectively. Half (50.0%) of all participants (n = 51) were high school graduates.

Table 1. Demographic and clinical characteristics of participants (n = 102).

Variables	Means (SD) or numbers (%)
Hospital	
Heiwa Hospital	58 (56.9%)
Cancer Institute Hospital of JFCR	44 (43.1%)
Male spouse	26 (25.5%)
Patient age (y), Mean (SD), [Min - Max]	68.3 (8.6), [40-83]
40 s and 50 s	17 (16.7%)
60 s	30 (29.4%)
70 s	48 (47.1%)
80 s	7 (6.9%)
Spouse age (y), Mean (SD), [Min - Max]	66.3 (7.8), [40-79]
40 s and 50 s	18 (17.6%)
60 s	45 (44.1%)
70 s	39 (38.2%)
Current cancer	
Primary site of cancer[1] (without multiple primary cancers)	96 (94.1%)
Gastrointestinal cancer[2]	27 (26.5%)
Hepatobiliary and pancreatic cancer[3]	21 (20.6%)
Thoracic cancer[4]	17 (16.7%)
Female-specific cancer[5]	15 (14.7%)
Head and neck cancer[6]	6 (5.9%)
Other cancers[7]	10 (9.8%)
Multiple primary cancers (multiple answers)	6 (5.9%)
Previous cancer[1] (multiple answers)	17 (16.7%)
Gastrointestinal cancer[8]	12 (11.8%)
Other cancers[9]	9 (8.8%)
Previous Treatment (multiple answers)	
Surgery	59 (57.8%)
Chemotherapy	90 (88.2%)
Radiation	40 (39.2%)
Other pharmacotherapies[10]	16 (15.7%)
No treatment	3 (2.9%)
Treatment Status	
Under treatment	2 (2.0%)
Treatment completed and stopped	100 (98.0%)

Continued

Recurrence/metastasis	
Yes	94 (92.2%)
ECOG Performance status[11]	
PS 0	0 (0.0%)
PS 1 and 2	15 (14.7%)
PS 3	37 (36.3%)
PS 4	50 (49.0%)
Period between occurrence of cancer and the present time	
Under 3 years	62 (60.8%)
At least 3 but less than 6 years	21 (20.6%)
6 years and over	19 (18.6%)
Disclosed prognosis to the spouse	
2 weeks or under	36 (35.3%)
1 month - 3 months	49 (48.0%)
4 - 6 months	6 (5.9%)
Uninformed	11 (10.8%)
Period between prognostic disclosure to the spouse and the present time	
Under 2 weeks	63 (61.8%)
At least 2 weeks but less than 3 months	21 (20.6%)
3 months and over	7 (6.9%)
Uninformed	11 (10.8%)
Child/Children	
Yes	90 (88.2%)
Number of children	
N = 0	12 (11.8%)
N = 1	17 (16.7%)
N = 2	58 (56.9%)
N = 3	15 (14.7%)
Children's ages (y) (multiple answers)	
Under 20 s	7 (6.9%)
20 s and 30 s	56 (54.9%)
40 s and 50 s	52 (51.0%)
No answer	1 (1.0%)
Living together with a patient	102 (100.0%)
Housemate other than a patient (multiple answers)	43 (42.2%)

Continued

Child/Children	38 (37.3%)
Grandchild/Grandchildren	7 (6.9%)
Others[12]	9 (8.8%)
Spouse's occupation	
Full time job	19 (18.6%)
Part time job	16 (15.7%)
Homemaker	39 (38.2%)
Retirement[13]	12 (11.8%)
Unemployed	6 (5.9%)
Others[14]	10 (9.8%)
Spouse's education	
Junior high school	5 (4.9%)
High school	51 (50.0%)
Vocational school and junior college	26 (25.5%)
Higher than a college degree	18 (17.6%)
No answer	2 (2.0%)

[1]Cancer categorization based on the website of Division of Cancer Information Service of Center for Cancer Control and Information Services of National Cancer Center Japan [18].
[2]Stomach cancer, esophagus cancer, colon cancer, and duodenal carcinoma.
[3]Liver cancer, bile duct cancer, gallbladder cancer, and pancreas cancer.
[4]Lung cancer.
[5]Breast cancer, uterine cancer, ovarian cancer, and fallopian tube cancer.
[6]Larynx cancer, carcinoma of gingiva, parotid gland cancer, and pharyngeal cancer.
[7]Bladder cancer, kidney cancer, prostate cancer, retroperitoneal sarcoma, peritoneal cancer, and brain cancer.
[8]Stomach cancer, esophagus cancer, colon cancer, or any combination of these.
[9]Prostate cancer, liver cancer, breast cancer, uterine cancer, ovarian cancer, bladder cancer, kidney cancer, thyroid cancer, lung cancer, or any combination of these.
[10]Hormone therapy and immunotherapy.
[11]ECOG: Eastern Cooperative Oncology Group.
ECOG Performance status (PS) scores [19] [20] [21]:
PS 0: Fully active, able to carry on all pre-disease performance without restriction.
PS 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
PS 2: Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3: Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
PS 4: Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
[12]Patient and spouse's parents, patient and spouse's grandparents, patient and spouse's siblings, and child-in-law.
[13]Retirement because of spouse's own request for patient's disease, mandatory age, and retirement from part time job.
[14]Taking a leave of absence from work due to patient's disease and other occupations (e.g., independent business, personal business, and real estate).

3.2. Descriptive Statistics for Study Variables

Table 2 shows the descriptive statistics of the psychosocial scales of the sample. Regarding the AGSFC, 34.31% (n = 35) of spouses' scores indicated high anticipatory grief.

Table 2. Descriptive statistics for study variables (n = 102).

Variables	Means (SD) or numbers (%)	Cronbach's alpha
Tool to assess social support needs of spouses of patients with cancer		
Social support needs regarding the disease and treatment of the patients	76.90 (39.61)	0.96
Medical condition and cure	39.99 (21.64)	0.96
Daily life and social support	34.69 (19.23)	0.92
Intimacy and employment	2.22 (4.95)	0.89
Social support needs of the spouses	17.21 (10.67)	0.88
Family psychological issues and social support	16.80 (10.32)	0.90
Intimacy, employment, and society	0.40 (1.32)	0.70
Anticipatory Grief Scale for Family Caregivers (AGSFC)	28.99 (11.36)	0.90
Spiritual pain in preparing for a loss	11.55 (4.36)	0.80
Physical and mental fatigability in daily life	6.83 (4.16)	0.81
Precedent anxiety regarding bereavement	6.68 (3.19)	0.80
Exhaustion	3.92 (2.49)	0.76
AGSFC high (≥35), n (%)	35 (34.31%)	
AGSFC middle (25 to 34), n (%)	33 (32.35%)	
AGSFC low (<25), n (%)	34 (33.33%)	

3.3. Simple and Multiple Regression Analyses for Variables Predicting Anticipatory Grief

Table 3 and Table 4 present the results of the simple and multiple regression analyses, respectively. The latter were conducted simultaneously to assess significant variables predicting anticipatory grief.

We employed simple regression analyses to determine the significant independent variables with respect to AGSFC total score as the dependent variable for the

multiple regression analysis. Demographic and clinical characteristics of participants, total score of "social support needs regarding the disease and treatment of the patients," subscale scores ("medical condition and cure," "daily life and social support," and "intimacy and employment"), total score of "social support needs of the spouses," and subscale scores ("family psychological issues and social support" and "intimacy, employment, and society") were entered into the simple regression analyses with AGSFC total score as the dependent variable. Among the independent variables, patient age, chemotherapy, no treatment, ECOG PS3 in patients, children aged under 20 years, total score of "social support needs regarding the disease and treatment of the patients" and subscale scores ("medical condition and cure," "daily life and social support," and "intimacy and employment"), and total score of "social support needs of the spouses" and subscale scores ("family psychological issues and social support" and "intimacy, employment, and society") were significant variables with respect to AGSFC total score for the multiple regression analysis (all $p < 0.05$; **Table 3**).

Table 4 displays the result of the multiple regression models for the independent variables predicting anticipatory grief. We conducted simultaneous multiple regression analyses to examine the significant independent variables predicting spousal AGSFC total score as the dependent variable. Multicollinearity was not a problem as all independent variables in Models 1 and 2 had $|r| < 0.9$ and VIF < 10 [22].

First, to explore the spousal characteristics and total scores of social support needs predicting anticipatory grief, patient age, chemotherapy, no treatment, ECOG PS3 in patients, children aged below 20 years, total score of "social support needs regarding the disease and treatment of the patients," and overall score of "social support needs of the spouses" were entered simultaneously into the multiple regression analysis with AGSFC total score as the dependent variable. Among the independent variables, chemotherapy and total score of "social support needs of the spouses" significantly predicted the value of AGSFC total score (both $p < 0.05$). This model accounted for an adjusted value of 37% of the variance in spousal AGSFC total score (Model 1, **Table 4**).

Second, to examine the spousal characteristics and subscale scores of social support needs predicting anticipatory grief, patient age, chemotherapy, no treatment, ECOG PS3 in patients, children aged under 20 years, and subscale scores of "social support needs regarding the disease and treatment of the patients" ("medical condition and cure," "daily life and social support," and "intimacy and employment") and "social support needs of the spouses" ("family psychological issues and social support" and "intimacy, employment, and society") were entered simultaneously into the multiple regression analysis with AGSFC total score as the dependent variable. Among the independent variables, "family psychological issues and social support" significantly predicted the value of AGSFC total score ($p < 0.05$), in which this model accounted for an adjusted value of 35% of the variance in spousal AGSFC total score (Model 2, **Table 4**).

Table 3. Summary of simple regression analyses for variables predicting anticipatory grief (n = 102).

Variables	B (95% CI)		R^2	*p*
Patient's age	−0.28	(−0.53, −0.02)	0.04	0.037*
Previous Treatment				
Surgery	1.09	(−3.45, 5.62)	0.00	0.635
Chemotherapy	−9.06	(−15.78, −2.34)	0.07	0.009*
Radiation	−2.57	(−7.14, 1.99)	0.01	0.266
Other pharmacotherapies[a]	1.00	(−5.16, 7.16)	0.00	0.748
No treatment	13.34	(0.33, 26.34)	0.04	0.045*
ECOG Performance status				
PS 1 and 2	−6.04	(−12.25, 0.18)	0.04	0.057
PS 3	5.25	(0.70, 9.79)	0.05	0.024*
PS 4	−1.82	(−6.29, 2.65)	0.01	0.421
Children's ages				
Under 20 s[b]	9.97	(1.28, 18.66)	0.05	0.025*
20 s and 30 s[b]	−1.34	(−5.89, 3.21)	0.00	0.561
40 s and 50 s[b]	−3.76	(−8.23, 0.71)	0.03	0.098
Social support needs regarding the disease and treatment of the patients	0.15	(0.10, 0.20)	0.27	<0.001*
Medical condition and cure	0.20	(0.11, 0.30)	0.15	<0.001*
Daily life and social support	0.32	(0.22, 0.42)	0.30	<0.001*
Intimacy and employment	0.74	(0.31, 1.17)	0.10	0.001*
Social support needs of the spouses	0.61	(0.43, 0.78)	0.32	<0.001*
Family psychological issues and social support	0.61	(0.43, 0.79)	0.31	<0.001*
Intimacy, employment, and society	2.24	(0.59, 3.88)	0.07	0.008*

*$p < 0.05$. [a]Hormone therapy and immunotherapy; [b]n = 101.

Table 4. Models of multiple regression analyses for variables predicting anticipatory grief (n = 101).

Variables	B (95% CI)		*β*	Adjusted R^2	*p*
Model 1					
Patient's age	−0.05	(−0.31, 0.22)	−0.03	0.37	0.741
Chemotherapy	−6.91	(−13.49, −0.33)	−0.20		0.040*
No treatment	2.11	(−10.11, 14.32)	0.03		0.733
ECOG PS3	3.12	(−0.70, 6.93)	0.13		0.109

Continued

Children's age: under 20 s	4.28	(−4.56, 13.12)	0.10		0.339
Social support needs regarding the disease and treatment of the patients	0.03	(−0.04, 0.10)	0.10		0.441
Social support needs of the spouses	0.46	(0.20, 0.72)	0.43		0.001*
Model 2					
Patient's age	−0.04	(−0.31, 0.24)	−0.03		0.787
Chemotherapy	−6.66	(−13.45, 0.14)	−0.19		0.055
No treatment	3.31	(−9.36, 15.98)	0.05		0.605
ECOG PS3	3.26	(−0.61, 7.13)	0.14		0.098
Children's age: under 20 s	2.66	(−7.91, 13.22)	0.06		0.618
Medical condition and cure	0.02	(−0.10, 0.14)	0.04	0.35	0.762
Daily life and social support	0.00	(−0.21, 0.21)	0.00		0.999
Intimacy and employment	0.26	(−0.22, 0.74)	0.11		0.292
Family psychological issues and social support	0.49	(0.16, 0.81)	0.44		0.004*
Intimacy, employment, and society	0.51	(−1.35, 2.38)	0.06		0.588

*$p < 0.05$.

4. Discussion

This study suggested that patients having no experience of "chemotherapy" and higher "social support needs of the spouses" in Model 1, and greater spouses' needs for "family psychological issues and social support" in Model 2 significantly predicted severe anticipatory grief among participants. To the best of our knowledge, it is the first demonstration of the association between patients' experience of chemotherapy and spousal anticipatory grief. Furthermore, spouses' own social support needs predicted spousal anticipatory grief at the end of life.

First, in Model 1, the data suggested that "chemotherapy," as patients' previous treatment, was a significant predictor for participants' anticipatory grief. Although there was no significant association between the two variables in Model 2, chemotherapy might have potentially predicted spousal anticipatory grief. Significant association between the two variables "chemotherapy" and "anticipatory grief" was observed in Model 1 and the B coefficient (partial regression coefficient) of "chemotherapy" in Model 2 was clinically meaningful (B = −6.66). Additionally, its p value was 0.055, which was close to the significant p value 0.05 in Model 2. We therefore considered this finding from the following two possible perspectives: "communication with the multidisciplinary team during chemotherapy" and "spousal fulfillment and regret."

In the first perspective, the spouses of those cancer patients having previous experiences of chemotherapy might have opportunities to consult the multidisciplinary chemotherapy staff regarding the treatment's side-effects and mental strain more than the spouses of those who did not undergo chemotherapy. Recently, the multidisciplinary team approach is advocated in cancer practice, including treatment decision-making [23] [24], adverse event management [24], and psychological intervention [23]. Specifically, this method during chemotherapy has become prevalent in Japan [25] [26]. Moreover, good communication with the multidisciplinary team during chemotherapy might reduce patients' anxiety toward the process. Another study showed that effective communication with doctors and nurses promotes chemotherapy utilization, for example, decision-making to undergo chemotherapy and dispelling negative expectations of the process of chemotherapy in patients with breast cancer [27]. However, poor communication with physicians proved to be a barrier [27]. These communications might affect not only the patients, but also their spouses. Consequently, good communication of the chemotherapy multidisciplinary team with patients and spouses might alleviate the latter's anticipatory grief during the terminal period.

In the second possible perspective, the previous experience of chemotherapy of patients with cancer might promote their spouses' fulfillment and reduce regret. Because they felt confident and had a sense of control regarding caregiving, did their best for patients by making them receive a standard cancer treatment, participated in decision-making regarding whether patients should undergo chemotherapy, and supported the process of chemotherapy including its side-effects and patients' daily life. Caregivers' confidence increased in recognizing and addressing the important side-effects at the mid-point of chemotherapy [28]; furthermore, the caregiving process became a routine or a second nature for them until the completion of chemotherapy [28]. By the mid-point of chemotherapy, for some caregivers, the treatment's routine and the familiarity of the associated symptom patterns reduced their uncertainty [28]. Although caregiving and the demands of patients' treatment remained unremitting, understanding the happenings provided a sense of control [28]. Additionally, strong promoters of chemotherapy use had family support (e.g., spousal participation in decision-making regarding undergoing chemotherapy or insisting the patient do so) and patients' positive attitudes about and perceptions of the effects and benefits of chemotherapy (e.g., the reality of undergoing chemotherapy was better than that expected) [27]. Therefore, spouses might have less regret at the patients' end of life because they could join and support essential decision-making processes when the latter choose to receive chemotherapy; further, they may find it easier to provide care than expected. Another study reported that bereaved caregivers of patients with advanced cancers experience gratitude, fulfillment, and peace from spending time with the latter and knowing that they were doing their best for them [29]. This positive experience of caregivers with patients transitioned from the active cancer treatment to the end of life [29]. It may apply to those spouses whose pa-

tients underwent chemotherapy because they could overcome a critical treatment period together while doing their best for them. This experience might reduce spousal regret as a reaction of anticipatory grief at the patients' terminal period. Barriers to chemotherapy use, however, include excessive information and that anxiety interfering with patients' ability to read materials about cancer, troublesome feelings experienced on obtaining information about chemotherapy from other cancer patients, and negative perception of the process based on family and other patients' illness experiences and historical background [27]. Risk factors associated with refusal of anti-cancer treatments including surgery, chemotherapy, radiation, or any combination of these were old age, low educational status, less weight, and poor performance status in lung cancer [30]. Characteristics associated with being untreated included advanced age, Black race, unmarried status, and insufficient private insurance for head and neck cancer [31]. Median survival for untreated patients across the cohort was 12 months, as compared to 100 months for treated patients in head and neck cancers [31]. Many factors might be related to untreated and refusal of anti-cancer treatments. Although there was no significant association between patients' being "untreated" and spousal anticipatory grief in our multiple regression models, spouses of patients who have not received chemotherapy may be more susceptible to regret than those of patients who have undergone it. This response may be because they were unable to convince patients to undergo this standard cancer treatment; additionally, it may be exacerbated by the fact that they could not participate in the decision-making process regarding the prognosis when patients intentionally refused chemotherapy. Further, this remorse may be associated with the decreased survival period of untreated patients. Moreover, when patients' physical conditions became exceedingly severe, resulting in an inability to receive chemotherapy, their spouses might blame themselves for failing to notice the patients' cancer symptoms sooner, and for financial unpreparedness and not having insurance for patients' treatment. Burnell and Burnell (1989) explained these emotional reactions to bereavement as "guilt" [7]. They mentioned that the survivor might feel remorseful for not taking certain crucial precautionary measures that could have prevented the death [7]. Guilt and self-reproach are normal grief feelings [32]. However, the level of guilt predicted complicated grief and depression later in bereavement [33]; the bereavement-related guilt had a closer association with complicated grief than depression [33]. "Regret," a similar reaction, may also be a unique marker of difficulties in the grieving process [34]. It is likely, therefore, that spouses of patients who have not undergone chemotherapy might feel a higher level of anticipatory grief than those of patients who have received it. Future research should assess the factors of patients' experience/no experience of chemotherapy that predict spousal anticipatory grief. Additionally, future studies should investigate the associations between the frequency and satisfaction of communication with medical staff during chemotherapy, spouses' positive experiences during chemotherapy (e.g., confidence and fulfillment of caregiving), their regret about patients' not having experience of

chemotherapy, and spousal anticipatory grief during the patients' terminal stage. For clinical implications, the viewpoint of patients having no experience of chemotherapy as a risk factor of spousal anticipatory grief is remarkable for medical staff. The medical team should explore the background of patients' not having experience of chemotherapy and pay attention to both positive and negative sides of spouses' experience/no experience regarding past patients chemotherapy when they listen to spousal caregiving description during the treatment period.

The multiple regression analyses represented the following: "social support needs of the spouses" in Model 1 and "family psychological issues and social support" in Model 2 may predict anticipatory grief significantly among spouses of patients with cancer at the terminal period. These results are analogous to those of previous studies suggesting that spousal psychosocial needs might promote greater levels of poor health themselves and that caregivers psychosocial issues tend to increase especially near the patients' terminal period. For example, a study explained that caregivers with significant unmet psychosocial needs were more likely to be those in poor health and to be caring for a patient who had reached the palliative care only stage [35]. In another study, more caregivers were depressed and had a higher level of perceived burden at the start of the terminal period compared to the start of the palliative care period [36]. In our original tool to assess social support needs of spouses of patients with cancer [13], the subscale items of "family psychological issues and social support" from "social support needs of the spouses" included: self-coping and information to deal with spouse's anxiety and depression; relationship and communication with people around the spouse; feeling burdened and isolated; support for spousal psychological issues from medical staff; advice regarding the patient's disease and medical treatment life; taking care of house chores; performing spousal responsibilities in the house; enjoying hobbies, recreations, and social activities; and excessive concerns about the spouse by the patient. Studies reported similar unmet psychosocial needs with our subscale items that were associated with caregivers' psychological distress and burden. For example, greater caregivers' emotional distress was associated with their higher unmet needs in the domains of healthcare service and information, as well as emotional and psychological needs [37]. Higher anxiety in caregivers was related to their higher unmet needs in two domains, that is, emotional and psychological needs and communication and family needs [37]. Caregivers' greater fatigue was linked to their higher information needs and healthcare professional/service needs [38]. Furthermore, caregivers' greater sleep disturbance was associated with their greater overall caregiving, daily living, and psychological/emotional needs [38]. These findings from previous studies support our results. Regarding the AGSFC's items [17], anticipatory grief includes psychological distress and burden among caregivers (spiritual pain in preparing for a loss, physical and mental fatigability in daily life, precedent anxiety regarding bereavement, and exhaustion). Hence, with

their own psychological and social support needs, they tend to have higher anticipatory grief at the end of the patients' life. The death of a spouse is the most stressful life event [1]. Therefore, spouses may have the highest psychological and physical needs among caregivers; moreover, they focus on dealing with patients' needs rather than their own. Regarding social support needs, most studies found that those who do not cope appropriately with bereavement have inadequate or conflicted social support [32]; further, an extended grieving alienates the social network [32]. Consequently, spouses' own higher social support needs might affect their severe anticipatory grief.

These findings are meaningful for clinical settings because they indicate that medical staff should pay greater attention to psychological and social support needs to reduce anticipatory grief of spouses of terminal cancer patients. For example, to support spousal unmet needs regarding family psychological issues and social support, we should assess these needs (e.g., whether or not spouses have a person and a place to share their feelings and experiences). Additionally, spouses should be offered consultations with clinical psychologists and psychiatrists, opportunities to access to doctors and nurses who listen to their emotions and experiences and offer guidance and support, information on brief relaxation techniques (e.g., breathing method, autogenic therapy, and mindfulness), and recommendations for respite hospitalization and spouses' own rest time. Spouses should be referred to the Cancer Counseling and Support Center and to peer support groups for the family, and offered advice on social welfare services (e.g., domestic helpers) by medical social workers. These approaches might be helpful for spouses' anticipatory grief as well. However, caregivers have higher unmet needs than patients [35] [39]. Further, family caregivers' needs pertaining to their relatives' cancer prevail for many years after the latter's death, and continued to breed the bereaved family members' suffering [40]. Therefore, the unmet needs' assessment among spouses of patients with cancer before their demise is especially important to prevent the former's continuous, complicated, and prolonged grief after the patients' death. In our previous study [13], using an online survey, we described the social support needs of 559 spouses of patients, mostly in their early cancer stage (e.g., 41.7% were undergoing treatment, 24.3% had recurrence/metastasis, and 57.6% were in ECOG PS0). Our results emphasize the social support needs of spouses of patients at their terminal stage in clinical settings to explore the effect on anticipatory grief using an original tool. We need, however, to modify this measure to make it easier and accessible for spouses. Our findings suggest that medical staff should pay attention to spouses who have a greater number of or more severe risk factors (patients having no experience of chemotherapy, social support needs of the spouses, and spousal needs for family psychological issues and social support). Their needs should be assessed carefully and adequate care should be provided for each need to alleviate anticipatory grief when medical staff meet spouses. It is hoped that these preventive viewpoints and approaches regarding anticipatory grief might help to

reduce complicated and prolonged grief of spouses after the patients' demise.

This study has several limitations. First, palliative care doctors recruited participants for whom they provided care in palliative care settings. It creates the possibility of sampling bias. Samples of participants whose patients are under cancer treatment in general wards and take palliative care in home care are needed in future research. Second, there may be additional sampling bias regarding the levels of anticipatory grief within our sample. Although 34.31% (n = 35) of participants scored high on anticipatory grief, spouses having extremely severe anticipatory grief might not have participated in this study. Furthermore, samples including the spouses of younger patients who were in their 20 s and 30 s, younger spouses who were in their 20 s and 30 s, and more male spouses are needed in future research. Nevertheless, this study found no significant differences between males and females on anticipatory grief. Third, there may be confounding factors in the association between "chemotherapy" and "anticipatory grief" as independent and dependent variables, respectively. Therefore, confounding factors in the independent variables would be needed to explore the relationship between the two. Regarding confounding factors, for example, the frequency and satisfaction level of communication with medical staff during chemotherapy, trust or distrust of the medical treatment, the level of cognitive function of patients and spouses to understand chemotherapy, the existence of disease complications and comorbidity, the stage of cancer at diagnosis, the level of family cohesiveness, conjugal attachment, marital quality, family finances, utilization of cancer insurance, and the frequency and satisfaction of access to peer support for patients and spouses during chemotherapy should be considered to examine the link between "chemotherapy" and "anticipatory grief" in future research. Fourth, we were unable to assess the background of patients' experience/no experience of chemotherapy that predicted spousal anticipatory grief in this research. Future studies should evaluate these aspects and the association between the risk factors (e.g., the frequency and satisfaction of communication with medical staff during chemotherapy, spouses' positive experiences during chemotherapy, and their regret about patients' not having experience of chemotherapy) and anticipatory grief at the terminal stage among spouses of patients with cancer. Fifth, the two models did not account for the adjusted values (adjusted R^2) of the variances' high percentage because there might be possibility of other more effective factors to affect anticipatory grief. Additional factors (independent variables), such as spouses' psychological distress and traits (e.g., anxiety and depression), quality of life, past psychiatric history, previous cancer experience, and satisfaction level and positive experience regarding medical staff's support in the prior and present hospitals may be related to anticipatory grief, and these factors are needed to enhance the adjusted values (adjusted R^2) of the models in future research. Furthermore, the tool used to assess social support needs of spouses includes negative sentences (e.g., insufficient information regarding how to take care of the patient from now on) and is lengthy (73 items)

[13]; hence, it should be revised for ease of administration. Finally, this scale is unstandardized [13]; however, its content validity was confirmed in multidisciplinary meetings [13]. Therefore, the results of this study should be interpreted with caution. Despite these limitations, this study is significant as it examined the characteristics and social support needs predicting anticipatory grief in the spouses of patients with cancer at the end of life in Japan. In future research, more representative clinical data should be collected for further validation of the outcomes of this study. Qualitative data using semi-structured interviews to obtain spouses' opinions of this tool would be useful to develop it. Additionally, it would help in describing the details of spousal social support needs predicting anticipatory grief to shed light on the findings of this study.

5. Conclusion

We found that patients having no experience of "chemotherapy" and higher "social support needs of the spouses" in Model 1, and greater spouses' needs for "family psychological issues and social support" in Model 2 were significant predictors of severe anticipatory grief among participants. These results suggested that medical staff should pay more attention to spouses who show these risk factors, assess their needs regarding psychological issues and social support carefully, and provide adequate care for each of the social support needs to alleviate anticipatory grief. Additionally, the perspective of patients having no experience of chemotherapy as a risk factor of spousal anticipatory grief was remarkable. Medical staff should explore the background of patients' not having experience of chemotherapy and concentrate on both positive and negative sides of spouses' experience/no experience regarding previous patient chemotherapy when listening to their caregiving descriptions during the treatment period. The next step would be to develop a tool to assess social support needs of spouses of patients with cancer for ease of administration in clinical settings and to describe the details of spousal social support needs predict anticipatory grief in further research. Although this study had several limitations, our findings have important implications. To the best of our knowledge, this is the first study to reveal that patients having no experience of "chemotherapy" and spouses' own social support needs predict spousal anticipatory grief. These preventive perspectives and approaches for anticipatory grief might help spouses as well as medical staff in clinical settings. They will potentially facilitate the prevention of complicated and prolonged grief after the patients' death.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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The Sarandria Score—Discussion of a New Scoring System in Clinical Medical Oncology

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Abstract

This paper focuses on discussing a novel scoring for stage III rectal cancer patients and all the challenges in creating and developing a clinical score. **Background:** It is fundamental in my opinion to give space to new generations of scientists, medical doctors and researchers to study and, backed with evidence-based information, improve the current knowledge of clinical medical science. It is fundamental for result obtained by medical researchers to bring their findings to the scientific community. Every scientific finding is of vital importance. In this essay a new Clinical Scoring system, the Sarandria Score, developed by myself is discussed, together with the methods and path in order for a young medical researcher with an idea to bring it to the scientific community. **Main topics:** Colorectal Cancer (CRC) is a major public health problem, representing the third most commonly diagnosed cancer in males and the second in females. Various studies have reported relevant differences related to CRC primary location site (right-sided colon, left-sided colon, rectum) including response to adjuvant chemotherapy and prognosis. In stage III CRC patients, previous findings showed that higher density of tumor-associated neutrophils (TANs) was associated with better response to 5-FU-based chemotherapy. Novel findings were discovered by Dr Nicola Sarandria on the role of neutrophils in rectal cancer, which include different factors which point to an anti-tumoral role of neutrophils in rectal cancer when in presence of chemotherapeutic agents (5-fluorouracil). The clinical significance of TANs was assessed and whether it can be different depended on the location of the primary CRC (right-sided colon, left-sided colon, rectum). **Conclusions:** This essay officially discusses a new clinical prognostic and predictive scoring (Sarandria Score) involving intratumoral neutrophilic infiltration in rectal cancer and the possibility of a new inclusion criteria based on this infiltrate for Stage III rectal cancer patients treated with 5-FU therapy. This paper includes data published on my medical degree thesis and in a previous review (on Journal of Cancer Therapy) showing that higher le-

vels of TANs densities were associated with better disease-free survival (DFS) in 5-FU treated patients affected by rectal cancer (while it was inversely related in patients without 5-FU therapy). This was also as further evidence in support possible conceptual division of what is now known as Colorectal cancer into Colon and Rectal cancer.

Keywords

New Clinical Score, Sarandria Score, Methodology, Rectal Cancer, Neutrophils, 5-Fluorouracil, Neutrophils and Cancer, Colorectal Cancer

1. Background

In the following section I will describe the way I came up with this scoring system (as discussed in my previous publication) [1]. The following data and tables of this "Background section" were first described in my medical graduation thesis and then in my review published last year [1]. In my years at Humanitas University as a medical student, I created one hypothesis and a research objective: to see whether TANs intratumoral (IT) density in Colorectal Cancer has different prognostic and/or predictive value according to tumor primary site location—left colon, right colon and rectum—and whether it differs according to presence or not of adjuvant chemotherapy—5-FU. My hypothesis was that neutrophils (of the N1 polarization) could indeed help the prognosis of the patient under 5-FU (also in accordance with the different publications showing neutrophilic role in the 5-FU action and therapeutic cycle). In the following text I will describe my research and findings (as published in my thesis).

The study type was a retrospective one—a study that compares two groups of people: those with the disease or condition under study (cases) and a very similar group of people who do not have the disease or condition (controls)—(cancer.gov definition of retrospective study) with the focus of finding a correlation between IT PMN in CRC and predictive or prognostic values. The study attempted to correlate polymorphonuclear neutrophil (PMN) tumoral infiltration (TANs) with CRC site—in the presence or absence of adjuvant therapy. It was inquired whether CRC site—whether it was right-sided, left-sided or rectal—had any effect on TANs density (intratumoral density) and whether these densities had any kind of prognostic value—be it in presence of adjuvant therapy or without any adjuvant therapy. According to previous publications, it was revealed that TANs were correlated with positive prognosis when the patients (pts), with Stage III CRC, underwent 5-fluorouracil as adjuvant therapy [2]. Also, it has been revealed that low TANs density in Stage II CRC, could be an index for adjuvant chemotherapy usage. This study focuses on finding whether this correlation holds for the aforementioned CRC sites and whether the pattern is the same for all of them—including focusing on the group of pts who did not undergo adjuvant therapy.

The initial hypothesis was that different site of CRC—right-sided, left-sided or rectal—may hold different values of TANs densities with different prognostic features. This assumption was based on the various differences that these anatomical locations have amongst them such as: different microbiome, different mechanical strains due to different intraluminal fecal consistencies from the cecal area to rectal area, area where maximum water reabsorption occurred in normal physiological process [3] [4] [5]. The tumor and tumoral microenvironment have key differences depending on tumor type and immunological infiltrate affecting it [6] [7] [8]. There is chronic inflammation in the tumor [9] [10] [11] [12] [13] and an abundance of neutrophils. Also, differences in embryological origin and mutational background, e.g. Higher MSI mutational burden in right-sided CRC [9].

Therefore, the principal aim of the study, the research objective, was to find whether these TANs densities (intratumoral) in different CRC sites have any prognostic relevance, in either the pts treated with adjuvant therapies and non-treated ones.

The reason for the study is a need for new prognostic markers for one of the commonest solid tumors in the world, namely the CRC. Also, the importance of understanding differences between CRC having as primary location different sites—focusing on right-sided colon, left-sided colon and rectum—could aid in the future adjuvant therapy selection for different classes of pts. In addition, whether TANs intratumoral density could be not only a prognostic marker but also a predictive marker was also inquired, by checking high TANs in adjuvant therapy pts and the efficacy of the therapy measured by survival parameters. As adjuvant therapy, 5-Fluorouracil was the therapy which was considered in the Galdiero *et al.* study, where a statistically significant correlation was found between patients treated with 5-FU with high intratumoral TANs vs those with low intratumoral TANs densities—namely pts with high TANs had a more favorable prognosis. In the study 178 pts were taken into considerations, 52 did not receive any adjuvant therapy while 126 received 5-FU as adjuvant therapy. All the patients (pts) were Stage III and Microsatellite Stable (MSS). Using the raw data, a multivariate analysis was performed to reach the objective of the study.

In the tumor microenvironment, Neutrophil granulocytes can be classified into N1/N2 type neutral granules, tumor-associated neutrophil TAN and Polymorphonuclear myeloid derived suppressor cells Cell PMN-MDSC [14] [15].

Neutrophils perform different functions when they adapt to different background environments. Neutrophils resist infection with pathogens, but constant infiltration of neutrophils can lead to chronic inflammation and tissue damage [16] [17].

To inquire whether TANs Intratumoral (IT) densities had predictive and/or prognostic value in regards to CRC site—left sided, right sided or rectal—in pts who underwent or not adjuvant chemotherapy with 5-FU, the raw dataset of patients (Stage III colorectal cancer patients) used in the Galdiero *et al.* [18] study from our lab was used.

Furthermore, as reported in a previous study, a new set of pts were taken to assess whether these TANs densities correlations with different CRC anatomical sites and prognosis in pts with 5-FU as adjuvant therapy existed with different types of adjuvant therapies, such as FOLFOX—made up of Folinic Acid (leucovorin—a molecule aiding in normal DNA replication—folate based DNA replication when high dose Metrotrexates, but increase cytotoxicity of 5-FU), 5-FU (a thymidylate synthase (TS) inhibitor and player in possible immune cell activation in the tumor microenvironment), Oxaliplatin (a cytotoxic compound)—or FOLFIRI—5-FU, Folinic Acid, Irinotecan (a topoisomerase inhibitor preventing DNA replication by blocking its unravelling) [19] [20]. Therefore, the research objective of the study was to see whether TANs intratumoral (IT) density in Colorectal Cancer has different prognostic and/or predictive values according to tumor primary site location—left colon, right colon and rectum—and whether it differs according to presence or not of adjuvant chemotherapy—5-FU.

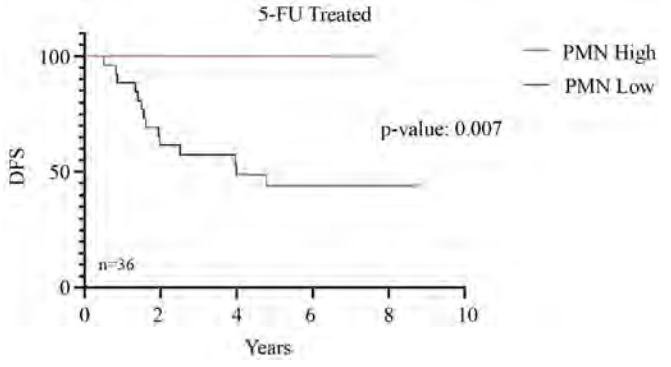
In the dataset, Intratumoral (IT) TANs were measured by Immunohistochemical process, labelling neutrophils via CD 66b + Ab labelling. While the analysis on that study focused on CRC and presence or not of 5-FU, here the focus of the analysis shifted to the three aforementioned CRC sites with the presence or not of Adjuvant therapy. Therefore, a different analysis with different parameters was performed on the set of pts mentioned before.

The primary sites of CRC which were taken into consideration were therefore three: Right-sided colon, Left-sided colon (not including rectum) and Rectum.

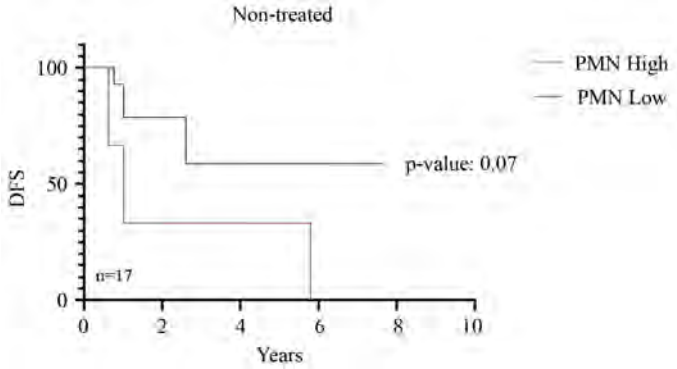
For 5-FU treatment the CRC site which was correlated to Intratumoral neutrophils in regards to Disease Free Survival of patients, was the rectum. The data revealed that High IT PMNs were strongly correlated to better DFS in 5-FU1 patients with rectum located CRC, compared to those with Low IT PMNs. This relationship was inversed in regards to 5-FU0 patients (High IT PMNs = Worst Prognosis).

In the data published in my thesis, a univariate analysis was also performed regarding the significance of IT TANs (PMNs) in rectal-cancer patients as shown in **Table 1**, where it can be seen that in patients with rectal cancer (stage III), there is a strong statistically significant better DFS in 5-FU treated patients having high IT PMNs (polymorphonuclear) density (HR: 0.06, p-value: 0.003) compared to patients with low IT PMNs density.

The data therefore suggest a possible predictive and prognostic value for IT PMNs (TANs) to be used in the clinical practice in patients with Stage III rectal cancer, where high Tumor Associated Neutrophils in the intratumoral histological section could be an inclusion criterium for 5-FU based adjuvant chemotherapy while a low value could be an exclusion criterium for this therapy (see **Figure 1**) and where high IT TANs in 5-FU treated patients could be a positive predictive and prognostic indicator for Disease Free Survival (DFS). In fact, it was also observed how high IT PMNs were associated with a worst DFS in patients with stage III rectal cancer but not treated with 5-FU (this possibly due to criteria of the patients.



(a)



(b)

Figure 1. Prognostic significance of CD66b in patients with Stage III CRC located in the rectum. Kaplan–Meier survival curves show DFS ((a), (b)) for patients presenting a high or low density of neutrophils (PMNhigh or PMNlow, respectively) in the IT (intratumoral). (a). shows DFS amongst IT PMN high vs. PMN low ones amongst 5-FU treated patients, n = 36, p-value: 0.007. (b). shows DFS amongst IT PMN high vs. PMN low ones amongst non-treated patients, n = 17, p-value: 0.07. Upper quartile values were employed to divide tumors into high and low CD66b+ immunoreactive area. The p-value was found using the Log-rank test.

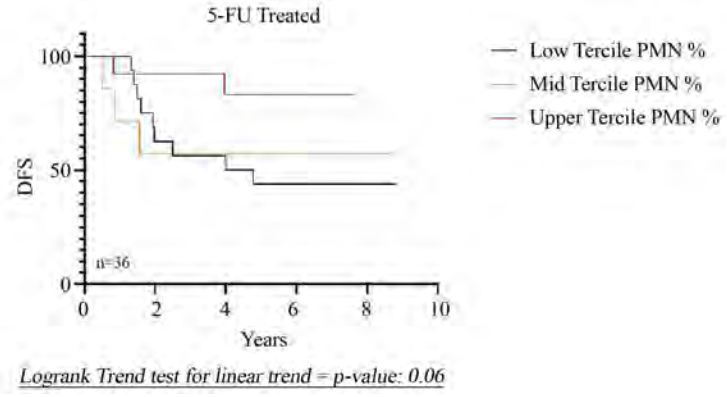
Table 1. Rectal cancer and IT PMNs.

Rectal cancer	Non-Treated Patients	5-FU treated patients
	Univariate analysis HR (95% CI) p-value	Univariate analysis HR (95% CI) p-value
IT PMNs Density	1.00 Ref.	1.0 Ref.
<1.197	3.5 (0.81 - 15)	0.06 (0.0005 - 0.45)
≥1.197	0.11	0.003*

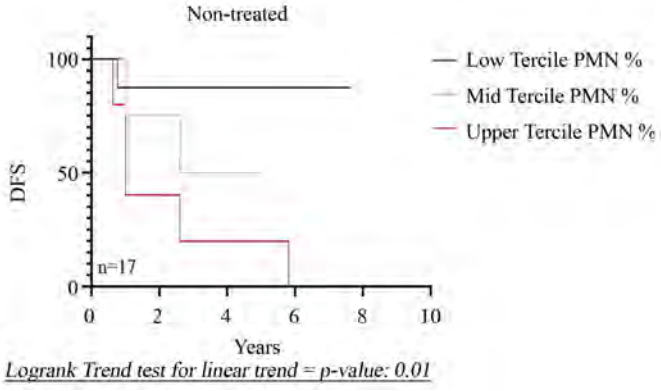
a. statistical test used: Firth's Method. *Statistically significant.

This was confirmed also when dividing in terciles to search for linearity (**Figure 2**). Figures and tables published on my thesis in 2020 [2].

For the patients with rectal cancer, I wanted to check also if the same association between IT PMNs density and DFS was present when looking at survival (DSS—Disease Specific Survival). See **Figure 3**.



(a)



(b)

Figure 2. Prognostic significance of CD66b in patients with Stage III CRC located in the rectum. Kaplan-Meier survival curves show DFS ((a), (b)) for patients presenting levels of PMN according to 3 terciles (low, mid, and upper terciles of IT PMN density) in the IT (intratumoral). (a) shows DFS amongst 5-FU treated patients, n = 36, p-value for linear trend: 0.06. (b) shows DFS amongst non-treated patients, n = 17, p-value for linear trend: 0.01. The Logrank Trend test was used to find the linear trend between the survival curves in each graph.

2. Main Topics

Therefore, in this section the Sarandria Score will be discussed in more detail. The discussed data showed (that I demonstrated in my graduation thesis for my medical degree) where patients with Stage III CRC located in the rectum and having High IT PMNs, benefit from receiving 5-FU adjuvant chemotherapy. While, patients with Low IT PMNs and CRC located in the rectum, do not benefit from 5-FU adjuvant chemotherapy (on the contrary they show a worst DFS compared to the patients who did not receive 5-FU).

Furthermore, there is a linear correlation between IT PMNs and DFS in both 5FU0 and 5FU1 patients having CRC located in the rectum (correlation not seen neither in the left-sided CRC nor in the right-sided CRC). This correlation was inversed in regards to 5-FU0 patients (High IT PMNs = Worst Prognosis). The data therefore suggest a possible predictive and prognostic value for IT PMNs (TANs) to be used in the clinical practice in patients with Stage III rectal cancer,

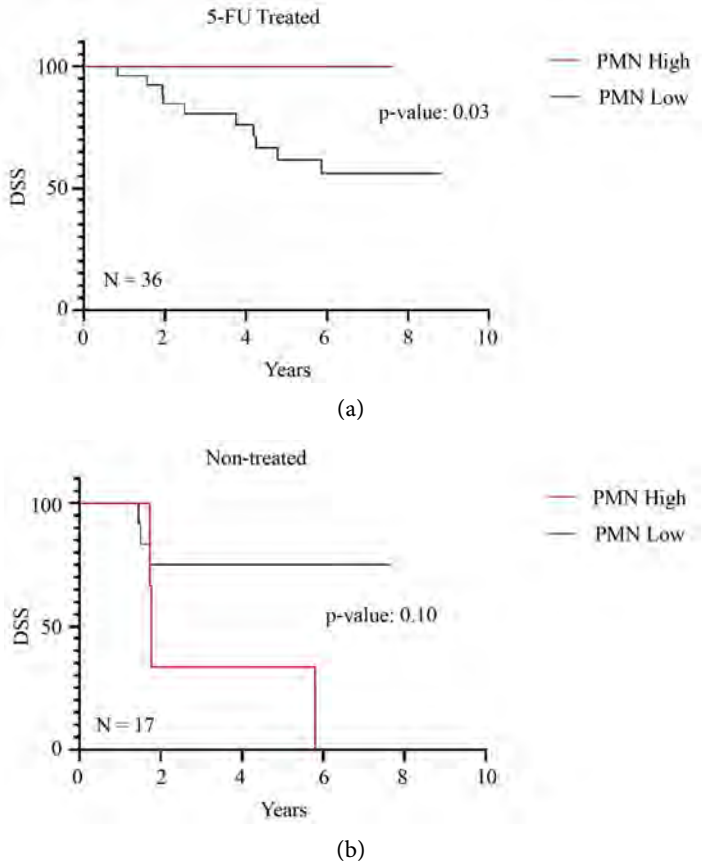


Figure 3. Prognostic significance of CD66b in patients with Stage III CRC located in the rectum. Kaplan-Meier survival curves show DSS ((a), (b)) for patients presenting a high or low density of neutrophils (PMNhigh or PMNlow, respectively) in the IT (intratumoral). (a) shows DFS amongst IT PMN high vs. PMN low ones amongst 5-FU treated patients, n = 36, p-value: 0.03. (b) shows DFS amongst IT PMN high vs. PMN low ones amongst non-treated patients, n = 17, p-value: 0.10. Upper quartile values were employed to divide tumors into high and low CD66b+ immunoreactive area. The p-value was found using the Log-rank test.

where high Tumor Associated Neutrophils in the intratumoral histological section could be an inclusion criterium for 5-FU based adjuvant chemotherapy while a low value could be an exclusion criterium for this therapy (see **Figure 1**) and where high IT TANs in 5-FU treated patients could be a positive predictive and prognostic indicator for Disease Free Survival (DFS) and Disease Specific Survival (DSS). This scoring system (named the "Sarandria Score" or in Italian nomenclature the "Scala di Valutazione Sarandria") could truly help in choosing candidates for 5-FU therapy (or possible other chemotherapeutical agents) among Stage III rectal cancer patients and could give prognostic and predictive insights to these patients. Furthermore, the fact that a worst DFS was found in patients not treated with 5-FU and having Stage III Rectal cancer, could be an important prognostic indicator for these subsets of patients also.

It is of relevance to do further studies in finding the correlation between neutrophils and rectal cancer, most importantly checking for: 1) Neutrophil polari-

zation (my supposition if that neutrophils in the tumor microenvironment of rectal cancer is of N1 phenotype). This can be checked with Arginase assay. 2) Correlation between neutrophils, rectal cancer and predictive/prognostic value also in patients undergoing different therapies—such as FF etc. It is my opinion, that neutrophilic infiltrate could become a staging system for rectal cancer patients for prognostic and predictive significance, much like immunoscore is now days used alongside TNM staging for colon cancer. As a matter of fact, it would be interesting to see whether the immunoscore (based on Jerome Galon's finding from 2006 which revealed a positive association of cytotoxic and memory T cells with survival of colorectal cancer patients) would change in terms of the location of the CRC (namely left, right or rectal cancer). Therefore, this review highlights also a new scoring system based on neutrophilic infiltration of intratumoral section of stage III rectal cancer patients developed by myself, Dr Nicola Sarandria MD [1] [2] (proposed name of the score: Sarandria Score, see **Table 2**). Furthermore, it is of my opinion that this could serve as further evidence in support of the future division of what is now known as Colorectal cancer into Colon and Rectal cancer, two different entities with different clinical and etiopathological courses. Therefore, as an addition to review the current state of knowledge on neutrophils and rectal cancer and with the aforementioned considerations in mind, the following scoring system, the Sarandria Score [1], can be seen in **Table 2**.

On a side note, regarding the process of advancing a medical researcher own ideas, backed by scientific evidence-based facts, it is of relevance to state that independently of everything that goes among peers and academic members, it is always the intellectually right and morally, duty-bound and scientifically correct path to advance with the focus to bring your findings to the public, and never surrender to forms of pressures from members of the academic boards (which independently of everything I have always respected, admired and extremely

Table 2. Sarandria score.

Sarandria Score: With Positive Predictive and Prognostic score: association with better prognosis and therapy outcome					
CD 66b stained Intratumoral cells density (Intratumoral neutrophils) (PMN Sum % Area)		**Resulting Predictive Score****	**Resulting Prognostic Score****	**5-Fluorouracil Therapy Inclusion***	**Resulting Prognostic Score (no 5-FU)*****
<1.197	**Low Intratumoral Neutrophils**	Negative	Negative	Low efficacy	Positive
≥1.197	**High Intratumoral Neutrophils**	Positive	Positive	Yes	Negative prognostic score

*Inclusion to a 5-Fluorouracil (5-FU) therapy to be considered in addition and conjunction to all other clinical aspects/criteria for the suitability and applicability of such therapy; **In patients being treated 5-FU chemotherapy; ***In patients not treated with 5-FU chemotherapy.

grateful for all the knowledge they passed on to me) to hide findings or stay silent. Furthermore, regarding my findings, it must be added that the same correlation in regards to IT PMNs and DFS in CRC patients undergoing 5-FU therapy, is not seen in the other CRC sites (left-sided and right-sided). Therefore, this score would be based on whether or not the intratumoral section at immunohistochemistry (CD 66 b ab stain) has a high value of neutrophilic infiltrate (set at ≥1.197 of neutrophilic density, calculated as "Sum % Area").

Regarding possible pathophysiological mechanisms of effect on why the high level of neutrophils was associated with a positive prognosis and had a predictive effect on therapy could be the association between the 5-FU therapy and the TANs, namely that studies have shown that 5-FU activates immune effectors and eliminates immunosuppressive cells [19].

3. Conclusion

In order to conclude, it is of vital importance for clinical medical findings to reach the scientific community. In this paper I have outlined my medical clinical score, the Sarandria Score. It is also relevant to do further research on the topic to see further findings regarding the association of tumor associated neutrophils and rectal cancer patients' prognostic and predictive score. It is fundamental for scientific results to be shown to the scientific community and to be discussed and its finding to be studied and advanced. In the end, the main aim of all medical clinical research is in my opinion to finally help save human lives and improve the quality and length of life for the patients worldwide. If there is even one possibility that a medical researcher finding could achieve this, that is to save human lives, then it is the moral, scientific and human duty of that person to bring to the scientific community the data.

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Conflicts of Interest

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

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Evaluation of the Influence of Fixed Orthodontic Treatment Duration on the Severity of Inflammatory Gingival Enlargement (Fixed Orthodontic Induced Gingival Enlargements) and Some Properties of Saliva

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Abstract

Background: Inflammatory gingival enlargement is a more common clinical feature with orthodontic therapy than other features. Therefore, this study was designed to **the** evaluation of the influence of fixed orthodontic treatment duration on the severity of inflammatory gingival enlargement (fixed orthodontic induced gingival enlargements) and some properties of saliva. **Material and Methods**: The sample size comprised 145 patients undergoing fixed orthodontic treatment for at least 6 months aged 13 - 32 years. They were divided according to orthodontic treatment duration into three groups. Group I (n = 47) included the patients who were treated for less than 6 months, group II (n = 51) included the patients who were treated for a period of 6 - 12 months, and group III (n = 47) included the patients who were managed for more than 12 months. Data were obtained from the outpatient clinics, college of dentistry, King Khalid University, Abha, Saudi Arabia, and some dental centers in Sana'a city, the Republic of Yemen. This study was conducted from October 2021 G to January 2022 G. Clinical examination was done for plaque index (PLI), gingival index (GI), and gingival enlargement indexes (GEI). Saliva was collected in sterile test tubes then salivary flow and pH were measured. Statistical analysis was done with SPSS (version 23) and ANOVA test to evaluate the impact of orthodontic treatment duration on the severity of in-

flammatory gingival enlargement and some properties of saliva. **Results**: The statistical analysis demonstrated the highest mean plaque index (PLI) was among groups III and I participants whereas, the highest mean gingival index and mean gingival enlargement were among groups II and III participants. The present study revealed an increase in salivary flow with decreased salivary pH values with an increase in orthodontic therapy duration. There were statistically significant differences in clinical findings and salivary flow and pH values were observed in the comparison between groups I, II and III except PLI ($p < 0.05$). **Conclusion**: There was a higher inflammatory gingival enlargement associated with a higher plaque index in patients under orthodontic treatment for more than 12 months more than the patients for less than 6 months and the patients for a period of 6 - 12 months. There were correlations between an increase of salivary flow and pH values and an increase of other variables in this study, such as plaque index, gingival index, and gingival enlargement index with an increased orthodontic therapy duration.

Keywords

Inflammatory Gingival Enlargement, Orthodontic Treatment Duration, Some Salivary Properties

1. Introduction

Periodontal disease initiation and progression rely on a balance between the host immune system and microbial effect [1]. Gingival enlargement is a multifactorial clinical condition that develops in response to different factors and interactions between the host defense and these factors such as plaque and systemic disturbances moreover a rare gingival enlargement (idiopathic gingival fibromatosis) [2]. The prevalence rate of gingival enlargement is 10%, and it is one of the main periodontal tissue problems related to fixed orthodontic appliances [3].

Fixed orthodontic appliances impact passively on periodontal tissue health by obstructing access to good oral hygiene resulting in the accumulation of plaque [4]. The most common periodontal tissue alterations detected during fixed orthodontic therapy were gingivitis, gingival recession, and gingival over growth [5] [6]. The increase of inflammatory cells in the inflamed gingival tissues leads to edema formation and increase gingival size [7].

Fixed orthodontic therapy can cause gingival enlargement due to the effect of some link risk factors such as the mechanical effect of bands, chemical effect of cement, accumulation of plaque, and improper maintenance of oral hygiene [8]. Thus, the associated gingival enlargement with orthodontic therapy is considered an inflammatory reaction due to difficulty in self-performed mechanical plaque control. The capacity to do oral hygiene measures is difficult for patients with gingival enlargements especially, patients with fixed orthodontic appliances. These may cause more inflammation and increase of plaque accumula-

tion then change of the gingival sulcus to a periodontal pocket creating difficult areas for plaque removal [9].

Inflammatory gingival enlargement during orthodontic therapy is a localized or generalized exaggerated gingival tissues growth reaching to marginal gingiva, interdental papilla, and attached gingiva [10]. Acute or chronic inflammatory gingival enlargement in cases of fixed orthodontic appliances can be easily seen in chronic cases [2]. According to previous clinical study, generally, there was a link between orthodontic treatment and periodontal health decrease [11]. A hypertrophic form of gingivitis is one of the unwanted periodontal alterations [6]. Moreover, retardation of oral health status [12]. Generally, the clinical studies revealed that the gingival alterations during orthodontic therapy are not permanent damage to the periodontal and tissues [13] [14].

Few studies were conducted to evaluate the link between gingival enlargements, such as the study of Zanatta *et al.* which revealed that there was a positive link between fixed orthodontic therapy and inflammatory gingival enlargement [15].

Saliva plays a significant role in oral hygiene where its PH and the other enzymes help to diagnose and determine oral health and progression of some diseases of oral mucosa and their risk factors [16] [17]. Furthermore, Orthodontic therapy causes alterations in the ecological factors of the oral cavity that leads to changes in salivary characteristics [18].

However, an assessment impact of fixed orthodontic treatment of more prolonged times on inflammatory gingival enlargement severity and some salivary properties among orthodontic patients' needs more studies. Therefore, the present study was designed to the evaluation of the influence of fixed orthodontic treatment duration on the severity of inflammatory gingival enlargement (fixed orthodontic induced gingival enlargements) and some properties of saliva.

2. Material and Methods

2.1. Design and Sample Size of the Study

The current cross-sectional study groups included 145 participants, 100 males (69%) and 45 females (31%) who were undergoing fixed orthodontic treatment. All participants were selected from patients treated in orthodontics clinics, college of dentistry, King Khalid University, and some dental centers in Sana'a city, the Republic of Yemen from October 2021 G to January 2022 G. They were divided according to orthodontic treatment duration into three groups. Group I (n = 47) included the patients who were treated for less than 6 months, group II (n = 51) included the patients who were treated for a period of 6 - 12 months, and group III (n = 47) included the patients were managed for more than 12 months. The age range of the participants was between 13 ys and 32 ys (**Figures 1-3**).

2.2. Inclusion Criteria

The identification of participants number was based on the expecting that there was 10% difference of gingival enlargement with 30% theoretical proportion as

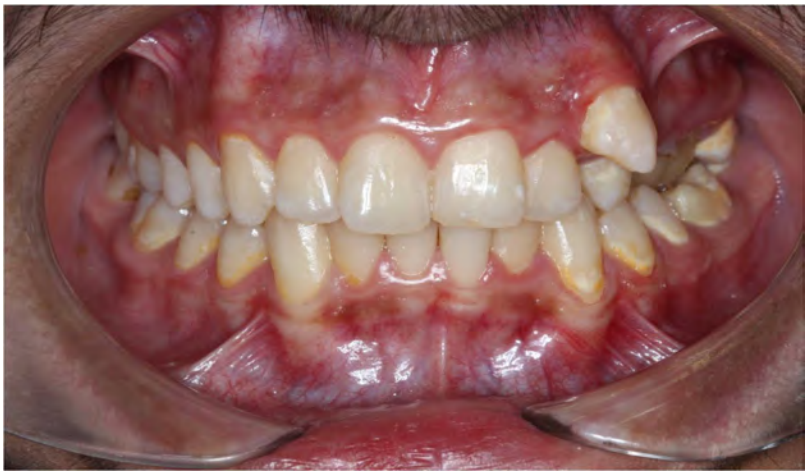

Figure 1. Clinical photograph of a patient before orthodontic treatment.

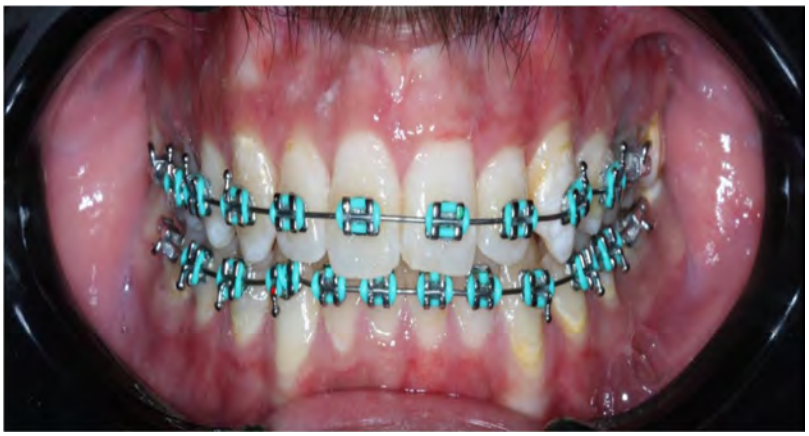

Figure 2. Clinical photograph of a patient was treated for a period of 6 - 12 months.

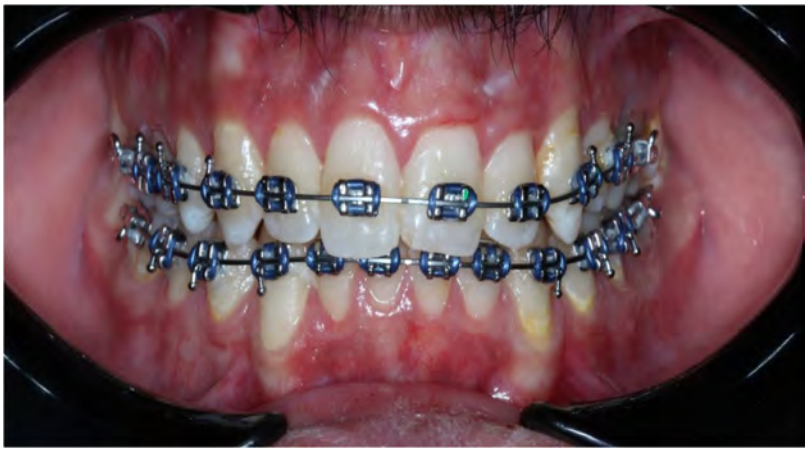

Figure 3. Clinical photograph of a patient was treated for more than 12 months.

the effect of orthodontic therapy duration on gingival tissues [4]. The patients who agreed to participate and signed an informed consent form, and the patients who were undergoing fixed orthodontic therapy for 6 months, 6 - 12 months, and more than 12 months were included in this study samples.

2.3. Exclusion Criteria

The exclusion from the samples of the current study were the patients of bacterial and viral infectious diseases such as COVID-19 that may be risks to the examiners, the patients who were using drugs inducing gingival enlargement, the patients who need antibiotics coverage for clinical examination, the patients who were affecting by the congenital anomaly, the patients with gingival cysts, and the patients with oral ulceration and acute gingival diseases or diabetic patients that maybe effect on clinical examination. Moreover, pregnant women, smokers, and breastfeeding mothers were also excluded.

2.4. Ethical Status

The protocol of this study was designed according to ethical approval requirements of the Institutional Review Board, college of dentistry, King Khalid University before this study started. The participants were informed about the study objectives, and a written informed consent form was obtained.

2.5. Clinical Examination

The clinical examination was conducted to record the periodontal parameters according to this study design. A manual conventional periodontal probe (Williams) was used for periodontal parameters evaluation in this study [19].

2.6. Assessment of Dental Plaque

Plaque index used to evaluate the dental plaque by Silness and Loë's plaque index (PLI) (0: No plaque; 1: non-visible plaque with the naked eye, but we can see it with a periodontal probe; 2: visible plaque with the naked eye; 3: abundantly visible plaque with the naked eye and extent to sulcus and the free gingiva margin) [20].

2.7. Assessment of Gingival Inflammation

Gingival index was used to evaluate the gingival inflammation by Loë and Silness gingival index (GI) (0: No inflammation, 1: mild inflammation, 2: moderate inflammation with gingival bleeding, 3: severe inflammation with spontaneously gingival bleeding) [21].

2.8. Assessment of Inflammatory Gingival Enlargement

Miller and Damm modified the original Angelopoulos and Goazindexused for evaluating the vertical gingival enlargement from cemento-enamel junction to the free gingival margin where there are three grades according to the covering of clinical crown (Grade 0: No gingival growth, Grade I: mild enlargement, ≤2 mm, gingiva covering the cervical third., Grade II: Moderate enlargement: 2 to 4 mm, gingival covering the middle third of the clinical crown and Grade III: Severe enlargement: ≥4 mm, gingival covering more than two thirds of the clinical crown [22].

2.9. Assessment of Some Salivary Properties

The Salivary samples were obtained according to the instructions of the WHO Organization for the collection of saliva. The saliva samples were collected in sterile glass containers (0.5 ml) for 10 minutes. pHep pocket-sized pH meter was used to measure the pH of salivary samples. It is a calibrated instrument between 0.0 to 14.0 manufactured by Hanna Instruments with a replaceable electrode. The instrument was calibrated every day by its buffer solution. The saliva quantity (milliliters per minute) was measured and divided by 10 to account for the flow rate in millimeters per minute [23].

2.10. Statistical Analysis

The data were coded and introduced to the computer then analyzed using SPSS (version 23). The descriptive statistics were represented in percentages, means, and standard deviations, while inferential statistics were used to detect significant differences at 0.05 alpha level. Analysis of variances (ANOVA) was used to identify the significant mean difference between study groups regarding age, gingival index, plaque index, gingival enlargement Index, and salivary flow and pH values.

2.11. Results

A total of 145 patients were included in this study, 47 (32.4%) of them were in treated for less than 6 months, 51 (35.2%) were treated for a period of 6 – 12 months, and 47 (32.4%) were managed for more than 12 months (Table 1 and Figure 4). The minimum age was 13 years old and maximum age was 32, while mean age for all study participants was 21.98 ± 3.6. The mean plaque index, gingival index, and gingival enlargement index were 1.67 ± 0.60, 1.60 ± 0.55, and 1.65 ± 0.56 respectively (Table 2). The mean age was the highest among group III (23.06 ± 3.49 years old), followed by mean of group II and group I with 21.82 ± 3.60 and 21.06 ± 3.4, respectively. The analysis of variances shows significant difference in age between patients treated for <6 months and those treated for >12 months with p = 0.017 (Table 3 and Figure 5).

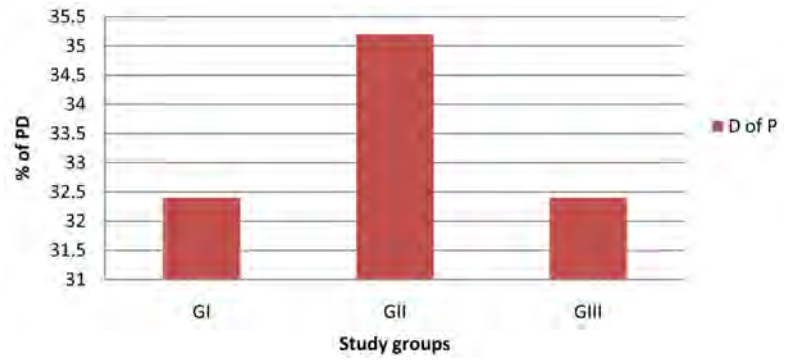

Figure 4. The distribution of study participants on study groups. D of P: Distribution of participants. GI: group I. GII: Group II. GIII: Group III. % of PD: Percentage of participants distribution.

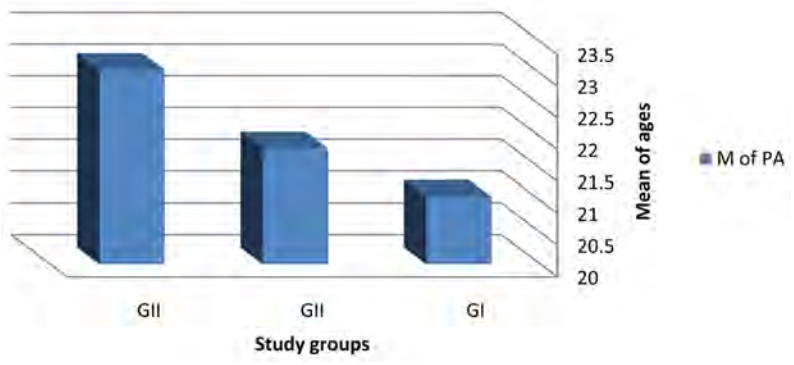

Figure 5. Comparing means of participants' age between study groups. GI: group I. GII: Group II. GIII: Group III.M of PA: Mean of patients' age.

Table 1. The distribution of study participants on study groups.

Study groups	Frequency	Percent (%)
Group I (less than 6 months)	47	32.4
Group II (6 - 12 months)	51	35.2
Group III (More than 12 months)	47	32.4
Total	145	100.0

Table 2. The descriptive statistics of study variables.

	Minimum	Maximum	Mean	Std. Deviation
Age	13	32	21.98	3.6
Plaque index	1	3	1.67	0.60
Gingival index	1	3	1.60	0.55
Gingival enlargement index	1	3	1.65	0.56

Table 3. Comparing means of participants' age between study groups.

Groups	Mean	(±SD)	Comparison	p value
Group I (<6 months orthodontic treatment)	21.06	3.40	Group I and II	0.532
			Group I and III	0.017*
Group II (6 - 12 months orthodontic treatment)	21.82	3.60	Group II and III	0.189
Group III (>12 months orthodontic treatment)	23.06	3.49		

*Significant difference.

The highest mean plaque index was reported among patients with treatment duration > 12 months (1.70 ± 0.51), while the lowest plaque index was in patients treated for a period 6 - 12 months. No significant difference of plaque index was seen between group I, II and III ($p > 0.05$). The highest mean gingival

index was reported in patients with >12 months orthodontic treatment (2.07 ± 0.50), while the lowest was reported among patients with <6 months orthodontic treatment (1.74 ± 0.57). The differences in plaque index between study groups were not statistically significant (p = 0.819). However, using ANOVA showed significant difference in gingival index between study groups (p = 0.047) and post hocTukeytests demonstrated that significant difference was between patients treated for <6 months and those treated for >12 months with p = 0.036.

Gingival enlargement index was the highest among patients with >12 months orthodontic treatment (**2**.72 ± 0.50) in comparison to means of 1.63 and 1.60 among patients with 6 - 12 months orthodontic treatment and those with <6 months orthodontic treatment, respectively. There were statistically significant differences in gingival enlargement associated with the duration of orthodontic therapy among the patients of groups II, III, and I (p < 0.05) (Table 4 and Figure 6).

On the other hand, Table 5 and Table 6 and Figure 7 and Figure 8 reveal the salivary pH and salivary flow rate values in the three groups. It was found that the mean salivary pH and salivary flow rate of group III participants were the highest when compared with groups I and II. Salivary flow rate and salivary pH

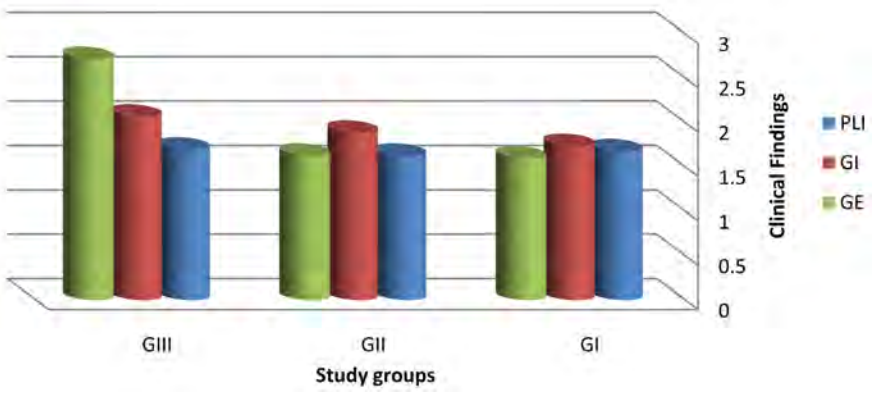

Figure 6. Comparing of periodontal health indices among study groups. PLI: Plaque index. GI: Gingival index. GEI: Gingival enlargement index. GI: group I. GII: Group II. GIII: Group III.

Table 4. Comparing means of periodontal health indices among study groups.

Periodontal Health Indices	Group			
	<6 months orthodontic treatment (GI)	**6 - 12 months orthodontic treatment (GII)**	**>12 months orthodontic treatment (GIII)**	**P value**
PLI	1.68 ± 0.66	1.63 ± 0.63	1.70 ± 0.51	0.819
GI	1.74 ± 0.57	1.89 ± 0.54	2.07 ± 0.50	0.047*
GEI	1.60 ± 0.61	1.63 ± 0.56	2.72 ± 0.50	<0.05*

PLI: Plaque index. GI: Gingival index. GEI: Gingival enlargement index. *Significant difference. **GI**: group I. **GII**: Group II. **GIII**: Group III.

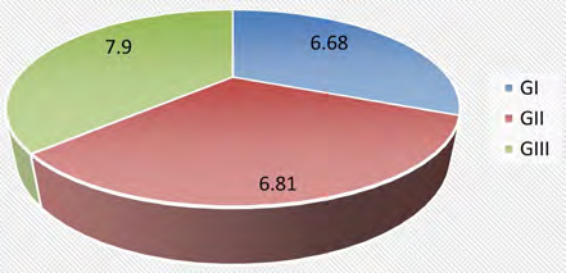

Figure 7. Comparing means of salivary pH values among study groups. GI: group I. GII: Group II. GIII: Group III.

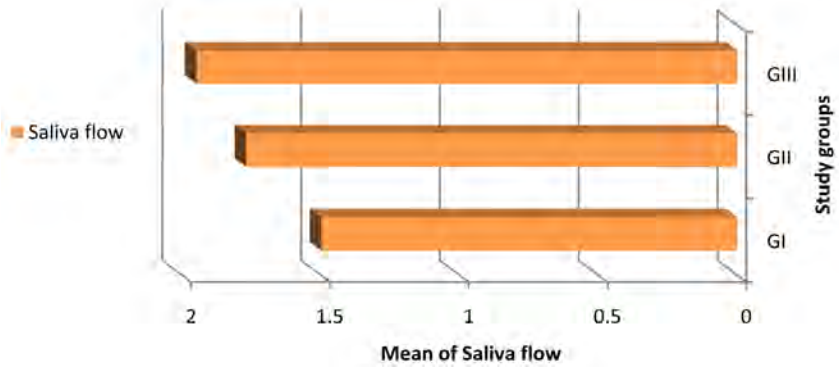

Figure 8. Comparing means of saliva flow values among study groups. GI: group I. GII: Group II. GIII: Group III.

Table 5. Comparing means of salivary pH values among study groups.

	Salivary pH		ANOVA	
	Range	Mean ± SD	F	P-value
Group I	5 - 8	6.68 ± 0.316		
Group II	6 - 8	6.81 ± 1.07	3.997	0.042*
Group III	6 - 9	7.9 ± 1.22		

*Significant difference.

Table 6. Comparing means of salivary flow values among study groups.

	Salivary flow		ANOVA	
	Range	Mean ± SD	F	P-value
Group I	1 - 2	1.12 ± 0.058		
Group II	1 - 2	1.77 ± 0.035	0.628	0.033*
Group III	1 - 2	1.95 ± 0.011		

*Significant difference.

decreased after commencing orthodontic therapy then significantly increased 6 and 12 months after orthodontic therapy. There were statistically significant differences between the mean salivary flow rate values ($p = 0.033$) and salivary pH values ($p = 0.042$) among the groups of the current study.

3. Discussion

Inflammatory gingival enlargement is a more common clinical feature with orthodontic therapy [6]. The presence of orthodontic appliances may lead to plaque accumulation and difficulty in oral hygiene maintenance [24]. When PLI, GI, and GEI were evaluated, statistically significant differences between these clinical parameters except PLI were observed, where the clinical relationship of these differences with orthodontic therapy duration revealed clinical differences for the severity of inflammatory gingival enlargement grades I and II. The clinical findings of our study revealed that there was an association between orthodontic therapy duration and dental plaque accumulation. This agrees with the clinical findings of other previous studies that have demonstrated an increase in plaque accumulation and change in the composition and types of oral bacteria during orthodontic therapy [25] [26]. The Plaque index (PLI) in the present study demonstrates the relation between plaque accumulation and duration of orthodontic therapy with the progression of inflammatory gingival enlargement. Consequently, the duration of orthodontic therapy may be considered a predisposing factor.

Gong Y and Ding X reported in their study that gingival enlargement is an inflammatory reaction against the microbiota dental plaque, and its products are attributed to that the orthodontic appliances facilitate the collection and the colonization of bacteria; consequently, the gingiva becomes more susceptible to inflammation and bleeding that corresponds with the results of the present study [1] [27]. According to the current study, the highest plaque index, gingival index, and gingival enlargement appeared among the patients of group III more than in other groups. But, no significant effect of duration on the severity of inflammatory was seen from 1 to 6 months of orthodontic therapy; this agrees with the similar plaque index and gingival index that appeared in these groups, thus supporting the inflammatory nature of an increase of gingival size in the current study. The increase of gingival tissue size in the present study may be due to gingival tissues being more sensitive to dental plaque and the hyperplastic reaction of the gingival tissues [28] that agrees with a previous study, reported that there were effects of fixed orthodontic appliances on the profile of oral microbiota, and added that gingival health is fundamental before beginning orthodontic therapy [29].

This effect of orthodontic therapy duration on the severity of inflammatory gingival enlargement may explain that the participants are more likely to have low preventive attitudes and habits with an increased time of orthodontic therapy. Thus, gingival phenotype and plaque control should be considered [30]. In this study, the amount of dental plaque and duration of orthodontic therapy played a role in the incident of gingival enlargement where plaque index and gingival enlargement index among the participants of group III more than other groups, that may be due to the various response and time for clinical reaction, moreover microbial challenge and individual local and systemic resistance [16]

[31]. These results agree with several previous studies which revealed that the fixed orthodontic therapy change the qualitative composition of dental plaque [24] [32].

On the other hand, the flow rate of saliva plays a significant role in oral health where the increase of saliva leads to physical cleansing action for accelerates clearance of substrates as well as raise its antimicrobial effectiveness, whereas low salivary flow rate adversely affects oral health [33].

In the present study, there was a significant decrease in salivary pH after starting orthodontic therapy. These findings are convenient with a previous study that revealed a decrease in pH after put fixed orthodontic appliances [23]. But another previous study demonstrated that there was a significant increase in salivary flow rate during orthodontic therapy [34]. These findings are in agreement with the results of the present study where salivary flow rate was an increase in 6 - 12 months and more than 12 months orthodontic therapy durations when compared to less than 6 months of orthodontic therapy duration. That may be due to the presence of orthodontic appliances, which act as a mechanical motivation in salivary secretion. These findings agree the results of studies that done by Kanaya *et al.*, Kanaya *et al.*, and Chang *et al.* [35] [36] [37].

Furthermore, another previous study showed increased salivary flow and pH during orthodontic therapy [38]. This agrees with the results of the present study, which explains that the increased salivary flow and pH may be due to the sensitivity against orthodontic appliances in the oral cavity as well as, the orthodontic appliances provide ideal areas for adhesion and proliferation of oral micro-biota that lead to defect in oral hygiene and difficulty in brushing during orthodontic therapy [39] [40].

Baliga, *et al.* detected an increase in salivary pH among the patients with chronic gingivitis more than in the control group [41]. That agrees with the findings of this study where there was a direct relationship between the increase in the salivary pH and the increase in the severity of gingivitis and inflammatory gingival enlargement, with the increased orthodontic therapy duration.

Salivary samples can be easily collected, compared to the serum and blood samples for comfort to the patient. Consequently, the saliva can be obtained in the dental office and used as an easy diagnostic aid [42] [43].

4. Strength and Limitations of the Study

The strengths of this study in demonstrating that there were side effects of orthodontic therapy duration on gingival tissues and salivary flow and salivary pH values. Consequently, they may be considered as predisposing factors of Orthodontic treatment-induced gingival enlargement that needs continuous recall visits of periodontal therapy during orthodontic therapy duration. The results of this study help to clarify the importance of patient motivation and patient compliance in the treatment of inflammatory gingival enlargement that may be associated with orthodontic therapy. Oral hygiene instructions and motivation

should begin at the first phases of orthodontic therapy to gain good results.

There were some limitations of this study, such as the cross-sectional design of the study as well as sample sizes were smaller, and standardization was not enough. Therefore, longitudinal studies, an increase of sample size, and standardization can assist in confirming the findings of this study regarding the impact of orthodontic therapy duration on the severity of inflammatory gingival enlargement and salivary flow and salivary pH values. Thus, at the end of this study, it can be recommended that the gingival parameters, salivary flow, and salivary pH values should be considered during orthodontic therapy times because the orthodontic appliances might negatively influence gingival tissues

5. Conclusion

We conclude that gingival index and gingival enlargement index as well as salivary flow and pH salivary values can be used to monitor the severity of inflammatory gingival enlargement during orthodontic therapy and can have prognostic values also for inflammatory gingival enlargement and its therapy. Using salivary samples as diagnostics aids are obtaining interest, and the present study considered a new insight into this aspect.

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Conflicts of Interest

The authors stated no possible conflicts of interest to this research manuscript authorship and publication.

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The Risk of Severe Acute Kidney Injury Requiring Renal Replacement Therapy in Viral Hemorrhagic Fevers. A Review of Literature

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Abstract

Objective: It demonstrates the correlation of the viral hemorrhagic fever with kidney failure and the treatment as well as the outcome. Method: A PubMed search of the English literature from 1999 to 2019 was performed using "viral hemorrhagic fever, Case Report, Renal Failure" as the subject. The inclusion criteria were the following: 1) case report and case series of two or more patients; 2) the report detailed the clinical presentation and reported the status of the renal system; 3) the report described the management of renal failure if any; and 4) the etiology of the infection is known and is one of the known agents of viral hemorrhagic fever, listed on the centers of disease control website. We excluded infections related to vaccination related to viral hemorrhagic fever. Result: We found the mean age of these patients was 41.5. The male to female ratio was about 3.5:1. Dengue and Hantaviruses constituted 70.5% of patients. The overall mortality of the study cohort was 32.2%. Half of the patients had acute kidney injury and required renal replacement therapy. The chi-square statistic is 0.41; The *p*-value is 0.51; The chi-square statistic is 6.4254. Overall mortality was 32.3% in one cohort of 78 patients. The illness goes through several stages [1] [2] of clinical features and some viruses in the group have a high case fatality rate. Conclusions: Early diagnosis with aggressive supportive care is critical for improving clinical outcomes. Renal involvement is common. Amongst the cohort reviewed, of patients who had acute kidney injury, half of the patients required renal replacement support. However, some viruses cause greater kidney injury than others, for instance, kidney injury is more severe in Dengue hemorrhagic fevers when compared to Hantaviruses. Simultaneous management of public health by prevention and control of outbreaks is particularly important.

Keywords

Acute Kidney Injury (AKI), Renal Replacement Therapy, Viral Hemorrhagic Fevers

1. Background

Viral hemorrhagic fevers (VHFs) are severe infections caused by a group of viruses belonging to several families. These infections are characterized by severe, multi-organ involvement with a high mortality rate. Acute kidney injury is often a component of the multisystem syndrome that includes involvement and dysfunction of the central nervous system, pulmonary, cardiovascular system, hematopoietic system, gastrointestinal system and liver. Renal replacement therapies (RRT) are often needed. We reviewed the literature to retrospectively study the extent to which RRT is utilized if there is any relationship between the use of RRT and mortality.

2. Methods

To assess whether and to what extent, published studies report acute kidney injury (AKI) requiring supportive renal replacement therapy (RRT) during viral hemorrhagic fever (VHF). A PubMed search of the English literature from 1999 to 2019 was performed using "viral hemorrhagic fever, Case Report, Renal Failure" as the key words. A manual search of the bibliographies of retrieved articles was also added. As a result, we reviewed over two hundred articles in detail. The inclusion criteria were the following: 1) Case report and Case series of two patients; 2) The report detailed the clinical presentation and reported the status of the renal system; 3) the report described the management of renal failure if any; and 4) the etiology of the infection is known and is one of the known VHF listed on the centers of disease control (CDC) website. We excluded infections related to vaccination related to VHF. 74 publications met the inclusion and exclusion criteria that reported 78 patients. The following data was collected from the eligible publications; 1) demographic data; 2) geographic data; 3) presenting symptoms; 4) the presence or absence of renal failure; and 5) the need for renal replacement therapy.

2.1. Statistics

Descriptive statistics and analytic statistics were conducted using a statistical calculator package available online at https://www.socscistatistics.com/tests. Age was presented as mean and interquartile range. Chi Square values were calculated and p-value of <0.05 was considered significant.

2.2. Results

There were 74 publications and 78 patients included in the study. All these pa-

tients were reported to have AKI. The mean age of these patients was 41.5 (IQR, 24). The male to female ratio was about 3.5:1. The Dengue and Hantaviruses constituted 70.5% of patients. Other viruses that constituted the remainder of the causes were puumala virus, Seoul virus, Ebola virus, yellow fever, Lassa fever virus etc. Overall mortality of the study cohort was 32.2%. Half of the patients who had AKI required RRT. Comparing patients who survived to those who died, there was no difference in the need for RRT. The chi-square statistic is 0.41 The p-value is 0.051; Not significant at $p < 0.05$. However, the need of RRT was etiology dependent. Hantavirus infections were less likely to require RRT when compared to Dengue and the group of Other viruses. The chi-square statistic is 6.4254. The p-value is 0.01. Significant at $p < 0.05$.

3. Discussion

3.1. Definition

VHFs causing viruses are listed on the CDC website (1). These viruses belong to several groups of viral families causing severe multisystem illness leading to failure and insufficiency of multiple end organs simultaneously. The mortality rates vary from 20% - 40% and in our cohort the mortality rate was 32.2%. These viruses can be divided into those which are classified as biosafety level four 4 (BSL-4) pathogens and those which are non BSL-4. The two non BSL-4 viruses cause Dengue and Yellow fever.

3.2. Epidemiology

These viruses are worldwide and each virus has a niche geographic location. Frequently travelers from one location to another may transport these viruses outside of the usual distribution. Hence the history of travel is important in the diagnosis of VHFs.

All continents except Antarctica are home to an endemic virus or viruses. For example, Dengue virus is frequent in Asia, Puumala virus in Europe. Dengue and the Hantaviruses are frequently most common amongst these viruses causing severe infections. In our cohort dengue and Hantaviruses accounted for 70% of the cases. Males are more frequently affected than females and this could be due to exposure to outdoors the vectors. The mean age in our cohort was 41.5 years with IQR (1 - 2) of 24.

3.3. Etiological Agent

The viruses causing VHFs belong to the following families and are mostly zoonosis; 1) Arenaviridae, 2) Bunyaviridae, 3) Flaviviridae, and 4) Filoviridae. All are enveloped, single stranded RNA viruses. The largest family is the Bunyviridae with over 300 viruses; Hanta viruses belong to this group. Arenaviridae have their single strand RNA bi segmented. Arenaviruses are classified as the New World viruses and the Old World or LCM/Lassa complex. The Ebola virus belongs to the Filoviridae family and this family is largely found in the African

continent. Ebola and Marburg viruses belong to this group. Flaviviridae has positive sense RNA while the other three families named above have negative sense RNA. Flaviviridae includes Dengue Fever, Yellow fever, Japanese encephalitis, West Nile and Zika viruses.

4. Pathophysiology of AKI in VHF

Acute kidney injury in viral hemorrhagic fevers is multifactorial, most of these diseases are endemic in resource limited countries, therefore, most of the data has been obtained through cases reports, and case series, AKI varies as well upon the moment of the course of the disease, *AKI's dengue fever* has been associated with, acute tubular necrosis, hemolytic uremic syndrome, proteinuria, glomerulopathy and nephrotic syndrome [3]. Direct cytopathic effect of the viral protein on the glomerular and tubular cells, tissue injury caused by immune complexes composed of viral antigens with antiviral antibodies, causing damage through inflammatory mediators which are released in response to the glomerular or tubular cytopathic effects of the viral antigens [4] [5] [6] Other causes of AKI in dengue fever are rhabdomyolysis [7] [8] [9] [10] [11], Hemodynamic instability, some cases with hemolytic uremic syndrome which is not well understood pathophysiology [12] [13] [14].

Hantavirus AKI mechanism is not well understood, studies have shown, damage of the podocytes, tubular epithelial and glomerular endothelial cells revealed disturbances in structure and integrity of cell to cell contacts, observed by redistribution and reduction of the light junction protein ZO-1 along with decreased transepithelial resistance in infected epithelial monolayers [15], There seems to be a relationship between human leukocyte antigen (HLA) haplotypes in the severity of the disease [16] [17], and T-cell mediated immune response. It is supported by the observed elevated CD8+ cell count. Furthermore, the principal characteristic described is the increased vascular permeability without apoptotic damage to the capillary endothelium, suggesting the likely breakdown of endothelium due to cytokine release, which means the insult and damage is immunological rather than anatomical to the endothelium and is reflected by the scarcity of renal lesions on kidney biopsies [18] [19] [20].

Ébola virus and Marburg virus are two of the more lethal diseases and both of them course with a high renal involvement and normally require RRT as part of the management, the AKI is caused due to systemic inflammatory response syndrome and capillary leakage, associated with massive fluid loss from vomiting and severe diarrhea, which lead to pre-renal azotemia [21], renal ischemia causing acute tubular necrosis (ATN), cytokine storm, superinfection with bacterial pathogen [21], Ebola virus has been shown to infects renal tubular cells, clothing abnormalities [20] [21].

The rest of the hemorrhagic viruses share characteristics in common with the previous ones, volume depletion, prerenal azotemia, kidney cell compromise, and the need for RRT as part of management.'

5. Risk Factors

See Table 1.

Clinical features: The incubation period for VHFs ranges from 2 to 21 days. Patients initially have a high fever, headache, tiredness, joint aches, muscle aches, nausea, abdominal pain, and non-bloody diarrhea that usually last about a week. High fever is an early sign, abrupt in onset, associated with headache and myalgias with exception of arenaviruses, where the fever and illness is more gradual in onset. Multisystem involvement is noted from the very early phase however the severity may vary in individuals. Capillary leak and endothelial dysfunction are the hallmarks of VHFs.

We found 78 severely affected patients, all of whom had AKI, 50% required renal support. Rhabdomyolysis occurred in 8 of the 78 patients and most likely caused acute tubular necrosis (ATN).

Gastrointestinal involvement is common in the form of nausea, vomiting, abdominal pain and diarrhea and was reported in 58% of the patients; which most likely caused pre renal AKI; however there could be other mechanisms of AKI but kidney biopsy was not frequently done.

Nervous system involvement in the form of headache, confusion, loss of consciousness or visual changes are seen in over half the patients with VHFs. Forty patients from our cohort (N = 78) [3] [12] [13] [14] [22]-[39] had some CNS involvement.

There were no clinical features in this cohort, with advanced disease, that was predictive of death. The use of RRT was also not different between the group that recovered and the group that succumbed to the disease. Although Hanta viruses can cause Renal syndrome, the proportion of patients requiring RRT was significantly less when compared to Dengue or Other viruses causing VHFs.

In advanced stages, confusion, hypotension, respiratory failure, nephrogenic edema, liver failure are noted. Imaging can show pulmonary infiltrates, and pleural effusions. EKG may show tachycardia, relative bradycardia, and conduction abnormalities.

Deep bleeding in the form of intracerebral bleeding, gastrointestinal bleeding, perirenal hematomas, genitourinary bleeding may be noted but is seldom life threatening and is noted in less than 10% of patients (6.5% in this cohort).

6. Diagnosis

The diagnosis of viral hemorrhagic fever is variable, first at all it is made in based

Table 1. Risk factors.

	Bunya	Arena	Filo	Flavi
Reservoir	Rodents	Rodent	Bat (UK)	Monkeys
Risk factor	Contact with rodent urine	Contact with Rodent excreta		Contact with ticks
Arthropod borne	No	Yes	UK	Yes
Person-to-Person	Yes	Yes	Yes	Yes

on clinical manifestation, however we have under our dispositions certain studies available: Virus Culture, Electron Microscopy, Nucleic Acid Detection, Immunohistochemistry, serology studies, etc. In our cohort diagnosis was defined as less than 3 days as enough time to make it, and only 54% made it in the period of time, 87% were made during the hospital admission.

61% of the diagnoses were made with seroogy studies, the combination of serology studies and RT-PCR (Reverse transcription polymerase chain reaction) were 14%. Serology studies, it is an easy diagnostic tool and faster to perform, and is under the possibility of performing in developing countries as well as underdeveloped countries. The PCR becomes the diagnosis preference of Ebola virus.

7. Therapy

In the context of hemorrhagic fever, there is a limited specific treatment for each virus. The treatment for hemorrhagic viral fever is principal just support and management of the complications that can result in lethal outcome.

We found the principal treatment was supported 0.83%, with hemodialisis, plasma, blood, erythrocytes, cryoprecipitate transfusion, and mechanical ventilation. Bleeding was identified in only 5 of the 78 patients (6.4%). However, along with support management 37% of the cases were managed with antibiotics empirically due to possible bacterial infection, treatment that was discontinued later when the diagnosis was confirmed, just 8.9% was treated with antiviral specific treatment and that cases were Ebola, Marburg, Crimean-Congo virus.

It is important made a mention of the specific antibiotic treatment for bacterial infections as result of hospital related infection due to prolonged admission, magament (Mechanical ventilation) or diseases at the same time (Dengue plus Malaria), in our cohort we found this causality It constitutes 14%, as well as the 46% did not received specific or empirical treatment as we mentioned it before.

An important part of all the management due to all this virus have the potential of causes bleeding ones more than other, and the management is base in which is the deficit or the clinical manifestations, in our cohort with found the 0.30%, the quantity of each packed used it, is variable but we can assure the cases in which we used it more are the cases as Ebola, Marburg, Crimean-Congo virus.

8. Prognosis

The prognosis seems to be related on which type of hemorrhagic fever it is, based in the Dengue and Hantaviruses constituted 70.5% of patients, the mortality rate in this specific cohort was 24%, the most lethal virus are the virus that proceed from African continent: Ebola, Marburg, Crimean-Congo virus, and Lassa virus, given the few cases that we have of this hemorrhagic fever associated with renal damage the mortality is over come at least 100% or more. The mortality between dengue virus was 21% and between hantavirus it was 13%. The worse prognosis and outcome related to sex was 16 male again 3 Female, that is

mean 84% were men.

9. Prevention

The prevention of each disease related with virus is related with the disponibility of vaccines that with have, and for the moment there are scarce vaccines for management of this diseases, recently the WHO approve the vaccine for dengue virus and lassa virus, and experimental vaccines for the other virus are in process or are being tested in the population, therefore the prevention it is confined to avoid the contact with source for example uses it of repellents, avoid travel to areas with a high prevalence.

The prevention of lethal outcome when the disease is ongoing mostly is based in support management as we discussed before in this cohort.

10. Conclusion

VHFs are serious diseases. Overall mortality was 32.3% in one cohort of 78 patients. The illness goes through several stages (3 - 5) of clinical features and some viruses in the group have a high case fatality rate. History of travel, knowledge of epidemiology, recognition of clinical syndrome are important for early diagnosis. Early diagnosis with aggressive supportive care is critical for improving clinical outcomes. Renal involvement is common. Amongst the cohort reviewed patients who had acute kidney injury, half of the patients required renal replacement support. However, some viruses caused greater kidney injury than others for instance, kidney injury is more severe in Dengue hemorrhagic fevers when compared to Hantaviruses. Simultaneous management of public health by prevention and control of outbreaks are particularly important.

Conflicts of Interest

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

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Adverse Short-Term Outcomes of Preterm Infants Born to Mothers with Preeclampsia by Doppler Cranial Ultrasound Investigation

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Abstract

Objective: In preeclampsia, abnormal fetal hemodynamics changes can be detected by Doppler ultrasound and predicted the perinatal outcome. But seldom studies focus on these preterm neonate's hemodynamics changes during 72 hours after birth and the adverse short-term outcomes. The present study is planned to assess the parameters of middle cerebral arteries and associate the short-term outcome at 37 weeks early term age in pregnancies complicated by preeclampsia. **Methods:** A total of 114 preterm neonates were included. The Doppler cranial ultrasound was performed to bilateral middle cerebral arteries within 12 - 24 hours, 36 - 48 hours, 60 - 72 hours after birth for all the eligible study neonates. The parameters of resistive index (RI), resistive index (PI) and middle cerebral velocity (MBFV) were recorded by Doppler cranial ultrasound and 106 infants survived assessed by the Neonatal Behavioral Neurological Assessment (NBNA) at 37 weeks early term-equivalent age. **Results:** There were a total of 106 subjects that finally completed the NBNA examination at 37 weeks of early term-equivalent age. In the surviving infants, there were a total of 26 infants with abnormal NBNA scores, among them, 12 infants' mothers were diagnosed with preeclampsia, accounting for up to 46.1%. In these preterm neonates, the lower velocity of bilateral middle cerebral arteries was observed in abnormal infants ($p < 0.05$) and the lowest velocity was observed in these abnormal babies with preeclampsia ($p < 0.05$). **Conclusion:** Velocity of middle cerebral artery is significantly abnormal in preeclampsia. The slower velocity in the 72 hours after birth, the higher associated with adverse perinatal short-term outcome.

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Keywords

Preeclampsia, Preterm Neonates, Doppler Cranial Ultrasound

1. Introduction

Preeclampsia (PE) is a major disease of pregnancy and is defined as the presence of maternal hypertension (>140/90 mmHg systolic/diastolic blood pressure) and proteinuria > 300 mg/24h) or a urine dipstick protein of 1+ during the second or third trimester of gestation and can present as late as 4 - 6 weeks postpartum [1] [2] [3]. It is a pregnancy-specific clinical disorder of widespread vascular endothelial malfunction and vasospasm and multisystem involvement. PE is a common unique to humans pregnancy and a global estimate of 3% to 5% of pregnancies and 15% with mild preeclampsia in China are complicated by PE with associated maternofetal morbidity and mortality [4] [5]. Although the etiology of preeclampsia is not clear, the placental insufficiency has been considered as a central figure in the etiology of PE, because a complex process of ischemia-reperfusion in the placenta reveals numerous placental infarcts and sclerotic narrowing of arterioles, meanwhile, the cytotoxic factors were released into the maternal circulation. There is a two-stage hypothesis model to explain the placenta ischemia-reperfusion, in stage one, the incomplete spiral artery was remodeled in the uterus. Then, antiangiogenic factors were released from the ischemic placenta into the maternal circulation which could cause the extensive endothelial damage (stage two) [1] [3] [5]. If the normal placenta artery remodeling process is impaired, then could lead to the repeated ischemia-reperfusion episodes and increase in oxidative stress damage in placenta, finally, this results in the systematic vascular endothelial dysfunction including exaggerated inflammatory response and cardiovascular complications. Until now, there is no cure for PE, thus it often requires termination of pregnancy, which could carry the inherent risks of impaired fetal growth and preterm birth [1] [2] [3] [6] [7].

Infants born preterm due to preeclampsia face a series of challenges in various areas of development problems and comorbidities disease [5]. The major short-term adverse effects of PE are intrauterine growth restriction, thrombocytopenia, neutropenia, and early and late-onset sepsis. Most important complications of prematurity include long-term neurodevelopmental problems, such as cerebral palsy, which would be at significantly increase risk 20-fold of being diagnosed with cerebral palsy [4], motor and cognitive impairment, visual and auditory deficits, and behavioral problems [5]. PE continues to have a high impact on the whole health system as it has numerous adverse effects on both mothers and infants.

There is limited literature on accurate prediction of the neurodevelopmental outcome of preterm infants born to PE mothers, thus, this study evaluated the

middle cerebral arteries parameters by cranial Doppler ultrasound at the first 72 hours post birth and early term 37 weeks gestational age neurodevelopmental assessment outcomes of infants born to PE mothers [8]. Furthermore, we try to establish the association of the early cranial hemodynamics parameters of preterm neonates with short-term neurodevelopment outcomes at their early term 37 weeks gestational age.

2. Materials and Methods

This prospective observational study was conducted at a neonatal intensive care unit of a tertiary-care hospital in China. Neonates born at 28 to 32 weeks of gestation were recruited. Neonates were excluded if they had major congenital anomalies, severe respiratory distress syndrome with invasive ventilation therapy, severe anemia (haemoglobin < 12 mg/dl) mean artery pressure less than 30 mmHg were excluded.

Copies of the study information sheet and the consent form were given to the interested parents when their infants were eligible for the study. All the participating parents were asked to complete a questionnaire about the pregnancy and medical history of the family. The parents brought the signed consent form and the completed questionnaire to the study candidate in the first baseline assessment. At the baseline assessment, the medical files of study neonates were reviewed to retrieve results of their physical examination and laboratory tests. Infants were stratified based on the gestational age at the time of delivery and presence or absence of maternal preeclampsia. The Doppler cranial ultrasound was performed to bilateral middle cerebral arteries within 12 - 24 hours, 36 - 48 hours, 60 - 72 hours after birth for all the eligible study neonates. The parameters of resistive index (RI), resistive index (PI) and middle cerebral velocity (MBFV) were recorded by Doppler cranial ultrasound. Before cUS Doppler investigation for each neonate, hand washing and standard cleaning of the transducers with disinfectant were performed to avoid cross-infection in the NICU.

The survived preterm neonates were assessed using the Neonatal Behavioral Neurological Assessment (NBNA) at their 37 weeks early term equivalent age before discharge from Neonates Intensive Care Unit.

The NBNA which is a comprehensive assessment on behavioral and neurological statuses of the infants [9] includes 20 items divided into four components: behavioral ability (6 items), active muscle tone (4 items), passive muscle tone (4 items), primary reflex (3 items) and general condition (3 items). Each item is graded on 3 levels (0, 1, and 2), with a total score of 40 points, the neonate would be considered as abnormal by total score less than 35 [9].

All statistical analyses were performed using SPSS version 24. Descriptive statistics included mean values and standard deviation for normally distributed continuous variables, median and interquartile range for skewed continuous variables, and frequencies and percentages for categorical variables. A value of $p < 0.05$ was considered statistically significant. Comparison between two groups

was done with independent sample T-test for normally distributed variables or Mann-Whitney U test for non-normally distributed data. Intra-group Doppler ultrasound parameters differences were tested using one-way repeated ANOVA for normally distributed data or Friedman Test for non-normally distributed data.

Study sample size was calculated using a confidence limit (α) of 95% and an absolute precision (D) of 20% with a significance level of 0.05 and the margin of error as 10%. In other words, 114 preterm neonates would be recruited in the present study.

3. Results

In this study, we observed a total of 114 preterm birth, among these neonates, one death (<28 weeks gestational age) within the first three days due to pulmonary hemorrhage, five deaths (28 - 32 weeks gestational age) due to the severe respiratory distress syndrome and two deaths (32 - 37 weeks gestational age) from severe sepsis in the second week after birth. Hence, 106 subjects completed the NBNA examination at 37 weeks of early term-equivalent age (Table 1). In the surviving infants, there were a total of 26 infants with abnormal NBNA scores, among them, 12 infants' mothers were diagnosed with preeclampsia, accounting for up to 46.1% (Table 2). Birth weight was not highly significantly different between the two PE groups and NON-PE group, the age of mother were higher in the PE group than those in the NON-PE group, also cesarean section had highly significant difference between two groups, all of neonates by cesarean in PE group.

There was no significant difference in the bilateral RI, PI value across the first 72 hours after birth in both PE and NON-PE group. A significant difference was found in the bilateral MBFV of NON-PE group across the three days ($p < 0.05$)

Table 1. Demographic and clinical variables in preterm neonates born to mothers with and without preeclampsia.

	All Neonates	Non-PE	PE	p*
Number of neonates	114	96	18	
Age of mother, years	31 (17 - 40)	31 (17 - 38)	33 (27 - 40)	0.042
Gestational age, weeks	31.2 (25.1 - 36.5)	31.2 (25.1 - 36.5)	31.5 (28.3 - 36.2)	0.215
Birth weight, grams	1540 (750 - 3020)	1560 (750 - 3020)	1485 (760 - 2285)	0.163
Vaginal delivery	51 (44.7%)	51 (100%)	0	
Cesarean	63 (60.3%)	45 (71.4%)	18 (28.6%)	<0.001

Table 2. NBNA assessment scores in surviving preterm neonates to mothers with and without preeclampsia.

	All Neonates	Non-PE	PE
Number of infants	106	88 (83%)	18 (17%)
Normal NBNA	80	74 (92.5%)	6 (7.5%)
Abnormal NBNA	26	14 (53.8%)	12 (46.1%)

*-tested using Mann-Whitney U test.

with the velocity of blood flow increasing gradually from day 1 to day 3 (Table 3).

There was a significant difference in velocity of middle cerebral arteries across three days measurements between preterm infants with normal NBNA and abnormal NBNA scores ($p < 0.05$), it was obviously decreased velocity in the abnormal groups (Table 4).

It was significant difference in the velocity of middle cerebral arteries in both PE and NON-PE group with abnormal NBNA scores, in the PE group, these abnormal neonates had lower velocity of bilateral middle cerebral arteries in the first 72 hours after birth (Table 5).

4. Discussion

Although the detrimental short-term and long-term effects of PE on both mother and infant have not been clarified. Fetal ultrasound and Doppler ultrasonography are considered as a noninvasive and clinically useful method for monitoring high-risk pregnancies and detecting the perinatal abnormal. In the recent study, these studies focus on the association of the parameters of middle cerebral artery and umbilical artery in predicting perinatal outcome in fetus complicated by PE with or without intrauterine growth restriction. Several similar studies have shown that the ratios of Middle cerebral artery/umbilical artery PI and RI had the maximum specificity but poor specific for predicting small-for-gestational-age and adverse perinatal outcome [6] [10]. However, one of meta-analysis was done by Morris *et al.* indicated that there was a low predictive accuracy of middle cerebral artery Doppler fetus ultrasound for predicting adverse perinatal outcome due to various limitations of studies [10].

Thus, the accurate prediction of the neurodevelopmental outcome is still under research. In this study, we explore the association of the parameters of bilateral middle cerebral arteries with the short-term outcome in the critical first 72 hours after birth and provide the timely intervention information.

There are two major brain injuries for preterm infants: severe intraventricular hemorrhage and periventricular leukomalacia, both of them are strongly associated with neurodevelopmental impairment. The pathophysiology of injury involves the premature infant's fragile immature cerebral vascular structures, any fluctuations in cerebral blood flow in the highly vascularized germinal matrix would increase the risk of the hemorrhage and immature autoregulatory

Table 3. Hemodynamic parameters in surviving preterm neonates to mothers with and without preeclampsia.

Hemodynamics parameters	PE	NON-PE
RI Left mean (min - max)		
Day 1	0.76 (0.56 - 1.29)	0.75 (0.57 - 1.85)
Day 2	0.73 (0.66 - 1.06)	0.77 (0.56 - 1.10)
Day 3	0.75 (0.60 - 1.19)	0.71 (0.54 - 1.20)
p*	0.57	0.66
PI left mean (min - max)		
Day 1	1.41 (0.85 - 1.90)	1.40 (0.82 - 1.70)
Day 2	1.23 (0.81 - 2.01)	1.29 (0.76 - 1.90)
Day 3	1.36 (0.97 - 1.90)	1.41 (0.78 - 1.75)
p*	0.55	0.77
MBFV Left mean (min - max)		
Day 1	22.7 (19.0 - 25.7)	26.2 (20.9 - 37.3)
Day 2	22.4 (19.0 - 28.0)	26.6 (19.2 - 38.0)
Day 3	23.1 (18.7 - 31.0)	27.7 (19.7 - 39.6)
p*	0.89	< 0.001
RI right mean (min - max)		
Day 1	0.73 (0.54 - 1.72)	0.75 (0.54 - 1.87)
Day 2	0.74 (0.51 - 1.70)	0.74 (0.53 - 1.00)
Day 3	0.77 (0.54 - 1.10)	0.76 (0.55 - 1.65)
p*	0.76	0.18
PI right mean (min - max)		
Day 1	1.28 (0.95 - 1.95)	1.41 (0.82 - 2.08)
Day 2	1.16 (0.71 - 1.90)	1.29 (0.76 - 2.16)
Day 3	1.27 (0.81 - 2.08)	1.42 (0.76 - 1.98)
p*	0.06	0.53
MBFV right mean (min - max)		
Day 1	22.4 (18.5 - 26.9)	25.2 (20.10 - 39.9)
Day 2	23.0 (17.6 - 28.8)	26.9 (19.50 - 38.9)
Day 3	22.1 (19.10 - 28.70)	27.8 (22.0 - 39.7)
p*	0.69	<0.001

Day 1 - 12 to 24 hours after birth; Day 2 - 36 - 48 hours after birth; Day 3 - 60 - 72 hours after birth. *-testing using Friedman Test. MBFV Left-velocity of left middle cerebral artery; MBFV Right-velocity of right middle cerebral artery; PI Left-pulsatility index of left side; PI Right-pulsatility index of right side; RI Left-resistive index of left side; RI Right-resistive index of right side.

Table 4. MBFV velocity in surviving preterm infants with normal or abnormal NBNA scores.

	Normal NBNA	Abnormal NBNA	p*
Number of neonates	80	26	
MBFV left day 1	26.3 (20.9 - 27.5)	23.6 (19.0- 27.3)	0.002
MBFV right day 1	25.3 (20.1 - 29.9)	22.6 (18.5 - 27.7)	0.002
MBFV left day 2	27.5 (19.2 - 28.8)	23.0 (19.0 - 28.3)	0.001
MBFV right day 2	27.6 (20.3 - 28.9)	23.9 (17.6 - 27.2)	<0.001
MBFV left day 3	27.9 (19.7 - 39.6)	23.5 (18.7 - 33.3)	<0.001
MBFV right day 3	28.3 (22.0 - 39.7)	24.5 (19.1 - 32.6)	<0.001

Day 1 - 12 to 24 hours after birth; Day 2 - 36 - 48 hours after birth; Day 3 - 60 - 72 hours after birth. *-tested using Mann-Whitney U test.

Table 5. MBFV in surviving preterm neonates with abnormal NBNA scores.

	Non-PE	PE	p*
Number of neonates	14	12	
MBFV left day 1	24.6 (21.5 - 27.3)	21.5 (19.0 - 22.5)	0.023
MBFV right day 1	24.4 (20.3 - 27.7)	22.0 (18.5 - 25.3)	0.004
MBFV left day 2	26.1 (20.4 - 28.3)	22.4 (19.0 - 27.5)	0.016
MBFV right day 2	25.7 (21.5 - 27.2)	23.0 (17.6 - 26.4)	0.047
MBFV left day 3	26.5 (21.7 - 33.3)	20.9 (18.7 - 27.6)	<0.001
MBFV right day 3	27.3 (22.0 - 32.6)	21.8 (19.1 - 28.7)	<0.001

Day 1 - 12 to 24 hours after birth; Day 2 - 36 - 48 hours after birth; Day 3 - 60 - 72 hours after birth. *-tested using Mann-Whitney U test.

system, with rapid changes in perfusion causing rupture of the germinal matrix vessels, or triggering repeated ischemia-reperfusion oxidative stress, leading to white matter injury which is the secondary injury from the persistently low blood pressure and low blood flow in the brain [11]. The pathophysiology of periventricular leukomalacia is a multifactorial and complex process, which is the result of hypoxia, ischemia and inflammation on the progenitor oligodendrocyte cells during trimester gestation [11] [12].

In this study, we observed the obvious decrease in velocity of middle cerebral arteries of infants with abnormal NBNA scores compared with other normal infants. Among these abnormal infants, whose mothers had preeclamptic, they had much lower velocity of bilateral middle cerebral arteries.

Due to pathology of PE, it is characterized with placental vascular lesions, and the main manifestations of fetus present the underlying chronic hypoxia and increase the fetal growth restriction. The previous studies reported that the levels of erythropoietin in cord blood of fetus with their mother suffered preeclampsia

were increased at birth or 48 hours before birth, which suggested chronic and acute hypoxia in these neonates. We know that erythropoietin which is a glycoprotein hormone and it can't cross the placenta, so the umbilical cord blood erythropoietin is of fetal origin, meanwhile, hypoxia stimulates the production of erythropoietin in the fetal liver.

Elevated umbilical cord erythropoietin levels are evidence of chronic fetal hypoxia, as this result, the compromised oxygen and glucose supply to the brain cells leads to cellular energy failure during critical development period [13]. From the beginning of the third trimester to the end of the third trimester, oligodendrocytes cells are formed in the ventricular zone which allows messages to travel down the length of the axon so that neurons can quickly communicate with each other, and these cells are vulnerable to oxidative stress, thus it means myelination deficient is inevitable due to preterm birth [14].

To our knowledge, this is the first study to observe the short-term outcomes in preterm neonates with or without mother preeclampsia. The main strengths of this study investigated the middle cerebral blood RI, PI and velocity dynamic changes at the first 72 hours after birth in the preterm birth, which provide the evidence that underlying factors for cerebral ischemia-reperfusion damage due to slower velocity of middle cerebral arteries in these neonates with their mother preeclampsia. And also due to low sample size in PE groups, data bias may occur. As our study limitation, in this study, we did not compare the Doppler data of these fetuses and miss the further long-term follow up for these abnormal infants and maybe they have confounder effects in final results.

5. Conclusion

Slower velocity of middle cerebral arteries in the first 72 hours after birth is associated with the adverse short-term outcome in preterm infants with mother preeclampsia.

Conflicts of Interest

The authors declare no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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