ORIGINAL ARTICLE

Blood Parameters and Osteoradionecrosis of the Jaw

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ABSTRACT

Introduction: A link between hematological parameters, radiation therapy, and osteoradionecrosis of the jaw has been described, but with limited evidence. Aim: The objective of this study was to identify the changes in the blood components and trend following completion of radiation therapy and during the period of osteoradionecrosis (ORN). **Methodology:** This was a retrospective record review study involving 60 patients' data dated from 2nd of August 2005 to 21st of October 2019. Full blood count (FBC) that included hemoglobin, hematocrit, platelet, neutrophils, and lymphocytes were analyzed. We divided the stages of FBC analysis into three stages from post-radiotherapy to the ORN period. **Results:** From the 60 patients, 19 (31.7%) patients were diagnosed with ORN. Median radiotherapy dose for all 60 patients was 66.0 Gy (IQR 10.0). Hemoglobin, platelets, neutrophils, and lymphocytes remained within the normal range following radiotherapy and throughout the development of ORN. The median hematocrit-to-hemoglobin ratio (HHR) and platelet-to-hemoglobin ratio (PHR) showed no significant difference in Stage 1 and Stage 2. Similarly, changes in the median neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were not statistically significant in the two stages ($p>0.05$). Both NLR and PLR exhibited a declining trend across all three stages. **Conclusion:** The blood components remained within the normal range after radiotherapy and during the development of osteoradionecrosis, while the median neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio were elevated relative to the hospital reference range. Notably, both ratios showed a declining trend from the post-radiotherapy period to the onset of osteoradionecrosis.

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INTRODUCTION

Radiotherapy has been known for its forte of being curative or palliative agent against head and neck cancers since it was first introduced by Henri Coutard in 1934 (1). Ionizing radiation targets the DNA of the malignant cells with direct and indirect mutilations making it beyond repair. However, such treatment comes with its setbacks as the neighbouring cells are equally affected leading to many detrimental conditions such as bone necrosis (2). One of the most debilitating long-term consequences of radiotherapy (RT) or concurrent chemoradiotherapy (CCRT) is radiation-induced osteoradionecrosis (ORN) and lower jaw is the most frequently affected site, possibly due to its relatively poor blood supply (3).

Osteoradionecrosis (ORN) of the jaws is defined as exposed irradiated bone that does not heal for at least three months, in the absence of persistent or recurrent tumour (4).

ORN can be classified according to its clinical presentation. Notani et al (2003) described three stages based on the bone involvement (5):

Stage I: ORN confined to alveolar bone
Stage II: ORN limited to the alveolar bone and/or mandible above the level of the inferior alveolar canal
Stage III: ORN involving the mandible below the level of the inferior alveolar canal and/or skin fistula and/or pathological fracture.

First documented by Regaud in 1922, ORN has

persisted as a concern for many decades (6). Despite the surmountable studies made, it continues to pose as a threat to physicians and harms patients' quality of life (7-9). The documented occurrence ranged from 3% to 11.8% but more recent research indicated a decline in number, in line with the advancement of radiation administration particularly the intensity modulated radiation therapy (10-14). Several theories elucidating ORN have been proposed, and they were used in the construction of treatment strategies. First, theory by Meyer as a subsequent infection resulting from trauma induced on the irradiated jaw bone (15). Second, Marx made a paradigm shift from infection to the inability of the tissue itself to support complete healing, due to the triad of hypoxia, hypovascularity, and hypocellularity as a result of radiation-induced damage to healthy vascular endothelium (4). Third, current theory of radiation-induced fibrosis showed abnormal activation and regulation of fibroblast activity (16,17).

Increased risk and severity of ORN is associated by a number of factors, namely advanced age and stage of the malignancy, radiotherapy (RT) dose, post-RT dental extractions (18). The onset of ORN most often occurs between 4 months and 2 years but the risk remains for life, although to a lesser degree (19). Patients may, in fact, exhibit marrow changes or vascular alterations on CT or MRI for months or years before clinically evident ORN (20).

Alterations in the hematological components, such as neutrophils, lymphocytes, and monocytes, commonly reflect the host immune system's response to tumours as well as to its treatment (21). The white cells have been used as markers for many conditions, both in acute and chronic diseases. The neutrophil-to-lymphocyte ratio (NLR) is widely recognized as a biomarker of the immune-inflammatory response to cancer and other diseases (22). On the other hand, pre-treatment hemoglobin-to-platelet ratio (HPR) have been explored by various researchers to predict survival outcomes for nasopharyngeal cancer (23-25). A series of studies from Yilmaz et al. and Somay et al. have delved into the application of routine haematological profiles (3, 26-29), particularly the HPR, in forecasting the occurrence of ORN in cases of locally advanced nasopharyngeal carcinoma. Their hypothesis revolved around the HPR acting as a potential biomarker due to its role in indicating hypoxic conditions, a concept elucidated by Marx and his associates (3,4,26-29). Apart from utilizing the HPR, other investigations have examined the haemoglobin to haematocrit ratio (HHR) as a potential risk indicator for the development of ORN, especially among children affected by sickle cell disease (30-32).

From the above theories and literature, vascular compromise, tissue hypoxia, persistent infection, chronic inflammation, and fibrosis have been recognized as key contributors to ORN development. However, the complex interplay between these factors necessitates further investigation, particularly regarding the role of hematological components in disease progression. The studies above have demonstrated that hematological markers, both individually and as ratios, serve as reliable indicators of systemic inflammation, immune status, and disease severity in various conditions.

Therefore, the objective of this study was to identify the changes in the blood components (hemoglobin, hematocrit, platelets, neutrophils, and lymphocytes) and trend following completion of radiation therapy and during the period of having ORN.

MATERIALS & METHODS

Study population

A retrospective record review was conducted at the Oral & Maxillofacial Surgery Clinic, Hospital Canselor Tuanku Muhriz (HCTM). Records of adult patients dated 2nd of August 2005 to 21st of October 2019 were reviewed .

Records of patients who met inclusion and exclusion criteria were incorporated into this study. The inclusion and exclusion criteria are as below:

The inclusion criteria:
1. Patients who received radiotherapy to the head and neck in the form of curative, adjuvant or palliative.
2. Records of full blood count were present both before and after radiation therapy.

The exclusion criteria were:
1. Documented case of recurrence or metastatic tumor to the ORN site.

Sample size was calculated based on OpenEpi source. The reference was from a Taiwanese ORN study (33).
- Number of populations included in the study: 522
- Prevalence of ORN post extraction in percentage: 5.17% (27 patients).

Thus, with a confidence level of 95%, the sample size needed were 66 records.

The records were collected using the Caring Hospital Enterprise System (C-HETS) system as well as hard-copy records. Data related to demographics such as age, gender, ethnic groups, smoking and alcohol consumption and clinical data such as diagnosis, tumour site, stage of tumour, radiotherapy, chemotherapy and surgery and date of ORN diagnosis were collected. The full blood was obtained from the medical records. We used the HCTM standard range for comparison which were as below:

Hemoglobin (12.0 - 15.0) g/l
Hematocrit (36 - 46) %,

Platelets (150 - 410) x109/L,
White Cell Count (4 - 10) x109/L,
Neutrophils (2.0 - 7.0) x109/L
Lymphocytes (1.0 - 3.0) x109/L.

i. Anemia was defined as a hemoglobin level lower than 12 g/dL and a hematocrit level less than 36%.
ii. Thrombocytosis was defined as having more than 410 x 10^9/L of platelets, and thrombocytopenia was defined as having less than 150 x 10^9/L.
iii. Leukopenia was defined as a total white blood cell count less than 4.0 x 10^9/L, and a neutrophil count less than 2.0 x 10^9/L was considered neutropenia.
iv. The dependent variable was ORN, whether it was present or absent. ORN was defined as presence of bony exposure for at least three months consecutively.

When it involved a tooth extraction, an unhealed socket (with ORN) was described as presence of bony exposure three-months post-extraction (34,35).

We categorized the full blood count (FBC) into three stages (Figure 1):

Stage 1: The median FBC was calculated from the start of radiotherapy until its completion.
Stage 2: The median FBC was measured from the post-radiation period until the diagnosis of osteoradionecrosis (ORN) in ORN cases. In non-ORN cases, Stage 2 continued indefinitely.
Stage 3: The median FBC was assessed after the diagnosis of ORN.

It is important to note that only ORN cases had FBC data in Stage 3.

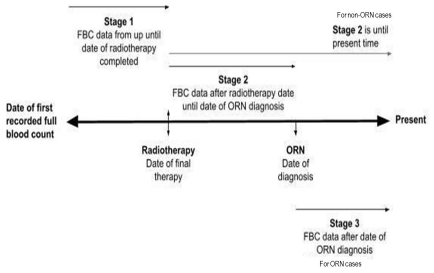

Figure 1: Showing the three stages of FBC following completion of radiotherapy and throughout the period of ORN.

Ethical Approval

The study protocol adhered to the ethical guidelines of the Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects and received the ethical approval from the Research Ethics Committee, Universiti Kebangsaan Malaysia (UKM PPI/111/8/JEP-2022-198 dated 14 April 2022).

Statistical analysis

IBM SPSS Statistics version 22.0 was used for data entry and analysis (Armonk, NY: IBM Corp.). Descriptive statistics on the characteristics of the study factors as well as the outcome (ORN) were reported in the form of frequencies, means, standard deviations (SDs), medians and interquartile ranges (IQRs) where appropriate. Mann-Whitney U test was used to compare the changes in blood parameters following completion of radiation therapy and during the period of having ORN. Mann-Whitney U test was performed because the data was not normally distributed. Significant level was set at 0.05.

RESULTS

A total of 60 patients were included for this study. From the 60 patients, 19 (31.7%) patients were diagnosed with ORN. In general, the patients' mean age was 50.43 years with standard deviation (SD) of 10.56 (Table I).

Table I: Demographic distribution and habits of the patients

DEMOGRAPHIC INFORMATION	NUMBER OF PATIENTS, n (%)		
	ORN n(%)	NON ORN n(%)	TOTAL 60 (100.0)
Age (years):			
Mean	50	50.63	50.43
Standard Deviation (SD)	9.53	11.12	10.56
Age Categories (years):			
≤45	6 (31.6)	16 (39.0)	22 (36.7)
>45	13 (68.4)	25 (61.0)	38 (63.3)
Gender:			
Male	11 (57.9)	23 (56.1)	34 (56.7)
Female	8 (42.1)	18 (43.9)	26 (43.3)
Ethnic groups:			
Malay	8 (42.1)	17 (41.5)	25 (41.7)
Chinese	11 (57.9)	21 (51.2)	32 (53.3)
Indian	–	2 (4.9)	2 (3.3)
Others	–	1 (2.4)	1 (1.7)
Smoking:			
Smoker	5 (26.3)	14 (34.1)	19 (31.7)
Non-Smoker	13 (68.4)	24 (58.5)	37 (61.7)
No Information	1 (5.3)	3 (7.3)	4 (6.7)
Alcohol drinking:			
Drinker	2 (10.5)	3 (7.3)	5 (8.3)
Non-drinker	14 (73.7)	32 (78.0)	46 (76.7)
No data	3 (15.8)	6 (14.6)	9 (15.0)

The age range was between 30-77 years. There were 34 males (56.7%) and 26 females (43.3%) in the series. Overall, most of the patients were Chinese (53.3%) and Malays (41.7%), followed by Indians (3.3%) and other ethnic groups (1.7%). For the ORN cases, most of the patients were non-smokers (68.4%) and non-drinkers (73.7%).

Overall, 51.7% of all the patients were diagnosed with nasopharyngeal carcinoma (NPC) followed by 35% with squamous cell carcinoma (SCC). Similarly, within the ORN cases, 52.6% of patients were diagnosed

with NPC, followed by 26.3% with SCC. For the non-ORN cases, 51.2% patients were diagnosed with NPC and 16% with SCC. 51.7% of the patients were Stage 3 and 4, and 30% in Stage 1 and 2, according to the TNM Staging. Median radiotherapy dose (Gy) for all 60 patients was 66.00 Gy (IQR 10.00). Among the ORN patients, 36.8% had radiotherapy dosage of lesser than 60 Gy while 63.2% had radiotherapy dosage of more than 60 Gy.

Twenty-eight (46.7%) patients underwent concurrent chemoradiotherapy (CCRT), where 11 (57.9%) patients were from ORN group and 17 (41.2%) patients were from the non-ORN group. There were six patients (10.0%) who had chemotherapy and one patient had ORN. 25(41.7%) patients did not undergo any chemotherapy or radiotherapy. One patient had no documentation regarding adjuvant therapy.

Most of the patients did not go through any surgery (68.3%) of the primary diseases. Of those who underwent surgery, 20% had mandibular surgery and 8.3% had maxillary surgery. For the ORN cases, 63.2% did not have any surgery while 31.6% had mandibular surgery and 5.3% had maxillary surgery. Tumour diagnosis and management are shown in Table II.

For the hematologic factors, of the 60 cases, 33 cases had their FBC data to be incorporated into Stage 1, which included 10 ORN cases and 23 non-ORN cases. For Stage 2, 54 cases were included, involving 16 ORN cases and 38 non-ORN cases. Lastly, Stage 3 included 11 ORN cases. Hematologic factors according to the stage are shown in Table IIIa, IIIb and IIIc.

Table II: Characteristics of the tumor and treatment

CLINICAL CHARACTERISTICS	NO. OF PATIENT, n (%)		
	ORN n(%)	NON ORN n(%)	TOTAL 60 (100.0)
Tumour site:			
Larynx	–	3 (7.3)	3 (5.0)
Oral & Oropharynx	6 (31.6)	13 (31.7)	19 (31.7)
Nasopharynx	10 (52.6)	21 (51.2)	31 (51.7)
Others	3 (15.8)	4 (9.8)	7 (11.7)
Malignancy diagnosis:			
SCC	5 (26.3)	16 (39.0)	21 (35.0)
NPC	10 (52.6)	21 (51.2)	31 (51.7)
Others	4 (21.1)	4 (9.8)	8 (13.3)
TNM staging:			
1–2	7 (36.8)	11 (26.8)	18 (30.0)
3–4	10 (52.6)	21 (51.2)	31 (51.7)
No information	2 (10.5)	9 (22.0)	11 (18.3)
Surgery history:			
No surgery	12 (63.2)	29 (70.7)	41 (68.3)
Mandibular surgery	6 (31.6)	6 (14.6)	12 (20.0)
Maxillary surgery	1 (5.3)	4 (9.8)	5 (8.3)
No information	–	2 (4.9)	2 (3.3)
Radiotherapy dosage (Gy):			
Median	66	66	66
Interquartile Range	10	10	10
Radiotherapy dosage (Gy):			
≤60	7 (36.8)	17 (41.5)	24 (40.0)
>60	12 (63.2)	24 (58.5)	36 (60.0)
Chemotherapy:			
Yes	1 (5.3)	5 (12.2)	6 (10.0)
No	7 (36.8)	18 (43.9)	25 (41.7)
Concurrent	11 (57.9)	17 (41.2)	28 (46.7)
No information	–	1 (2.4)	1 (1.7)

Table IIIa: FBC data before radiotherapy (Stage 1)

FULL BLODD COUNT	NO. OF PATIENT (%)			p-value (Mann-Whitney)
	ORN n=10	NON ORN n=23	TOTAL n=33	
Duration FBC before RT (Years):				0.21
Median	0.31	0.5	0.44	
Interquartile range	0.61	2.99	1.24	
Min	0.03	0.01	0.01	
Max	1.65	16.63	16.63	
Hematocrit (%)				0.27
Median	40.05	35.68	36.3	
Interquartile range	12.85	3.76	6.1	
Min	28.9	29.86	28.9	
Max	49.64	43.6	49.64	
Hemoglobin count (g/dL)				0.29
Median	13.42	12.18	12.25	
Interquartile range	4.03	1.74	2.07	
Min	8.9	9.94	8.9	
Max	17.05	14.5	17.05	
Platelet count (/mcL)				0.34
Median	297.23	242.8	258.75	
Interquartile range	80.65	110	96.05	
Min	204.81	167	167	
Max	483	434	483	
Total white cell count (/mcL)				0.66
Median	9.5	8.57	8.93	
Interquartile range	2.36	4.95	3.96	
Min	7.1	4.95	4.95	
Max	11.17	15.74	15.74	
Neutrophil (/mcL)				0.66
Median	7.08	6.7	6.83	
Interquartile range	2.11	4.33	3.31	
Min	4.2	2.95	2.95	
Max	9.03	13.26	13.26	
Lymphocytes (/mcL)				0.71
Median	1.21	1.29	1.28	
Interquartile range	1.49	0.49	0.64	
Min	0.3	0.56	0.3	
Max	3.2	2.85	3.2	

Table IIIb: FBC data after radiotherapy (Stage 2)

FULL BLODD COUNT	NO. OF PATIENT (%)			p-value (Mann-Whitney)
	ORN n=10	NON ORN n=23	TOTAL n=33	
Duration FBC between RT until ORN or present (Years):				0.54
Median	5.7	8.08	7.11	
Interquartile range	5.76	8.37	7.65	
Min	0.62	0.09	0.09	
Max	19.04	27.24	27.24	
Hematocrit (%)				0.15
Median	40.77	37.44	38.78	
Interquartile range	7.87	7.41	6.72	
Min	33.9	28.44	28.44	
Max	45.83	48.6	48.6	
Hemoglobin count (g/dL)				0.13
Median	13.67	12.4	12.88	
Interquartile range	1.96	2.78	2.38	
Min	10.92	9.47	9.47	
Max	15.6	16.13	16.13	
Platelet count (/mcL)				0.82
Median	253.53	245.96	249.46	
Interquartile range	84.04	107.35	95.09	
Min	126.71	113.19	113.19	
Max	384.5	706.67	706.67	
Total white cell count (x109/L)				0.48
Median	6.6	7.5	7.04	
Interquartile range	2.71	4.29	3.08	
Min	4.87	3.26	3.26	
Max	11.12	19.73	19.73	
Neutrophil (/mcL)				0.97
Median	4.62	4.73	4.7	
Interquartile range	2.16	2.85	2.61	
Min	3.33	2.21	2.21	
Max	8.53	16.5	16.5	
Lymphocytes (/mcL)				0.22
Median	1.11	1.25	1.24	
Interquartile range	0.68	0.81	0.86	
Min	0.3	0.46	0.3	
Max	1.9	4.96	4.96	

Hemoglobin

For Stage 1, the median hemoglobin (Hb) was 13.42 g/dL (IQR 4.03) for the ORN cases and 12.18 g/dL (IQR 1.74) for the non-ORN cases. For Stage 2, the median hemoglobin (Hb) was 13.67 g/dL (IQR 1.96) for the ORN cases and 12.40 g/dL (IQR 2.78) for the non-ORN cases. At Stage 3, the median Hb was 12.67 g/dL with IQR 1.90.

Hematocrit

The median hematocrit (Hct) for Stage 1 ORN case was 40.05 % (IQR 12.85) and 35.68% (IQR 3.76) for the non-ORN cases. In Stage 2, the median Hct was 40.77% (IQR 7.87) for the ORN cases, and 37.44% (IQR 7.41) for the non-ORN cases. In Stage 3, the median Hct was 38.00% (IQR 6.60).

Platelet count

For the ORN cases, the median platelet count was 297.23/mcL (IQR 80.65) in Stage 1, 253.53/mcL (IQR 84.04) in Stage 2 and 255.67/mcL (IQR 115.15) in Stage 3. For the non-ORN cases, the median platelet count was 242.80/mcL (IQR 110.00) in Stage 1 and 245.96/mcL (IQR 107.35) in Stage 2.

Total white cell count

For the ORN cases, the median total white cell count was 9.50/mcL (IQR 2.36) in Stage 1, 6.60/mcL (IQR 2.71) in Stage 2 and 7.60/mcL (IQR 2.19) in Stage 3.
For the non-ORN cases, the median total white cell count was 8.57/mcL (IQR 4.95) in Stage 1 and 7.50/mcL (IQR 4.29) in Stage 2.

Neutrophil

For the ORN cases, the median neutrophil count was 7.08/mcL (IQR 2.11) in Stage 1, 4.62/mcL (IQR 2.16) in Stage 2 and 5.57/mcL (IQR 3.45) in Stage 3.For the non-ORN cases, the median neutrophil count was 6.70/mcL (IQR 4.33) in Stage 1 and 4.73/mcL (IQR 2.85) in Stage 2.

Lymphocytes

For the ORN cases, the median lymphocyte count was 1.21/mcL (IQR 1.49) in Stage 1, 1.25/mcL (IQR 0.35) in Stage 2 and 1.11/mcL (IQR 0.68) in Stage 3. For the non-ORN cases, the median lymphocyte count was 1.29/mcL (IQR 0.49) in Stage 1 and 1.25/mcL (IQR 0.81) in Stage 2.

Table IV shows the blood factors ratio, i.e. hematocrit to hemoglobin ratio, platelet to hemoglobin ratio, platelet to lymphocyte ratio and neutrophil to lymphocyte ratio.

Hematocrit to hemoglobin ratio

Both the hematocrit (Hct) and hemoglobin (Hb) levels were used to ascertain the presence of anemia (36). The median hematocrit to hemoglobin ratio (HHR) for all the stages and between ORN and non-ORN cases did not show much change compared to the normal values and ratio from our hospital, HCTM. The median HHR remained constant throughout the three stages.

Platelet to haemoglobin ratio

Platelet to hemoglobin ratio (PHR) was shown to be related to many vascular diseases (37). Throughout the three stages, the median PHR were within the HCTM normal range, for both the ORN and non-ORN cases.
In relation to the trend, the highest median PHR was observed among the ORN cases in Stage 1, and the ratio declined following radiotherapy.

Table IIIc: FBC data after the diagnosis of ORN for the ORN group only (Stage 3)

FULL BLODD COUNT	NO. OF PATIENT (%)
	ORN n=11
Duration FBC between RT until ORN or present (Years):	
Median	2.84
Interquartile range	7.11
Min	0.5
Max	13.42
Hematocrit (%)	
Median	38
Interquartile range	6.6
Min	31.9
Max	49.53
Hemoglobin count (g/dL)	
Median	12.67
Interquartile range	1.9
Min	10.75
Max	16.76
Platelet count (/mcL)	
Median	255.67
Interquartile range	115.15
Min	109.27
Max	327
Total white cell count (x109/L)	
Median	7.6
Interquartile range	2.19
Min	4.3
Max	10.01
Neutrophil (/mcL)	
Median	5.57
Interquartile range	3.45
Min	2.6
Max	7.85
Lymphocytes (/mcL)	
Median	1.25
Interquartile range	0.35
Min	0.8
Max	2.15

Platelet to lymphocyte ratio

Platelet to lymphocyte ratio (PLR) was a novel marker for inflammation (38). The median PLR was observed to be higher than the normal HCTM values in all the stages and for both the ORN and non-ORN cases. The trend of median PLR among the ORN cases declined with the stages.

Neutrophil to lymphocyte ratio

Peripheral neutrophil to lymphocyte ratio (NLR) was a marker for the immune-inflammation status of a patient (21). In this study, the median NLR was observed to be higher than the normal HCTM values in all the stages and for both the ORN and non-ORN cases. The trend of median NLR among the ORN and non-ORN cases declined with the stages.

In summary, the changes observed in the blood components and the blood factor ratios were not statistically significant.

Table IV: Blood factor ratios in Stage 1,2 and 3

HCTM values (range)	Blood factor ratio	Stage 1			Stage 2			Stage 3
		ORN	Non-ORN	Man Whitney P-value	ORN	Non-ORN	Man Whitney P-value	ORN
	Hct & Hb							
Hct: 36-46	Median Hct	40.05	35.68	0.43	40.76	37.43	0.69	38
Hb: 12-15	Median Hb	13.42	12.18		13.67	12.4		12.67
HHR: 3-3.06	Median HHR	2.96	2.95		2.96	2.97		2.96
	Interquartile range HHR	0.11	0.13		0.06	0.09		0.07
	Plt & Hb							
Plt: 150-410	Median Plt	297.23	242.8	0.86	253.53	245.96	0.3	255.67
Hb: 12-15	Median Hb	13.42	12.18		13.67	12.4		12.67
PHR: 12.5-27.3	Median PHR	19.57	21.34		18.55	19.96		18.29
	Interquartile range PHR	7.01	10.3		6.96	6.59		9.31
	Plt & lymphocyte							
Plt: 150-410	Median Plt	297.23	242.8	0.5	253.53	245.96	0.52	255.67
Lymph-ocyte: 1.0-3.0	Median lymph-ocytes	1.21	1.29		1.11	1.25		1.25
PLR: 137-150	Median PLR	230.14	208.4		218.55	208.7		186.04
	Interquartile range PLR	265.12	95.32		163.98	116.79		196.31
	Neutrophil & lymphocyte							
Neutro-phil: 2.0-7.0	Median neutrophil	7.08	6.7	0.48	4.62	4.73	0.2	5.56
Lymph-ocyte: 1.0-3.0	Median lymphocyte	1.21	1.28		1.11	1.25		1.25
NLR: 2-2.3	Median NLR	7.07	5.42		4.83	3.93		4.97
	Interquartile range NLR	6.75	3.58		2.21	3.08		5.35

Abbreviations: HCTM: Hospital Canselor Tuanku Muhriz; ORN: osteoradionecrosis; Hct: hematocrit; Hb: hemoglobin; HHR: hematocrit to hemoglobin ratio; Plt: platelet; PHR: platelet to hemoglobin ratio; PLR: platelet to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio

DISCUSSION

In this study, the majority of patients were diagnosed with head and neck cancers, such as nasopharyngeal carcinoma (NPC) (51.7%) and squamous cell carcinoma of the oral cavity (35.0%). Additionally, 51.7% of cases were classified as TNM stages 3 to 4. Most of these patients were around 50 years old. A total of 56.7% underwent combined radiotherapy and chemotherapy, while the remaining 43.3% received radiotherapy alone. Both treatments have a significant impact on blood components.

All blood components originate from pluripotent hematopoietic stem cells, which differentiate into various cell lineages (39). Generally, all cells primarily develop and mature in the bone marrow, except the lymphocytes and the bone marrow is sensitive to radiation (40,41). Leukopenia and neutropenia were the most common high grade hematologic toxicities that occurs during the acute phase of chemoradiation therapy and the effect is often temporary (42).

Similar to chemotherapy, reduction in the number of white blood cells, red blood cells, and platelets may occur depending on the area treated and the radiation dosage administered, as a consequence of radiation-induced bone marrow depression (43). While such decreases are typically temporary due to the treatment itself, some can be irreversible (43).

Our research aimed to investigate the characteristics of the hematological profile among the post-radiotherapy patients, particularly those with ORN. We categorized the irradiated patients into three stages as described in the Methodology.

For the hemoglobin and hematocrit, there was a slight increase in the median in Stage 2 compared to Stage 1 and declined in Stage 3 for the ORN cases, whereas there was not much change observed in the non-ORN cases in Stage 1 and 2. Similar pattern was described by some studies (43,44). The median hematocrit to hemoglobin ratio (HHR) also did not show much change when compared to our hospital's normal values. This could be explained that mature erythrocytes are acutely resistant to radiotherapy (45) even up to doses exceeding 200 Gy (39). The majority of patients in this study received a radiation dose exceeding 60 Gy, with 12 (20%) of them developing ORN, while 7 (11.7%) other patients with ORN had received a radiation dose below 60 Gy.

The hemoglobin to hematocrit ratio or also known as mean corpuscular Hb concentration (MCHC) was shown as a significant predictor for a type of osteonecrosis, which was the avascular necrosis (AVN) among children with sickle cell disease (30). AVN is an osteonecrosis that results from bone ischemia (30). Similarly, in the ORN pathogenesis, hypovascular, hypocellular and hypoxia characteristics of the tissue was first described by Marx in 1983 (4) before challenged by Delanian et al. (2004) with their fibroatrophic theory (16).

The platelets, just like the hemoglobin, are not very much affected by radiation therapy (39). The number may reduce slightly but still within normal range and recover within a short period of time. Swanson et al (2022) showed the platelet counts in their patients declined to 12.7% and returned to the reference line after more than three months (39). A study by Yilmaz et al. (2023) demonstrated that low pre-treatment hemoglobin to platelet ratio (HPR) levels can result in a higher occurrence of ORN following chemoradiation (3,26).

In relation to the white cells, lymphocytes were shown to be the most radiosensitive compared to the granulocytes (neutrophils, eosinophils and basophils) (39). The functional qualities of granulocytes were not compromised even with 50 Gy radiation (46). In our study, the decrease in the lymphocytes was more apparent in the ORN cases compared to the non-ORN cases. The neutrophils declined slightly in Stage 2 compared to Stage 1 and recovered to a higher number in Stage 3 (although not as high as in Stage 1) in the ORN cases. The decline and recovery of neutrophils were shown by Swanson et al. (2022) (39).

Platelets interact with the leukocytes in the radiation-induced inflammation (47). PLR is often used as a potential inflammatory prognostic indicator in radiation therapy studies (48). An elevated PLR indicates a relative increase in the platelet count or a relative decrease in the lymphocyte count (48).

In this study, the NLR and the PLR, were observed to increase from Stage 1 to Stage 2, before dropping to a level that remained higher than normal. A study on irradiated patients with nasopharyngeal carcinoma (NPC) showed a high NLR trend, suggesting a positive immune response to RT and indicating a good prognosis (21).

When compared to erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as inflammatory markers, various results can be observed from various literature (49-50). Pani et al. (2024) showed that CRP and ESR were superior to other markers, including the platelet-to-lymphocyte ratio (PLR) in mandibular odontogenic space infections (49). Another study demonstrated that the combination of CRP and the neutrophil-to-lymphocyte ratio (CRP-NLR) is a more reliable and effective biomarker for assessing the severity of odontogenic infections compared to CRP and NLR individually (50).

Limitation of study

The current study's retrospective nature and small sample

size posed significant limitations. Being conducted in a single centre further restricts the generalizability of the findings. The constrained sample size hindered the establishment of stricter exclusion criteria, potentially limiting the depth of understanding regarding the relationships between hematological factors and the disease.

Additionally, the presence of selection bias in the data collection process may skew the results and compromise their representativeness of the broader population.
Overall, the blood components and their ratios did not demonstrate a statistically significant association. To determine whether a true association exists, larger, multi-centre studies employing rigorous methodologies will be necessary in the future.

CONCLUSION

The individual blood components, hemoglobin, platelets, neutrophils, and lymphocytes, remained within the normal range during the period following radiotherapy and osteoradionecrosis. However, the median neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were elevated compared to the hospital reference range. Notably, both ratios exhibited a declining trend from the post-radiotherapy period to the development of osteoradionecrosis.

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