Treatment regimens and survival among patients with head and neck squamous cell carcinoma from Mizo tribal population in northeast India – a single centre, retrospective cohort study

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Summary

Background Patients with early-stage head and neck squamous cell carcinoma (HNSCC) are treated using a single-modality approach that involves either surgery (S) or radiotherapy (RT). Conversely, those with advanced-stage disease are treated using a multi-modality approach incorporating a combination of chemotherapy (CT), RT and S. In addition to behavioural factors, such as alcohol and tobacco use, clinical parameters, such as leukocyte and neutrophil counts and T and N classification, have been linked to the survival of patients with head and neck cancer. This retrospective study was designed to provide insights into the types of treatment (induction chemotherapy [IC], concurrent chemoradiotherapy [CCRT], S and RT) administered to patients with HNSCC in Mizoram, analyse their 2-year outcome, and identify potential factors that may affect the response to treatment.

Methods A retrospective cohort study was conducted using patients diagnosed with HNSCC between 2017 and 2020 in Mizoram, northeast India. Data on clinical and demographic factors and treatments provided were collected from medical records from the Mizoram State Cancer Institute, Mizoram. Overall survival (OS) and progression free survival (PFS) were determined for each factor using the Kaplan–Meier method and compared using the log–rank test. Cox regression analysis was used to identify the factors that affected OS and PFS. Multicollinearity test was performed between the predictors using a variance inflation factor cut-off point of 2.

Findings A retrospective study was performed on 210 patients with HNSCC who were followed up for a period of 2 years. The findings revealed that hypopharynx was the most affected site, followed by the nasopharynx, oral cavity, oropharynx, and larynx. Regarding treatment regimens, 85/210 (40.5%) of the patients received IC along with CCRT or RT in a sequential manner. Moreover, 86/210 (41.0%) underwent CCRT alone, 22/210 (10.5%) received RT alone and 17/210 (8.1%) underwent surgery followed by adjuvant CCRT or RT. Two-year OS and PFS estimated using the Kaplan–Meier analysis were 78.1% (95% CI = 72.4%–84.2%) and 57.4% (95% CI = 50.8%–64.8%), respectively. Log–rank test showed that leucocytosis (p = 0.015) and neutrophilia (p = 0.014) exerted effects on OS, whereas nodal involvement (p = 0.005), neutrophilia (p = 0.043) and IC (p = 0.010) exerted effects on PFS. Multivariate analysis indicated that leucocytosis (p = 0.010 [OS], 0.025 [PFS]), neutrophilia (p = 0.029, 0.033), cancer site (laryngeal) (p = 0.009, 0.028) and nodal involvement (N2) (p = 0.020, 0.001) were predictors of poor OS and PFS.

Interpretation OS was better than PFS in HNSCC patients from Mizo population. Multi-modality approach offered survival advantages over single-modality approach. Leucocytosis, neutrophilia, nodal involvement, and cancer sites were associated with poor OS and PFS. More comprehensive research with a larger sample size is needed to confirm the findings from this study.

Funding There is no funding for this study.

Keywords: Head and neck cancer; Induction chemotherapy; Concurrent chemoradiotherapy; Overall survival; Progression free survival

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Research in context

Evidence before this study

The persistent challenges of poor oral health continue to affect various tribal and indigenous communities in India. Previous studies have focused on Malayali and Narikurava tribes (Tamil Nadu), Kurichiya and Paniya tribes (Kerala), Santhals (Jharkhand), Bhils (Rajasthan), Bharias (Madhya Pradesh), and many tribal populations in northeast India. Poor oral health is coupled with issues such as tobacco and betelnut consumption, excessive alcohol intake, lack of awareness, and limited healthcare access. Such challenges contribute to the burden of periodontal disease and pose risk factors for head and neck cancers and precancerous lesions in tribal populations. Findings of our previous study on Mizo tribal population (Mizoram, India) indicated that family history of cancer (first degree) could be a risk factor for head and neck cancer. Prior to the current study, no survival analysis had been conducted for head and neck cancer in the Mizo population.

Added value of this study

This study a preliminary investigation of head and neck squamous cell carcinoma (HNSCC) in Mizo population. It provides the first insights into the types of treatment modalities and factors influencing overall survival and progression free survival among the Mizo population.

Implications of all the available evidence

Overall survival was better than progression free survival in HNSCC patients from Mizo population. The study suggests that multimodality approaches demonstrated better survival benefits compared to single modality approaches. Notably, increased nodal involvement, high total leukocyte count, and high absolute neutrophil count were identified as significant predictors of survival outcomes. However, further research with a larger sample size and better treatment stratification is necessary to establish more valid conclusions.

Introduction

Head and neck squamous cell carcinoma (HNSCC) accounts for more than 0.9 million cases and 0.4 million deaths worldwide.[1] In India, there are more than 0.22 million cases and 0.12 million deaths according to the GLOBOCAN, 2020.[1] The head and neck is one the leading sites of cancer among men and women in Mizoram, northeast India.[2] Mizoram, a small state in the northeastern region of India, is predominantly inhabited by indigenous Mizo populations.[3] The people of Mizoram are racially mongoloids belonging to the Tibeto-Burman ethnic group and exhibit a distinct culture and lifestyle different from that of mainland India.[3] Tumours thar arise from the mucosal epithelium of the oral cavity, hypopharynx, oropharynx, nasopharynx and larynx are collectively termed as HNSCC. Being a heterogenous cancer, each subsite varies in terms of risk behaviours, disease presentations, population-wide prevalence and treatment approaches.[4]

According to National Comprehensive Cancer Network (NCCN) guidelines, early-stage patients are treated using a single-modality approach with surgery (S) or radiotherapy (RT). On the contrary, for patients with advanced-stage disease, a multi-modality approach that includes chemotherapy (CT), RT and S is recommended.[5] The CT regimen includes cisplatin, 5-fluorouracil, docetaxel, paclitaxel and/or carboplatin administered either alone or in combination.[5] Induction chemotherapy (IC) and concurrent chemoradiotherapy (CCRT) have been shown to improve response rates, but no statistical differences have been observed in the overall survival (OS).[6,7] The most effective combination for IC has not been established despite the fact that RT and CCRT are the major HNSCC treatment modalities.[5,7] Poor survival rates in HNSCC have been associated with cigarette smoking, betelnut chewing and higher T and N staging.[7–9] A study by Pachuau and colleagues observed that drinking alcohol, smoking certain types of cigarettes and having a family history of cancer increase the risk of HNSCC in the Mizo population.[3] In addition, a study by Milrud and colleagues reported that HNSCC is associated with an elevated leukocyte and neutrophil count, which is linked to survival.[10] Numerous studies have also related leucocytosis and neutrophilia to the outcome of HNSCC after evaluating different therapeutic strategies.[11–14] This study aimed to investigate each of the aforementioned parameters and their relationships with the cohort's response to the treatment regimen.

This retrospective study, which is the first of its kind to explore the survival outcomes of patients with HNSCC within the Mizo population, was conducted to provide insights into the treatment modalities adopted in Mizoram and analyse the 2-year outcome of patients with HNSCC. This study also aimed to assess the variables that might have an impact on the OS and progression free survival (PFS) of patients with HNSCC.

Methods

This retrospective cohort study included patients with HNSCC diagnosed from 2017 to 2020 and followed up for 2 years at the Mizoram State Cancer Institute (MSCI) located in Mizoram, Northeast India. Data were collected from medical records at MSCI, Mizoram. A total of 850 patients were diagnosed with head and neck cancer between 2017 and 2020, of which 210 patients with HNSCC were selected based on the inclusion and

exclusion criteria presented in Fig. 1. This study only included patients with HNSCC. Only those with squamous cell carcinoma arising primarily from the oral cavity, hypopharynx, nasopharynx, oropharynx, or larynx at the time of diagnosis were included. All selected cancers were in the M0 (Metastasis) stage at the time of diagnosis. Only patients belonging to the Mizo population and residing within Mizoram were selected. Many patients diagnosed within the state but not registered in the studied institute were excluded. Similarly, patients registered in MSCI but given referrals to other states or hospitals were excluded. The patients who left before initiation of the treatment or lost to follow up were excluded from the study. Patients registered in MSCI but either refused to or were unfit to receive RT were also excluded. Ethical clearance for this retrospective cohort study was obtained from the Institutional Ethics Committee (IEC), Civil Hospital, Aizawl, Mizoram (Ethical approval No.B.12018/1/13-CH(A)/IEC/69). The study was reported in accordance with the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies.[15]

Clinical and demographic data extracted from the medical records included age, sex, primary tumour site, TNM classification (tumor [T], nodes [N], and metastases [M]), leucocytosis, neutrophilia, treatment regimen, tobacco habits (smoking/smokeless), consumption of alcohol and betelnut chewing habits. Smokeless tobacco included consuming tobacco in the form of snuffing, liquified tobacco-infused water called *tuibur* or chewable tobacco, such as gutkha products. Classification of tumours was based on International Classification of Diseases, 10th Revision. The American Joint Committee on Cancer 8th edition was used for TNM classification.[16] This cohort study comprised heterogenous sites of head and neck cancer, and the staging system for each cancer site had different classifications of T and N. In this study, the T and N classification was used separately to avoid misinterpretation of the stages for each cancer site. Tumour grades were recorded as well-differentiated, moderately differentiated, poorly differentiated or undifferentiated. No information was available on Human Papillomavirus and Epstein Barr virus. Patients were grouped into four categories according to the treatment plan received: (i) Induction chemotherapy plus concurrent chemoradiotherapy/radiotherapy, (ii) concurrent chemoradiotherapy, (iii) radiotherapy only and (iv) surgery plus adjuvant concurrent chemoradiotherapy/radiotherapy. Computer tomography scan was used for routine evaluation before treatment as well as for determining tumour progression during follow-up.

The patients who underwent RT were followed up 45 days later, which was continued every 6 months for 2 years. CT scan was performed at each visit. Treatment response was assessed based on RECIST v1.1 criteria (Response Evaluation Criteria in Solid Tumors), and patients were grouped into complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). OS was defined as the time elapsed from the initiation of treatment until death from any cause. PFS was defined as the time elapsed from the initiation of treatment until PD, death or SD. Initiation of treatment was CT, RT, or S, whichever was administered first. Leucocytosis was defined as a total leukocyte count (TLC) of >10 thou/cumm (thousand cells per mm^3), and neutrophilia was defined as an absolute neutrophil count (ANC) of >7 thou/cumm.

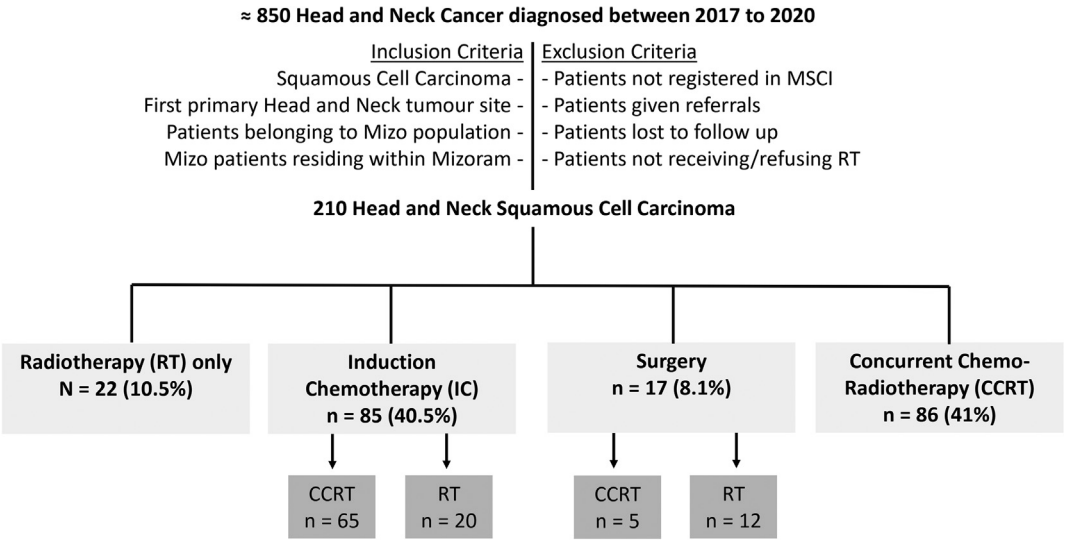

***Fig. 1:* Flowchart for inclusion and exclusion criteria plus patient treatment distribution in the study.** MSCI, Mizoram State Cancer Institute; RT, radiotherapy.

Characteristics	n	%
Age (years)		
Minimum	21	
Maximum	84	
Median	55	
Gender		
Male	166	79
Female	44	21
Site		
Hypopharynx	67	31.9
Larynx	25	11.9
Nasopharynx	48	22.9
Oropharynx	31	14.8
Oral Cavity	39	18.6
T Classification		
1	68	32.4
2	86	41.0
3	32	15.2
4	24	11.4
N Classification		
0	62	29.5
1	89	42.4
2	55	26.2
3	4	1.9
Grading		
Well differentiated	20	9.5
Moderately differentiated	63	30.5
Poorly differentiated	23	11
Undifferentiated	11	5.2
Not available	93	43.8
Total leukocyte count		
≤10 thou/cumm	108	51.4
>10 thou/cumm	24	11.4
Not available	78	37.1
Absolute neutrophil count		
≤7 thou/cumm	107	51.0
>7 thou/cumm	21	10.0
Not available	82	39.0
Cigarette smoking		
No	29	14.3
Yes	164	78.1
Not available	17	7.60
Alcohol intake		
No	86	41.0
Yes	107	51.0
Not available	17	8.10
Smokeless tobacco		
No	82	39.0
Yes	111	52.9
Not available	17	8.10
Betelnut chewing		
No	23	11.0
Yes	170	81.0
Not available	17	8.10
Family history of cancer		
(Table 1 continued on next column)		

Characteristics	n	%
(Continued from previous column)		
No	112	53.3
Yes	71	33.8
Not available	27	12.9

thou/cumm, thousand cells per mm^3.

Table 1: **Characteristics of Head and Neck Cancer patients included in the current study.**

Frequencies were generated for each categorical variable, and median values were computed for the numerical variables. Univariate and multivariate cox regression analyses for OS and PFS were performed using Statistical Package for Social Sciences (SPSS) Version 23 (IBM, Armonk, NY). Statistical analyses involved univariate analyses for OS and PFS, and each clinical and demographic factor and treatment administered were evaluated individually. Missing data coding was given to unknown data for that variable. The identified significant variables were then considered as covariates in the subsequent multivariate analysis. To ensure the accuracy and reliability of the multivariate models, a multicollinearity test was conducted on the predictors. A variance inflation factor (VIF) cut-off point of 2 was used as the threshold for assessing multicollinearity among the predictors. Log–rank test and survival analysis plots using the Kaplan–Meier method were generated using R Studio.[17] A p-value of <0.05 was considered statistically significant.

Role of the funding source
Not applicable.

Results
The patients' age range was 21–84 years, with a median age of 55 years, and 79% of them were men (166 out of 210) (Table 1). In the 210 patients with cancer, the most affected site was the hypopharynx with 67 (31.9%) cases, followed by the nasopharynx with 48 (22.9%) cases, the oral cavity with 39 (18.6%) cases, the oropharynx with 31 (14.8%) cases and the larynx with 25 (11.9%) cases. The most common T classification in the study was T2 with 86/210 (41.0%) cases, and in the N classification, N1 was the most common one with 89/210 (42.4%) cases. In this study, 164/210 (78.1%) of the patients smoked tobacco and 107/210 (51%) consumed alcohol. Majority of the patients consumed alcohol or tobacco or smoked cigarettes (Supplementary Table S1). Furthermore, 108 (51.4%) patients had leucocytosis, and 107 (51.0%) had neutrophilia. Data were missing for variables such as grading, TLC, ANC, cigarette smoking, alcohol, smokeless tobacco, betelnut chewing and family history of cancer (Table 1).

Table 2 depicts the treatment modalities offered to the patients. The treatment regimen was categorised into four groups: patients receiving IC and then continued with CCRT or RT–otherwise known as sequential chemoradiotherapy, patients receiving CCRT alone, patients receiving RT alone and finally patients who underwent surgery and then received adjuvant CCRT or RT (Table 2). Of the 210 patients, 85 (40.5%) received IC along with CCRT or RT, whereas 86 (41.0%) received CCRT only. RT alone was administered to 22 (10.5%), and surgery was performed on 17 (8.1%) patients with oral cancer. Of the 22 patients treated with RT alone, 15 were of early stage with no nodal involvement, whereas 7 patients had nodal involvement. Of the remaining seven patients, two underwent palliative RT without CT, three patients declined treatment, and the other two were too old to receive CT. The frequency distribution of treatment modalities between tumour and nodal involvement is given in Supplementary Table S2. Cisplatin/carboplatin along with paclitaxel/docetaxel was mostly administered for IC. Of the patients receiving IC, 54 (25.7%) received cisplatin plus paclitaxel. Single agents, such as cisplatin, carboplatin, or paclitaxel, were administered for CCRT. Cisplatin was given to 123 (58.6%) of the patients receiving CCRT. The doses of chemotherapeutic drugs administered in the study are listed in Supplementary Table S3. Patients undergoing palliative RT typically received a total dose of 30 Gy, which was administered in 10 fractions. On the contrary, for those intended to undergo curative radical or adjuvant RT, the prescribed dose ranged from 60 to 66 Gy, delivered in 30–33 fractions. Of the total patient cohort, 184 individuals (87.6%) underwent radical RT, 17 (8.10%) received adjuvant RT, and 9 (4.30%) were treated with palliative RT. CR was observed in 55.7% (117/210) of the patients, PR in 3.81% (8/210), SD (SD) in 0.48% (1/210) and PD in 40% (84/210).

The 2-year OS for the 210 patients was 78.1% (95% CI = 72.4%–84.2%) and PFS was 57.4% (95% CI = 50.8%–64.8%) based on the Kaplan–Meier analysis. Considering the various treatment plans, the lowest survival rate for OS was 70.4% in patients receiving RT only. Conversely, those receiving IC + CCRT/IC + RT had the lowest survival rate (47.3%) for PFS (Table 3, Supplementary Figures S1 and S2). However, the differences between these groups were not statistically significant. Patients who received cisplatin plus 5-flourouracil among the IC groups showed the poorest OS and PFS (Supplementary Figures S3 and S4). In the IC groups, the median PFS was attained at 22.2 months. The statistically significant difference between the PFS of the IC groups and the overall groups of all patients without IC was revealed by the log–rank p value (p = 0.010) (Fig. 2). However, the difference was not statistically significant for OS (Supplementary Table S5). TLC ≤10 thou/cumm was associated with a better survival rate of 81.3% when compared with patients having >10 thou/cumm (p = 0.015) (Fig. 3). Likewise, patients with lower ANC had better OS and PFS rates (Figs. 4 and 5). The survival probabilities of different N classifications were also found to be different (p = 0.005) (Fig. 6). N2 patients were observed to have the worst

Variables	n	%
Treatment type		
IC + CCRT/IC + RT	85	40.5
CCRT	86	41.0
RT alone	22	10.5
S + CCRT/S + RT	17	8.1
IC regimen		
Cisplatin + Paclitaxel	54	25.7
Cisplatin + 5-Fluorouracil	12	5.7
Cisplatin + Docetaxel	3	7.1
Carboplatin + Paclitaxel	15	1.4
Carboplatin + Docetaxel	1	0.5
Not received	125	59.5
Number of IC cycles		
Median	3	
Range	1 to 7	
CCRT		
Cisplatin	123	58.6
Carboplatin	22	10.5
Paclitaxel	4	1.90
Not Available	4	1.90
Not received	57	27.1
Number of CCRT weekly cycles		
Median	6	
Range	1 to 8	
RT intention		
Radical	184	87.6
Adjuvant	17	8.10
Palliative	9	4.30
RT dose (Gray)		
Median	66	
Range	24 to 70	
Overall survival		
Alive	168	80.0
Dead	42	20.0
Progression free survival		
Complete Response	117	55.7
Partial Response	8	3.8
Stable Disease	1	0.4
Progressive Disease	84	40.0
Progression		
Distant Metastasis	9	
Regional Metastasis	3	
Recurrence	20	

IC, Induction Chemotherapy; CCRT, Concurrent Chemoradiotherapy; RT, Radiotherapy; S, Surgery.

Table 2: **Characteristics of treatment regime and response.**

Characteristics	N	Overall survival			Progression free survival		
		Survival rates (%)	95% CI (%)	p-value	Survival rates (%)	95% CI (%)	p-value
Overall	210	78.1	72.4–84.2		57.4	50.8–64.8	
Treatment type							
IC + CCRT/IC + RT	85	73.7	64.3–84.4	0.294	47.3	37.2–60.0	0.062
CCRT	86	83.7	75.9–92.2		66.0	56.5–77.1	
RT	22	70.4	53.0–93.5		61.8	44.1–86.7	
S + CCRT/S + RT	17	80.0	62.1–100		56.2	36.5–86.7	
IC regimen							
CP + PAX	54	77.5	66.6–90.3	0.463	51.7	39.5–67.8	0.075
CP + 5-FU	12	44.4	21.4–92.3		18.8	05.4–65.0	
CP + DOX	3	66.7	30.0–100		66.6	30.0–100	
CB + PAX	15	72.2	52.4–99.6		30.0	12.3–73.4	
IC vs No IC							
IC	85	73.7	64.3–84.4	0.216	47.3	37.2–60.0	0.010[a]
No IC	125	80.9	74.1–88.4		63.9	55.8–73.1	
Total Leukocyte Count							
≤10 thou/cumm	108	81.3	73.9–89.6	0.015[a]	56.9	47.9–67.6	0.076
>10 thou/cumm	24	58.4	40.7–83.9		39.2	23.6–65.2	
Absolute Neutrophil Count							
≤7 thou/cumm	107	81.1	73.6–89.4	0.014[a]	57.5	48.4–68.2	0.043[a]
>7 thou/cumm	23	57.0	39.2–83.1		36.4	21.0–63.3	
Site							
Hypopharynx	67	83.7	74.9–93.5	0.101	65.7	55.0–78.4	0.525
Nasopharynx	48	88.0	78.5–98.5		51.9	38.7–69.7	
Larynx	25	75.1	59.6–94.6		63.0	46.4–85.6	
Oropharynx	31	69.4	54.5–88.3		53.9	38.8–75.0	
Oral Cavity	39	66.7	52.8–84.1		48.2	34.4–67.5	
N							
N0	62	86.1	77.7–95.5	0.062	68.3	57.5–81.2	0.005[a]
N1	89	79.4	71.1–88.6		60.2	50.4–71.7	
N2	55	65.7	53.1–81.4		39.8	28.1–56.5	
N3	4	75.0	42.6–100		50.0	18.8–100	

IC, Induction Chemotherapy; CCRT, Concurrent Chemoradiotherapy; RT, Radiotherapy; S, Surgery. CP, Cisplatin; PAX, Paclitaxel; 5-FU, 5-Flourouracil; DOX, Docetaxel; CB, Carboplatin. thou/cumm, thousand cells per mm^3. [a]Statistically significant (p-value <0.05).

Table 3: **Kaplan–Meier estimates and log-rank test for two years overall survival (OS) and progression free survival (PFS) of treatment regimen.**

PFS, i.e., 39.8%, with a median of 22.2 months. The PFS plot between high and low TLC and OS plot for levels of N classification are given in Supplementary Figures S6 and S7. For primary tumour location, oral cavity showed the worst OS and PFS of 66.7% and 48.2%, respectively (Supplementary Figures S8 and S9). The highest OS rate of 88.0% was observed for nasopharyngeal cancer, whereas hypopharyngeal cancer showed the best PFS rate of 65.7%.

Univariate cox regression analysis revealed that T and N classification, TLC and ANC were statistically significant predictors of OS. Multicollinearity (VIF >2) was detected for TLC and ANC; therefore, ANC was adjusted for T and N classification, whereas it was removed for the multivariate models for the remaining variables. Multivariate analysis showed that cancer site, N classification, TLC and treatment type were the statistically significant predictors of OS (Table 4). The hazard ratio (HR) indicated the laryngeal site to be a good predictor of poor survival (HR = 5.165, p = 0.009). HR increased with the increase in nodal involvement, which was statistically significant for N2 (HR = 3.835, p = 0.020). TLC >10 thou/cumm was a good predictor of poor OS. In univariate cox regression analysis for PFS, N2 classification and ANC were the significant predictors (Table 5). As multicollinearity was detected between ANC and TLC, TLC was adjusted for N classification only. After adjusting for covariates in the multivariate models, site (larynx), N2 classification, leucocytosis and neutrophilia were found to be the good predictors of PFS. Laryngeal (HR = 2.844, p = 0.028) cancers were observed to be good predictors of poor response. Like OS, leucocytosis (HR = 2.035, p = 0.025) and neutrophilia (HR = 1.946, p = 0.033) were

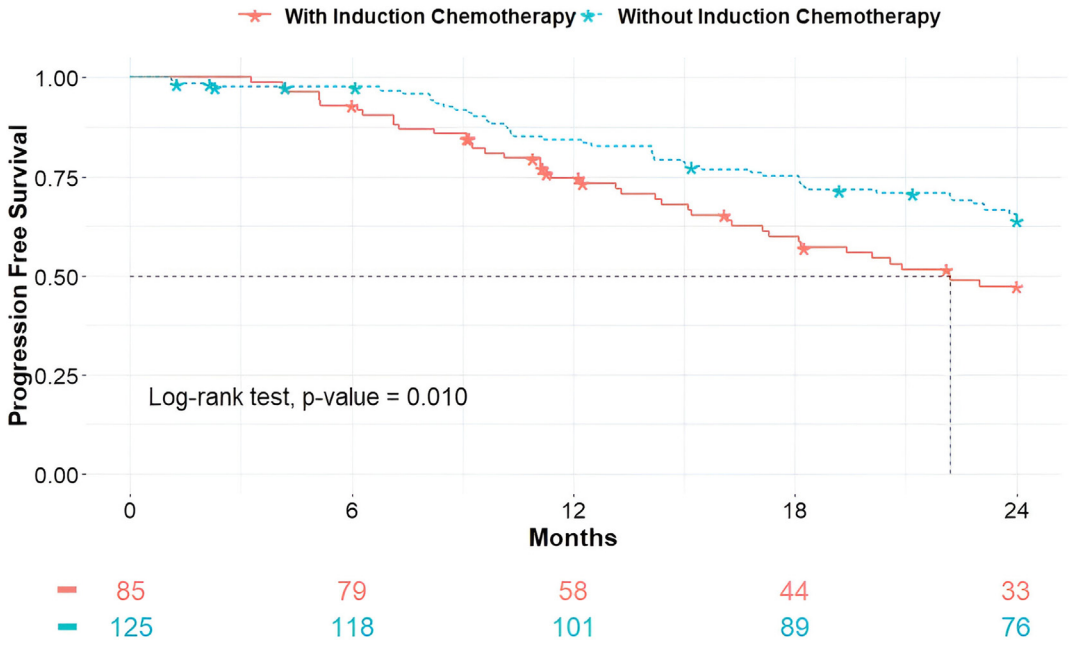

Fig. 2: **Kaplan-Meier plot and log-rank test for progression free survival in patients who received versus who did not receive induction chemotherapy**.

statistically significant predictors of PFS. In addition, the N classification showed an increase in HR with an increase in N involvement, which was statistically significant for N2 (HR = 3.483, p = 0.001).

Discussion

This study is a single cancer centre-based retrospective study aimed at providing valuable insights into the various treatment modalities and the factors influencing

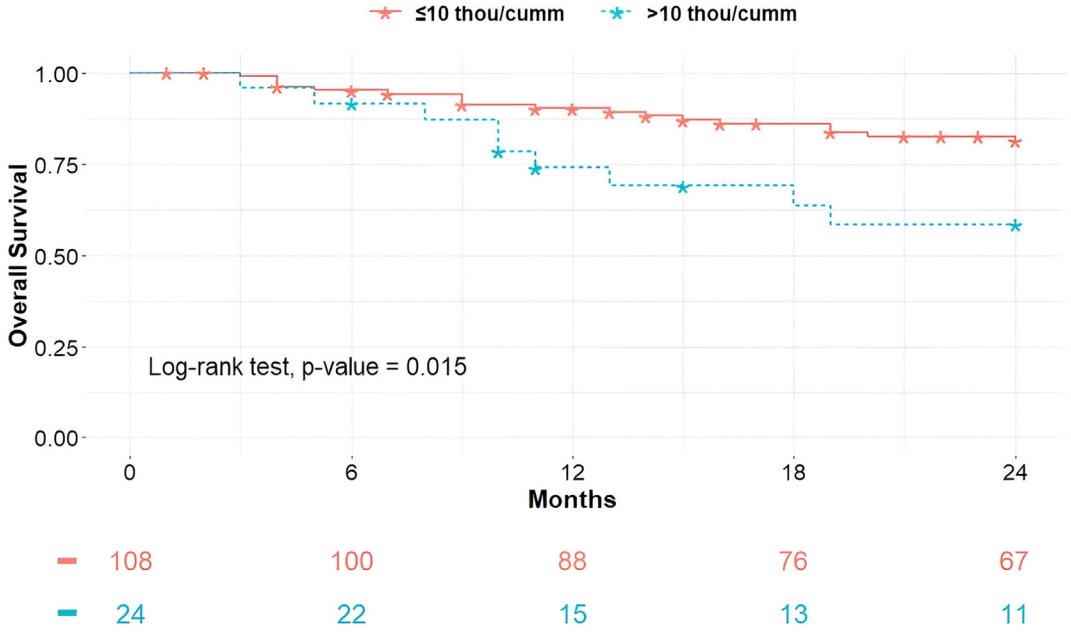

Fig. 3: **Kaplan–Meier plot and log-rank test for overall survival between total leukocyte count (TLC) ≤10 and >10 thou/cumm** (thou/cumm, thousand cells per mm^3).

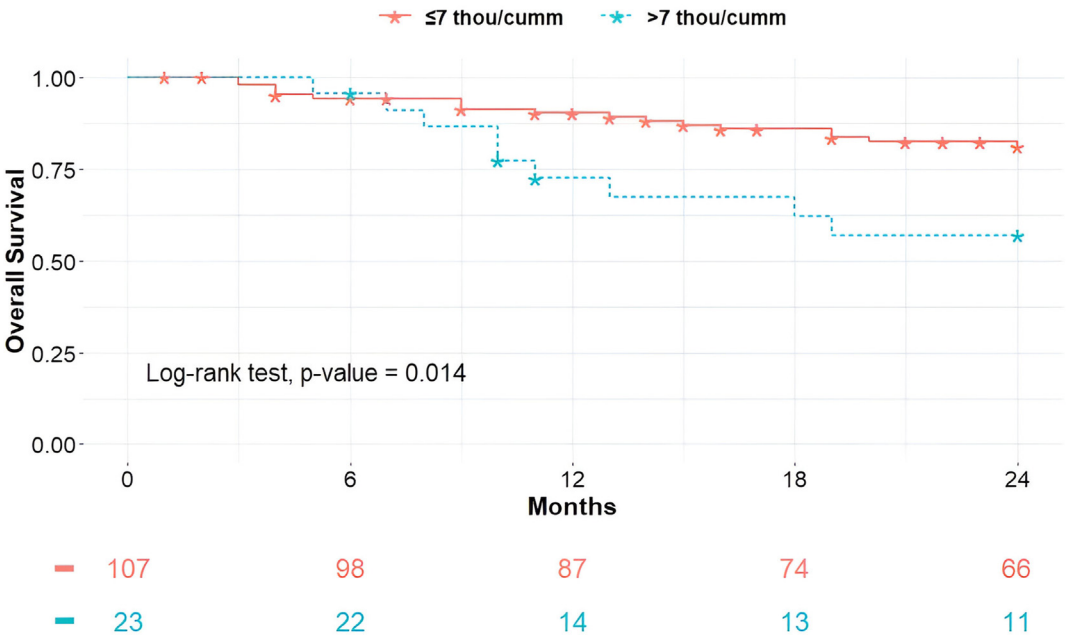

Fig. 4: **Kaplan–Meier plot and log-rank test for overall survival between absolute neutrophil count (ANC) ≤7 and >7 thou/cumm (**thou/cumm, thousand cells per mm^3).

the 2-year survival outcome of patients with HNSCC. The study found that the 2-year OS rate was 78.1%, which was higher than the 2-year PFS rate of 57.4%. The analysis identified several factors that influenced the survival outcomes, including TLC, ANC, N2 nodal stage and cancer site, particularly laryngeal cancer. Of the 210 patients, 188 (89.5%) were treated with a multi-modality approach, whereas 86 (41.0%) primarily received CCRT,

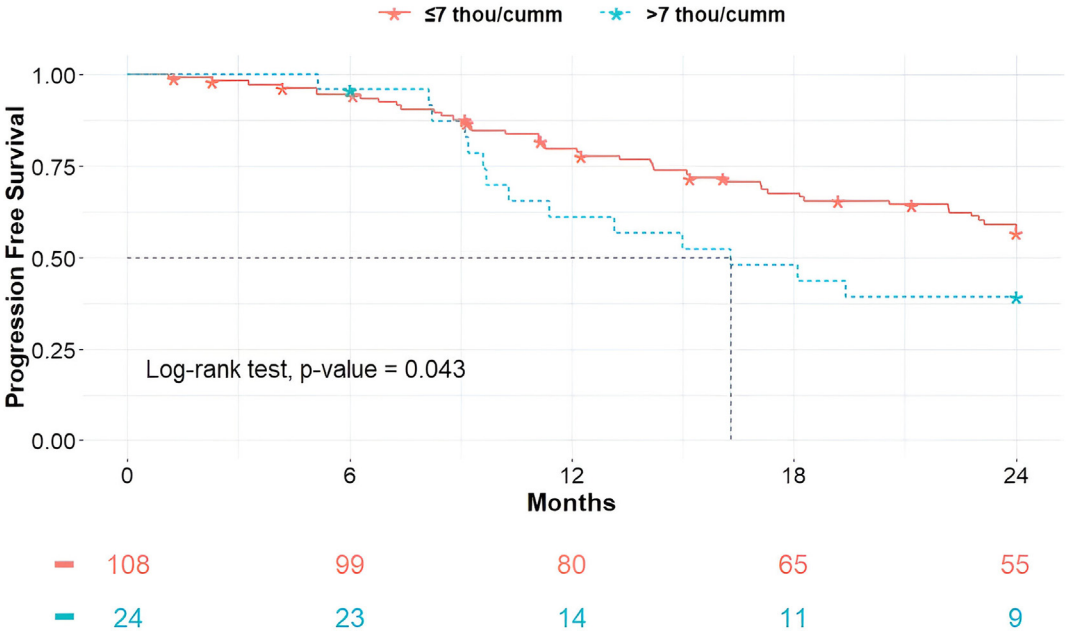

Fig. 5: **Kaplan–Meier plot and log-rank test for progression free survival between absolute neutrophil count (ANC) ≤7 and >7 thou/cumm (**thou/cumm, thousand cells per mm^3).

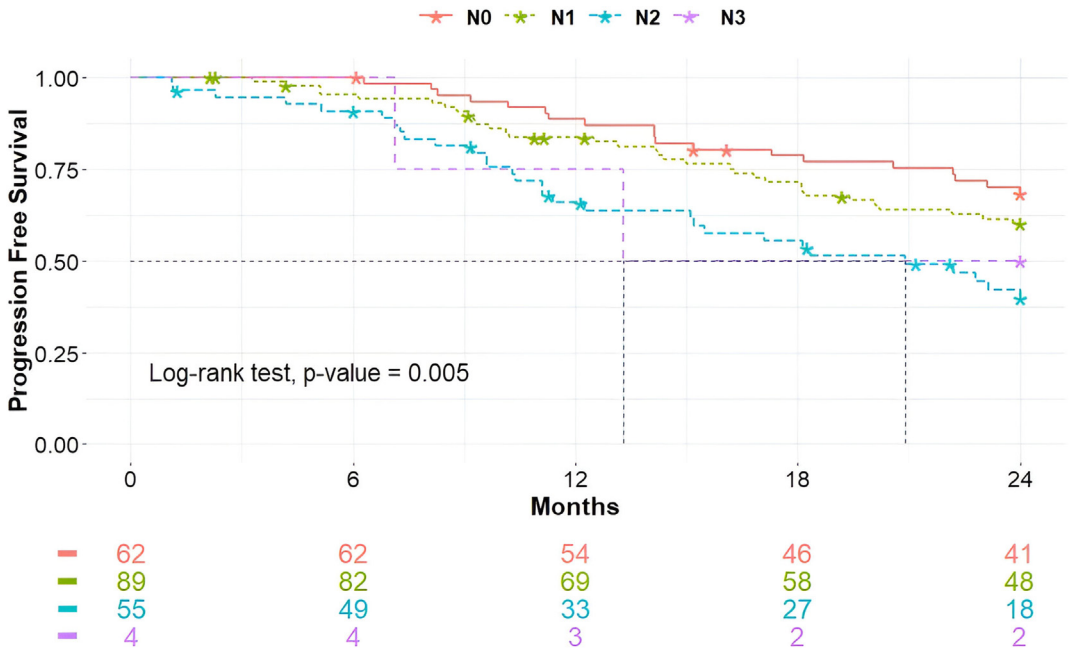

Fig. 6: **Kaplan-Meier plot and log-rank test for progression free survival between levels of nodal (N) involvement.**

which was closely followed by 85 (40.5%) patients treated with CCRT along with IC, and only 17 (8.1%) patients opted for S along with CCRT and/or IC. The single-modality therapy involving RT alone was administered to 22 (10.5%) patients. CCRT demonstrated survival advantages compared with other treatment modalities, both in terms of OS and PFS, although the difference was not statistically significant.

A similar investigation conducted among Indonesian population by Irawan and colleagues observed that the 2-year PFS was similar to our study (50%).[8] The OS rate in our cohort study was almost equivalent to that of a Korean cohort where the 2-year OS rate was reported to be 79.8%.[6] Another study conducted in north India by Badola and colleagues at a tertiary cancer care centre reported a lower 2-year survival rate of 58.8% at 18 months of follow-up.[18] The study results also indicated that patients who underwent IC experienced a less favourable PFS than those who did not receive IC. Additionally, despite an almost equal number of patients receiving CCRT alone and IC along with CCRT, the OS and PFS rates were notably poorer for those receiving IC. The purpose of IC is to either reduce the size of the tumours or enhance their sensitivity to RT, suggesting that patients receiving IC are likely to gain an advantage. However, the results indicate a different outcome. The benefits of IC in the management of head and neck cancer remain uncertain.[19] Several randomised trials have consistently shown a lack of substantial difference between IC followed by CCRT and CCRT in the outcome of patients with head and neck cancer.[20–24]

The selection of a treatment plan is based on the patient's body weight, comorbidities, and the size, location, and nodal involvement of the tumour. The purpose of curative treatment is tumour reduction and organ preservation.[6,25–27] The reason for poor response to IC can be residual toxicity as the treatment is usually administered to patients with higher T and N staging.[6] Undoubtedly, the increase in nodal involvement has also been shown to be a significant predictor of poor response. In our study cohort, 70.4% of the patients presented neck nodal involvement at the time of diagnosis, which could be an attributable factor to poor response. Within 2 years, 85 patients were assessed to be bad responders (1 with stable disease and 84 with progressive disease) to treatment, of which 32 patients progressed to local recurrence and regional and distant metastasis. Neck nodal involvement has been shown to be highly associated with poor survival and recurrence.[28,29] A randomised Phase III trial conducted by Cohen and colleagues has also reported that IC did not improve the OS compared with CCRT alone in patients with N2 and N3 HNSCC.[23]

Leucocytosis and neutrophilia are significant predictors of poor OS and PFS. Studies have shown that leucocytosis can predict the OS and PFS of patients with HNSCC treated using concurrent cisplatin and radiation.[11] Leucocytosis has been linked to tumour recurrence and metastasis after surgery in oral squamous cell carcinoma and oropharyngeal cancer.[11–14] In another study by Jensen and colleagues demonstrated that pretreated leucocytosis and neutrophilia were associated

Variables	Univariate		Multivariate	
	HR (95% CI)	p-value	HR[a] (95% CI)	p-value
Age	1.007 (0.977–1.038)	0.658	1.003 (0.963–1.046)	0.880
Sex				
Male	Reference			
Female	0.914 (0.423–1.976)	0.820	0.404 (0.092–1.773)	0.230
Site				
Hypopharynx	Reference			
Larynx	1.760 (0.639–4.843)	0.274	5.165 (1.518–17.570)	0.009[b]
Nasopharynx	0.732 (0.250–2.141)	0.569	0.452 (0.117–1.744)	0.249
Oropharynx	2.109 (0.857–5.192)	0.104	1.655 (0.518–5.285)	0.395
Oral Cavity	2.226 (0.962–5.154)	0.062	2.273 (0.768–6.728)	0.138
T Classification				
1	Reference			
2	1.305 (0.611–2.786)	0.492	0.883 (0.347–2.248)	0.794
3	1.052 (0.366–3.028)	0.925	0.740 (0.156–3.510)	0.705
4	2.822 (1.169–6.815)	0.021[b]	2.073 (0.698–6.156)	0.189
N Classification				
0	Reference			
1	1.621 (0.699–3.756)	0.260	2.329 (0.814–6.664)	0.115
2	2.954 (1.263–6.908)	0.012[b]	3.835 (1.231–11.946)	0.020[b]
3	2.506 (0.313–20.051)	0.387	–	–
Total Leukocyte Count (TLC)				
≤10 thou/cumm	Reference			
>10 thou/cumm	2.603 (1.167–5.803)	0.019[b]	2.951 (1.290–6.748)	0.010[b]
Absolute Neutrophil Count (ANC)				
≤7 thou/cumm	Reference			
>7 thou/cumm	2.625 (1.177–5.852)	0.018[b]	2.500 (1.100–5.684)	0.029[b]
Alcohol intake				
No	Reference			
Yes	1.888 (0.956–3.727)	0.067	2.487 (0.957–6.460)	0.061
Smoking				
No	Reference			
Yes	1.666 (0.592–4.689)	0.333	1.423 (0.326–6.211)	0.639
Betelnut use				
No	Reference			
Yes	1.148 (0.408–3.230)	0.794	2.446 (0.523–11.430)	0.256
Smokeless tobacco				
No	Reference			
Yes	0.798 (0.426–1.496)	0.418	0.788 (0.359–1.731)	0.553
Family history of cancer				
No	Reference			
Yes	0.545 (0.255–1.169)	0.119	0.935 (0.340–2.572)	0.896
Grading				
Well differentiated	Reference			
Moderately differentiated	0.790 (0.278–2.243)	0.658	2.826 (0.302–26.475)	0.363
Poorly differentiated	0.623 (0.149–2.609)	0.517	1.942 (0.136–27.677)	0.624
Undifferentiated	0.332 (0.040–2.960)	0.332	0.622 (0.034–11.261)	0.748

[a]Hazard Ratio adjusted for T classification, N Classification and Total Leukocyte Count (TLC) except for Absolute Neutrophil Count (ANC). ANC was adjusted for T and N Classification. [b]Statistically significant (p-value <0.05).

Table 4: **Univariate and Multivariate analysis for characteristics of patients, tumour and treatment regimen with overall survival.**

Characteristics	Univariate		Multivariate	
	HR (95% CI)	p-value	HR[a] (95% CI)	p-value
Age	1.003 (0.982–1.024)	0.789	1.624 (0.807–3.268)	0.174
Sex				
Male	Reference			
Female	0.890 (0.517–1.534)	0.675	0.439 (0.174–1.107)	0.081
Site				
Hypopharynx	Reference			
Larynx	1.180 (0.544–2.564)	0.675	2.844 (1.117–7.244)	0.028[b]
Nasopharynx	1.439 (0.791–2.617)	0.233	1.236 (0.603–2.532)	0.563
Oropharynx	1.537 (0.786–3.004)	0.209	1.853 (0.793–4.329)	0.154
Oral Cavity	1.636 (0.885–3.023)	0.116	1.757 (0.752–4.103)	0.193
T Classification				
1	Reference			
2	1.023 (0.615–1.701)	0.930	0.806 (0.424–1.531)	0.510
3	1.109 (0.572–2.149)	0.760	1.917 (0.799–4.600)	1.145
4	1.555 (0.788–3.071)	0.203	1.038 (0.447–2.409)	0.931
N Classification				
0	Reference			
1	1.366 (0.777–2.403)	0.279	1.582 (0.782–3.198)	0.202
2	2.574 (1.452–4.562)	0.001[b]	3.483 (1.706–7.110)	0.001[b]
3	2.104 (0.490–9.034)	0.317	6.527 (0.830–51.347)	0.075
Total Leukocyte Count (TLC)				
≤10 thou/cumm	Reference			
>10 thou/cumm	1.718 (0.939–3.144)	0.079	2.035 (1.095–3.782)	0.025[b]
Absolute Neutrophil Count (ANC)				
≤7 thou/cumm	Reference			
>7 thou/cumm	1.849 (1.009–3.389)	0.047[b]	1.946 (1.056–3.586)	0.033[b]
Alcohol intake				
No	Reference			
Yes	1.167 (0.746–1.825)	0.499	1.501 (0.849–2.651)	0.162
Smoking				
No	Reference			
Yes	1.719 (0.827–3.570)	0.147	2.182 (0.670–7.105)	0.195
Betelnut				
No	Reference			
Yes	0.801 (0.424–1.515)	0.495	1.443 (0.656–3.176)	0.362
Smokeless tobacco				
No	Reference			
Yes	1.082 (0.692–1.691)	0.731	1.124 (0.645–1.958)	0.680
Family history of cancer				
No	Reference			
Yes	0.755 (0.462–1.235)	0.263	0.991 (0.502–1.955)	0.979
Grading				
Well differentiated	Reference			
Moderately differentiated	0.861 (0.398–1.862)	0.704	2.682 (0.557–12.924)	0.219
Poorly differentiated	1.427 (0.601–3.391)	0.420	2.506 (0.466–13.478)	0.284
Undifferentiated	0.819 (0.252–2.661)	0.740	2.052 (0.362–11.648)	0.417

[a]Hazard Ratio adjusted for N classification and Absolute Neutrophil Count (ANC) except Total Leukocyte Count (TLC) which was adjusted for N classification only. thou/cumm, thousand cells per mm^3. [b]Statistically significant (p-value <0.05).

Table 5: **Univariate and Multivariate analysis for characteristics of patients, tumour and treatment regimen with progression free survival.**

with a poor response to radiotherapy.[30] Several studies have indicated leucocytosis and neutrophilia to be predictors of poor OS and PFS in other cancers, such as anal, oesophageal and lung cancers.[31–33]

Smoking and alcohol consumption are established risk factors for HNSCC.[9] Studies have observed that cigarette smoking decreases the 2-year PFS of patients with HNSCC.[7,34,35] Consumption of alcohol has been found to have a negative influence on OS and increase the mortality risk for patients who had quit drinking or continued to drink.[36–38] However, in our study, alcohol consumption and smoking did not significantly influence the OS or PFS. Su and colleagues had indicated that a history of betelnut chewing along with smoking was associated with poor prognosis in patients with HNSCC.[9] Although 81.4% of the patients in our study had the habit of betelnut chewing, we did not observe a significant effect on OS or PFS even after adjusting for smoking. Likewise, a common practice, such as the consumption of smokeless tobacco in the form of '*tuibur*', was not linked to the prognosis in our study. Although having a family history of cancer has been reported to increase the risk of developing HNSCC,[9] it did not influence the treatment response in our population. This finding is consistent with the study by Getz and colleagues in which a similar HR was observed between family history of cancer and survival.[39]

This study has several limitations, such as the small sample size which prevented us from adequately stratifying the samples by cancer sites or stages to achieve a stronger statistical power. Furthermore, the retrospective nature of this study limited us from gathering direct information on patients' quality of life, diagnosis, and complete reports on their overall wellbeing, including toxicity profiles that can have a potential impact of confounding by indication. Moreover, information on the presence of human papillomavirus or Epstein–Barr virus was not available as these tests are not a part of routine tests in the state. Also, there were a few missing details in some of the parameters, which could not be traced back. In addition, this study is a preliminary and exploratory study with many shortcomings that weaken the statistical power of the study, such as the disadvantages in using univariate analysis for selecting the variables to be used in multivariate analysis.[40,41] The findings of this study are tentative and require in-depth investigation to arrive at more definitive conclusions. However, despite these shortcomings, this study methodology and objectives can be applied to data from any clinical investigations in remote autonomous cancer care centres with limited resources. The results of this study are comparable to cancer clinic findings from any patient cohort.

To the best of our knowledge, this is the first survival analysis on HNSCC from a region of high cancer prevalence in the country. The 2-year OS and PFS were 78.1% and 57.4%, respectively. The multi-modality approach, particularly CCRT, showed survival advantage over other treatment modalities, including the sequential approach. Poor prognosis was influenced by factors such as high TLC, high ANC, high nodal involvement, and laryngeal cancer site. Performing a more comprehensive study with a larger sample size, assessing the long-term effects by extending the follow-up period, refining the treatment stratification, and incorporating molecular data are required to validate the findings from this study.

Contributors

NSK, ZB and HL conceptualised and supervised the study. ZB, LK, LH, CL, VH clinically validated and curated the data. ZZ and LP collected and sort the data. ZZ performed the analysis, visualisation and wrote the original draft of the manuscript. All the authors reviewed and revised the manuscript.

Data sharing statement

Data will be made available on request from researchers.

Declaration of interests

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

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