Biomolecules and Biomedicine

ISSN: 2831-0896 (Print) | ISSN: 2831-090X (Online)
Journal Impact Factor® (2022): 3.4

CiteScore® (2022): 5.3
www.biomolbiomed.com | blog.biomolbiomed.com

Global immune-nutrition-inflammation index as a novel comprehensive biomarker in predicting the radiation-induced trismus rates in locally advanced nasopharyngeal carcinoma patients

Efsun Somay[1*], Erkan Topkan[2], Sibel Bascil[3], Nilüfer Kılıc Durankuş[4a], Şükran Senyürek[4b], Düriye Ozturk[5], Berrin Pehlivan[6], Ugur Selek[4c]

[1]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Baskent University, Ankara, Turkey

[2]Department of Radiation Oncology, Faculty of Medicine, Baskent University, Adana, Turkey

[3]Department of Periodontology, Faculty of Dentistry, Baskent University, Ankara, Turkey

[4a]Department of Radiation Oncology, School of Medicine, Koc University, Istanbul, Turkey

[4b]Department of Radiation Oncology, School of Medicine, Koc University, Istanbul, Turkey

[4c]Department of Radiation Oncology, School of Medicine, Koc University, Istanbul, Turkey

[5]Department of Radiation Oncology, Bahcesehir University, Istanbul, Turkey

[6]Department of Radiation Oncology, Faculty of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey

***Corresponding author:** Efsun Somay; E-mail: efsuner@gmail.com

Associate editor: Gaetano Isola

DOI: https://doi.org/10.17305/bb.2024.10616

Submitted: 15 April 2024/ **Accepted:** 31 May 2024/ **Published online:** 10 June 2024

Conflicts of interest: Authors declare no conflicts of interest.

Funding: Authors received no specific funding for this work.

Data availability: The data supporting this study's findings is available from the corresponding author, Efsun Somay, upon a reasonable special request.

ABSTRACT

In this study, we aimed to evaluate whether the novel pretreatment Global Immune-Nutrition-Inflammation Index (GINI) can predict radiation-induced trismus (RIT) in locally advanced nasopharyngeal carcinoma (LA-NPC) patients undergoing concurrent chemoradiotherapy (CCRT). Data of LA-NPC patients presenting without RIT were reviewed retrospectively. Any post-CCRT maximum mouth openings (MMO) ≤ 35 mm were considered RIT. The GINI index was calculated using the formula: GINI = (CRP x Monocytes x Platelets x Neutrophils) ÷ (Albumin x Lymphocytes). We used receiver operating characteristic (ROC) curve analysis to examine the potential correlation between pretreatment GINI measures and post-CCRT RIT status. Logistic regression analysis examined the independence of the association between confounding factors and RIT rates. The study comprised 230 participants, and 52 (22.6%) received an RIT diagnosis. The optimal pre-CCRT GINI cutoff that dichotomizes RIT rates was determined to be 1,424 (area under the curve [AUC]: 76%; sensitivity: 75.0%; specificity: 71.7%; J-index: 0.463). RIT incidence was significantly higher in the GINI ≥ 1424 group than in its GINI < 1424 counterpart (43.3% vs. 9.3%; Hazard ratio: 4.76; $P < 0.001$). Multivariate logistic regression analysis revealed that a pre-CCRT GINI ≥ 1424 was an independent predictor of increased RIT rates after definitive CCRT in this patient group ($P < 0.001$). In conclusion, the present results revealed that elevated pre-CCRT GINI measures (≥ 1424) can efficiently and independently predict elevated RIT rates in LA-NPC patients after CCRT.

KEYWORDS: Radiation-induced trismus, Global Immune-Nutrition-Inflammation Index (GINI), concurrent chemoradiotherapy, nasopharyngeal carcinoma

INTRODUCTION

Radiation therapy (RT) is a vital treatment modality for various head and neck cancers (HNC), including nasopharyngeal cancers (NPC). However, despite its effectiveness, it can bring about complications that can cause significant discomfort and impair the patient's quality of life [1]. One of these complications is radiation-induced trismus (RIT), a condition characterized by the restriction of mouth opening, jaw stiffness, and pain [2]. RIT can significantly impact the patient's ability to perform daily activities, such as speaking, swallowing, eating, and performing daily oral hygiene leading to a decline in overall well-being [3]. The incidence of RIT varies significantly depending on the size and location of the tumor, and the literature reports rates ranging from 5% to 42% of HNC patients [4,5].

High doses of ionizing radiation produce RIT by damaging the muscles, connective tissues, and blood vessels in the masticatory region, resulting in radiation-induced fibrotic tissue repair [6]. Although these changes may lead to RIT development, the underlying mechanisms remain unknown. However, there is a growing interest in using inflammatory biomarkers to diagnose and manage RIT, as it is well-recognized that inflammation plays a crucial role in its development and progression [3, 5]. Proinflammatory cytokines such as transforming growth factor-beta (TGF-β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) are known to contribute to the inflammatory process and promote fibrotic changes in irradiated tissues, thus playing a pivotal role in the genesis of RIT [7]. Previous studies by Somay et al. [8-10] and Topkan et al. [11] have provided compelling data about the impact of inflammatory biomarkers on RIT. They have shown that pre-treatment ratios such as neutrophil-to-platelet ratio (NLR), hemoglobin-to-platelet ratio (HPR), pan-immune-inflammation value (PIV), and Valero's Host Index (which includes neutrophils, monocytes, lymphocytes, hemoglobin, and albumin) have a significant impact on the occurrence of RIT [8-11].

Global Immune-Nutrition-Inflammation Index (GINI), created by Topkan et al., is another index that integrates neutrophils, monocytes, platelets, lymphocytes, albumin, and C-reactive protein (CRP) into its formula [12]. In their original study, Topkan et al. demonstrated that GINI holds a promising prognostic value in stage IIIC non-small cell lung cancer patients (NSCLC) who underwent concurrent definitive chemoradiotherapy (CCRT). Motivated by this emerging data, and given that the novel GINI index provides nearly all-in-one immunological, inflammatory, and nutritional biomarkers by combining the cellular and biochemical components of these processes, we hypothesized that the GINI index could also accurately predict treatment-related toxicities, such as RIT, in which all of these factors play essential roles in its initiation and progression. Therefore, the present retrospective cohort analysis was planned to investigate the value of the GINI index in predicting the incidence of RIT in LA-NPC patients undergoing definitive CCRT.

MATERIALS AND METHODS

Study population

A retrospective data search was conducted on patients with LA-NPC diagnoses who underwent CCRT and were evaluated at the Radiology, Dentistry, Medical Oncology, and Radiation Oncology Departments of the Baskent University Faculty of Medicine between January 2010 and January 2023. This period was chosen to prevent treatment technique-related biases, as the IMRT option became available at our institution in 2010. To be eligible for the study, patients had to meet the following criteria: Being at least 18 years old, having a confirmed diagnosis of squamous cell NPC, and being classified as LA-NPC (T1-2N1-3M0 or T3-4N0-3M0) based on the AJCC staging framework (8^{th} edition). Additionally, they should not have had a prior diagnosis of temporomandibular disorder (TMD) or trismus before CCRT, based on the current diagnostic criteria (DC) for TMD, namely the DC/TMD.

A history of previous RT or chemotherapy, as well as insufficient cardiac, renal, hepatic, or pulmonary function, were considered exclusion criteria for this study. In a similar vein, participants with confirmed active infections, chronically active immune or inflammatory disorders, recent receipt of steroids or antibiotics within the previous 30 days, or recent blood transfusions within 90 days were excluded from the study to reduce the potential influence of these conditions and the medications used to treat them on the variables under investigation. Patients who had undergone surgery for neck trauma, muscle-related pain, myofascial pain syndrome, primary tumors, or lymph node invasion of masticatory muscles were also excluded from the study. Additionally, patients who are being treated for local recurrence, have a history of surgery and/or RT to the head and neck region and have a follow-up period of fewer than six months were not allowed to participate in the study.

Treatment protocol

Our recommended treatment for LA-NPC is simultaneous integrated boost intensity-modulated radiotherapy (SIB-IMRT). To identify the target volumes for RT, we use pretreatment co-registered computed tomography (CT), 18-fluorodeoxyglucose-positron emission CT (PET-CT), and/or magnetic resonance imaging (MRI) images of the entire neck and the affected nasopharyngeal primary. The present study followed established guidelines to determine target volumes and corresponding dosages for radiation therapy, as previously reported [13]. The following is a summary of the doses that were given to the planning target volumes (PTVs): Single daily RT fractions in 33 days (5 days/week) were used to administer total doses of 70.0 Gy, 59.4 Gy, and 54.0 Gy for high-risk, intermediate-risk, and low-risk PTVs, respectively [13]. Weekly cisplatin (40 mg2) was prescribed as the concurrent chemotherapy. Two cycles of adjuvant cisplatin and 5-fluorouracil combination (every 21 days) were recommended for all patients deemed to tolerate it. As part of the supportive care

protocol, patients were administered analgesics, antiemetic medications, and nutritional supplements when needed.

Baseline and follow-up oral evaluation and the determination of RIT

All the oral evaluations and maximum mouth opening (MMO) measures were conducted by an experienced oral and maxillofacial surgeon (ES). To define RIT, we used the threshold of MMO of 35 mm or less as per the criteria set by Dijkstra et al. [4]. We used Therabite® (Atos Medical AB, Hörby, Sweden) for validated, disposable, and easily used features, to measure the MMO [14]. Patients were instructed to expand their mouths as much as possible while wearing the Therabite® motion scale to measure the distance between the lower edge of one upper central incisor and the matching upper edge of one mandibular central incisor. The mean MMO was calculated using the average numerical value of three successive measurements taken throughout each session. To assess the state of RIT, we took the measurements of MMO again for each patient at 1, 3, 6, 9, and 12 months following CCRT. Additional measurements were performed as needed or at each subsequent scheduled appointment after that.

Calculation of the global immune-nutrition-inflammation index (GINI)

The GINI was calculated using the original formula [12] : $GINI = (CRP \times M \times P \times N) \div (Albumin \times L)$, where CRP, M, P, N, and N correspond to the counts of C-reactive protein, monocytes, platelets, neutrophils, lymphocyte, and albumin measures read prior to the administration of the initial CCRT dose.

Ethical statement

The retrospective research design used in the present study (project No: KA23/196) received approval from the institutional review board at Baskent University Medical Faculty. The

research followed the Guidelines for Good Clinical Practice and the Declaration of Helsinki, including any future revisions regarding its principles and standards. Before undergoing CCRT, all patients were required to provide their signed informed consent, which permitted researchers to examine their clinical and blood test data and publish any pertinent discoveries.

Statistical analysis

The primary objective of this investigation was to analyze the correlation between pre-CCRT GINI measures and post-CCRT RIT rates. We employed percentage frequency distributions to quantify categorical variables, while medians and ranges were utilized to explicate continuous variables. The Student's t-test, the Chi-square test, or Spearman correlation analysis were executed for intergroup comparisons. These analytical methods were chosen based on their appropriateness for the data set and statistical objectives. The current study utilized receiver operating characteristic (ROC) curve analysis, a widely recognized robust and valid statistical tool for evaluating the diagnostic accuracy of a test or a biomarker, to estimate the optimal pre-CCRT cutoffs that can effectively stratify the research cohort into two GINI groups with significantly distinct outcomes. All comparisons were two-sided and a p-value less than 0.05 was deemed significant. The univariate analysis included all the factors exhibiting significance in the association between post-CRT RIT rates and the baseline or treatment-related characteristics, while the multivariate logistic regression analysis included only the factors exhibiting significance or a strong trend toward significance ($p < 0.10$) in the univariate analysis.

RESULTS

Patient characteristics and treatment modalities

The present study included 230 LA-NPC patients who fulfilled the eligibility criteria. As shown in Table 1, the median age was 56 years (range: 18–76 years) for the whole cohort,

with 158 (68.7%) male patients. The rates of tobacco and alcohol consumption were 63.5% and 32.2%, respectively. Most patients had advanced disease stages: 171 (73.5%) had T3-4, and 183 (79.6%) had N2-3 disease stages. The final post-CCRT MMO measurements demonstrated a median reduction of 3.2 mm (7.73%; range: 1.4-39.7%) from a pre-CCRT median of 41.4 mm (range: 37.4-46.8 mm) to a final median of 38.2 mm (range: 25.9-44.0 mm) (Tables 1 and 2). During the follow-up period, 52 patients (22.6%) received RIT diagnosis based on Dijkstra's trismus criteria for cancer patients (MMO ≤ 35 mm) [3], with a median CCRT to RIT duration of 10 months (range: 6-18 months).

In the present study, we conducted a ROC curve analysis to investigate the potential correlation between the incidence rates of RIT and the baseline GINI levels. The analysis revealed that a meaningful relationship could be observed at a cut-off of 1,424 [Area under the curve: 76%; sensitivity: 75.0%; specificity: 71.7%, J-index: 0.463] (Figure 1). Therefore, we divided the study population into two groups: Group 1 (GINI <1,424; N = 140) and Group 2 (GINI≥1,424; N = 90). We subsequently utilized the Chi-square test to cross-tabulate the incidence of RIT between the two groups. Suggesting a strong association between higher baseline GINI measures and increased rates of post-CCRT RIT rates, our results revealed that the incidence of RIT was significantly higher in Group 2 (GINI≥1,424) than in Group 1 (GINI <1,424) [43.3% vs. 9.3%; Hazard ratio (HR): 4.76; P < 0.001].

The results of univariate and multivariate analysis

The outcomes of univariate analyses revealed a significant association between elevated RIT incidences and certain patients groups as shown in Table 3: median MMO < 41.4 mm (38.4% vs. 10.4 % for ≥ 41.4 mm; P < 0.001), T_{3-4} tumor stage (25.7 % vs. 13.6 % for T_{1-2}; P = 0.009), pre-CCRT GINI measures ≥ 1424 (43.3% vs 9.3 for < 1424, P < 0.001), mean masticatory apparatus dose (MAD) ≥37.2 Gy (37.8% vs 8.4 % for mean MAD < 37.2), P < 0.001), MAD V53.2 Gy ≤ 38.6% (31.8 % vs. 10.2% for V53.2 > 38.6%; P < 0.001).

Although the female gender showed a trend for elevated RIT rates (29.2 % vs 19.6% for the male gender; P=0.072), the difference did not achieve statistical significance (P=0.072). The results of multivariate logistic regression analyses including these six factors confirmed that all factors, except for the female gender, were independent and significant predictors of RIT in patients with LA-NPC who underwent definitive CCRT ($P < 0.05$ for each), as shown in Table 3 and Figure 2.

DISCUSSION

The primary objective of this retrospective study was to evaluate the feasibility of employing pre-CCRT GINI levels as a reliable biomarker for predicting RIT rates in patients with LA-NPC. Our most striking result was that patients with a GINI ≥ 1,424 before CCRT had a significantly higher incidence of RIT than those with a GINI < 1,424 [43.3% vs. 9.3%; HR: 4.76; $P < 0.001$]. The other significant findings were the exhibition of a substantial correlation between the elevated rates of RIT and pre-CCRT MMO < 41.4mm ($P < 0.001$), T3-4 stage ($P = 0.009$), mean MAD > 37.2 Gy ($P < 0.001$), and MAD V53.2 Gy ≥ 38.6% ($P < 0.001$).

We have examined several factors that may be associated with RIT. Among them, MMO < 41.4mm ($P < 0.001$), T3-4 disease stage ($P < 0.001$), and MAD V53.2 ≥ 38.6% ($P < 0.001$) have shown significant associations with RIT rates. Several previous studies have investigated the effects of pre-CCRT MMO and MAD on RIT rates in patient groups similar to our current cohort. However, the number of studies conducted is limited, and various MMO cutoffs have been proposed including < 46 mm [15], < 40 mm (16), and ≤ 40.7 mm [9]. Recently, Somay et al. determined 41.4 mm as the optimal MMO cutoff for LA-NPC patients, which is quite similar to our finding of 41.6 mm [10]. The common thread among these studies is that they demonstrate that patients who are close to or below the lower limit of the normal MMO range (40-60 mm) before RT or CCRT are more likely to experience

RIT after treatment [17]. In a study by Dworkin et al., an MMO of less than 40 mm was associated with mastication muscle disorders. Although this value may not be an exact limit that is applicable to all individuals, it has been reported that individuals without TMD may experience measures below this critical MMO level due to parafunctional habits such as bruxism [17,18]. In this context, patients with MMO measures close to the definition of RIT (< 35 mm) may have a greater risk of experiencing RIT due to the consequential effects of RT-induced fibrosis in the masticatory muscles, synovial fluid, and TMJ, as even a relatively small reduction in MMO width may fall their measures below the widely recognized RIT cutoff measures. Therefore, it is prudent to advise close and strict follow-up of patients presenting with MMO < 40-45 mm to promptly initiate preventive and/or therapeutic measures against the development and progression of RIT.

Various researchers have identified a wide variety of additional patient, disease, clinical, and dosimetric factors that contribute to the occurrence of RIT [19,20]. Among these, a crucial variable is the size or the volume of the tumor, which leads to the unavoidable irradiation of neighboring tissues with higher doses of radiation. Larger radiation volumes are mandatorily used in more advanced malignancies, namely T3-4 LA-NPCs, which, unfortunately, expose the masticatory apparatus components to higher RT doses [21]. Higher radiation doses to the larger volumes of masticatory muscles, TMJ, and associated ligaments may induce aggravated and persistent local and systemic inflammation, vascular occlusion, tissue hypoxia, and ultimately, tissue fibrosis, which are more prominent in higher T-stage NPCs due to the dose-volume relationship between the irradiated volume size and the probability of radiation-induced toxicities, including RIT [5]. While there may be additional pathophysiological mechanisms at play, the information presented provides a rational explanation for the potential association between the advanced T-stages and increased rates of RIT (25.7 % for T3-4 vs. 13.6 % for T1-2; P = 0.009) observed in this study and its predecessors.

Although there is limited research on MAD, studies have shown that the dose received by the components of the masticatory apparatus, measured as a dosimetric parameter for 100% volume, is associated with RIT rates [8, 9]. Our research findings indicate that RIT is significantly more likely to occur when the mean MAD is > 37.2 Gy ($P < 0.001$) and MAD V53.2 Gy is ≥ 38.6% ($P < 0.001$). These findings align with a retrospective study conducted by Somay et al. [9], which also examined the impact of MAD on RIT rates in 198 patients who received RT for LA-NPCs, which determined the critical dose as a mean MAD >57.2 Gy. These results suggest that the mean MAD and MAD Vx% effectively measure the level of damage in the masticatory apparatus, which functions as a parallel organ. The mean dose captures the extent of damage occurring throughout the entire organ, while MAD Vx% quantifies the volume of the affected organ, namely the masticatory apparatus in this scenario. Therefore, while there is currently a lack of information from more extensive studies to provide strict recommendations for exact threshold doses in routine RT planning processes, it is still advisable to include mean MAD and MAD Vx% values as appropriate metrics in dose planning. We believe this approach can effectively reduce masticatory apparatus dosages, thereby mitigating the risk of radiation-induced toxicity (RIT) without compromising the efficacy of tumor control rates if RT plans are executed carefully.

Our analysis made a unique and vital addition to the literature on LA-NPC by finding pre-CCRT GINI values as a robust predictor of RIT rates. In this respect, we discovered that patients with a pre-CCRT ≥ 1,424 had significantly higher RIT rates than their comparators with a GINI < 1,424 [43.3% vs. 9.3%; HR: 4.76; $P < 0.001$]. Although assigning this finding to a single reason without relevant data is challenging, we can infer some plausible mechanisms by dividing GINI into separate components. Among many others, one reasonable approach is to reformulate GINI as PIV × CRP-to-Albumin Ratio (CAR), which denotes the combination of a cellular and a biochemical biological marker. Somay et al. [10] recently conducted a study on 223 patients with LA-NPC. The study sought to identify the

optimal cut-off point for PIV. The research results indicated 850 as the optimal PIV cut-off, and RIT rates were significantly higher in the PIV > 850 group than its PIV ≤ 830 counterparts (60.3% vs. 5.0%; OR: 5.79; P<0.001). This effect is most likely associated with the combined effect of the imbalanced counts of platelets, monocytes, neutrophils, and lymphocytes [PIV = (P×M×N) ÷ L] [27], which directly or indirectly aggravates the inflammatory, hypoxic, hypovascular, and fibrotic pathogenesis and progression of RIT [8,9,22,23].

The impact of pre-CCRT CAR measures on the rates of RIT has yet to be studied, rendering our data impossible to compare. It is well established that RT causes an imbalance in cytokine levels, leading to a persistent inflammatory response and, thus, the increased production of acute-phase proteins such as CRP, a component of the CAR formula [24]. CRP serves as a reliable systemic inflammation marker, while albumin is a well-known indicator of leanness and nutrition. Consequently, related studies have shown that the CAR is a valuable metric for evaluating systemic inflammation and nutritional status [25,26]. Increased C-reactive protein (CRP) levels are consistently associated with decreased hepatocyte albumin synthesis. This reduction leads to an elevation in the measure of the CAR, regardless of the underlying cause. Therefore, it is imperative to consider the CAR as a marker of systemic inflammation in various clinical settings, as it is a reliable indicator of the inflammatory response in the body. Elevated levels of CRP and associated CAR can stimulate macrophages to produce tissue factor, a potent procoagulant that can result in increased intravascular coagulation and thrombosis during inflammatory states [27]. This process can lead to a state of tissue hypoxia, thereby exacerbating existing systemic and local inflammation. Increased CRP levels facilitate tissue fibrosis in different disease states by initiating transforming growth factor-β (TGF-β)/Smad signaling via both TGF-β1-dependent and TGF-β1-independent pathways [27]. Unfortunately, no previous research exists examining CAR's predictive power in determining the RIT rates of HNC patients treated with

RT or CCRT. Yet, in light of the cumulative information, the GINI index appears to be a comprehensive measure encompassing all components of the cellular PIV and biochemical CAR indices. Therefore, GINI integrates six factors, four cellular and two biochemical, rendering it a holistic novel biomarker compared to PIV, CAR, or their fragmented blends. Each cellular or biochemical component of the GINI index plays a crucial role in every step of the initiation, development, and progression of RIT, including vascular occlusion, hypoxia, hyperinflammation, and hyperfibrosis, which are characteristic hallmarks of RIT pathogenesis. Although further research is needed to confirm our findings, the pre-CCRT GINI index appears to be a novel and robust biological marker that reliably categorizes LA-NPC patients into two RIT risk groups.

The present study is subject to certain limitations. First, the results of this retrospective study were conducted by a single institution and may have been influenced by unanticipated biases that are common in research of this nature. Second, we did not examine any potential correlations between the GINI groups and other biomarkers, such as the cytokines and chemokines produced and released by the specific GINI components. And third, it is compulsory to note that our findings were based on a single instance of GINI data taken just before CCRT, which may limit the accuracy of our results as GINI levels can fluctuate dramatically during and after C-CRT due to changes in tumor burden, inflammatory status, and host immunity. Therefore, our findings should be considered exploratory and require further research to establish a conclusive link between pretreatment GINI levels and RIT rates.

CONCLUSION

This research investigated whether pre-treatment GINI values hold predictive value for RIT in patients with LA-NPC who receive definitive CCRT. Our findings indicate that this innovative and all-inclusive index can categorize patients into two distinct RIT groups.

However, due to the retrospective and single-center nature of the study, further research is needed to validate these findings before recommending this index as a new RIT stratification tool for LA-NPC patients undergoing definitive CCRT.

ACKNOWLEDGMENTS

Consent for publication: Each participant has provided written informed consent for collecting, analyzing, and disseminating their results.

Ethics approval and consent to participate

Before acquiring any information from the patient, the study design was approved by the Institutional Review Board of Baskent University School of Medicine while adhering to the principles of the Declaration of Helsinki and its amendments. Informed consent forms were obtained from all patients before commencing the evaluation process to obtain and analyze the patients' sociodemographic, dental, and medical records and blood samples and disseminate the outcomes in academic societies.

Authorship contribution statement

All authors contributed significantly and equally, and all authors approved the final form of the manuscript.

REFERENCES

1. Anderson G, Ebadi M, Vo K, Novak J, Govindarajan A, Amini A. An updated review on head and neck cancer treatment with radiation therapy. Cancers (Basel). 2021;13(19):4912.
2. Somay E, Yilmaz B, Topkan E, Kucuk A, Pehlivan B, Selek U. Definitions of radiation-induced trismus in head and neck cancer: Current concepts and controversies. In: Sergi

CM, ed. Advancements in Cancer Research. Brisbane (AU): Exon Publications; August 17, 2023.

3. Louise Kent M, Brennan MT, Noll JL, Fox PC, Burri SH, Hunter JC. et al. Radiation-induced trismus in head and neck cancer patients. Support Care Cancer. 2008;16(3):305-09.
4. Dijkstra PU, Huisman PM, Roodenburg JL. Criteria for trismus in head and neck oncology. Int J Oral Maxillofac Surg. 2006;35(4):337-42.
5. Raj R, Thankappan K, Janakiram C, Iyer S, Mathew A. Etiopathogenesis of trismus in patients with head and neck cancer: An exploratory literature review. Craniomaxillofac Trauma Reconstr. 2020;13(3):219-25.
6. Ramia P, Bodgi L, Mahmoud D, Mohammad MA, Youssef B, Kopek N, et al. Radiation-induced fibrosis in patients with head and neck cancer: A review of pathogenesis and clinical outcomes. Clin Med Insights Oncol. 2022;16:11795549211036898.
7. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol. 2014;6(10): a016295.
8. Somay E, Yilmaz B, Topkan E, Kucuk A, Pehlivan B, Selek U. Initial neutrophil-to-lymphocyte ratio predicts radiation-induced trismus in parotid gland cancer. Oral Dis. 2023;29(7):2772-79.
9. Somay E, Yilmaz B, Topkan E, Kucuk A, Haksoyler V, Pehlivan B, et al. Hemoglobin-to-platelet ratio in predicting the incidence of trismus after concurrent chemoradiotherapy. Oral Dis. 2023;29(7):2962-70.
10. Somay E, Yilmaz B, Topkan E, Ozdemir BS, Ozturk D, Besen AA, et al. Worth of pan-immune-inflammation value in trismus prediction after concurrent chemoradiotherapy for nasopharyngeal carcinomas. Int J Biol Markers. 2024:3936155231223198.

11. Topkan E, Somay E, Yilmaz B, Pehlivan B, Selek U. Valero's host index is useful in predicting radiation-induced trismus and osteoradionecrosis of the jaw risks in locally advanced nasopharyngeal carcinoma patients. BMC Cancer. 2023;23(1):651.
12. Topkan E, Selek U, Pehlivan B, Kucuk A, Ozturk D, Ozdemir BS, Besen AA, et al. The prognostic value of the novel global immune-nutrition-inflammation index (GINI) in stage IIIC non-small cell lung cancer patients treated with concurrent chemoradiotherapy. Cancers (Basel). 2023;15(18):4512.
13. Yilmaz B., Somay E., Selek U., Topkan E. Pretreatment systemic immune-inflammation index predict needs for teeth extractions for locally advanced head and neck cancer patients undergoing concurrent chemoradiotherapy. Ther. Clin. Risk Manag. 2021;17:1113–21.
14. Bhargava D, Jain M, Deshpande A, Singh A, Jaiswal J. Temporomandibular joint arthrocentesis for internal derangement with disc displacement without reduction. J. Maxillofac. Oral Surg. 2015;14:454–59.
15. Kraaijenga SA, Hamming-Vrieze O, Verheijen S, Lamers E, van der Molen L, Hilgers FJ, et.al. Radiation dose to the masseter and medial pterygoid muscle in relation to trismus after chemoradiotherapy for advanced head and neck cancer. Head Neck. 2019;41(5):1387-94.
16. Owosho AA, Pedreira Ramalho LM, Rosenberg HI, Yom SK, Drill E, Riedel E, et.al. Objective assessment of trismus in oral and oropharyngeal cancer patients treated with intensity-modulated radiation therapy (IMRT). J Craniomaxillofac Surg. 2016;44(9):1408-13.
17. Li XY, Jia C, Zhang ZC. The normal range of maximum mouth opening and its correlation with height or weight in the young adult Chinese population. J Dent Sci. 2017;12(1):56-9.

18. Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord. 1992;6(4):301-55.
19. Johnson J, van As-Brooks CJ, Fagerberg-Mohlin B, Finizia C. Trismus in head and neck cancer patients in Sweden: incidence and risk factors. Med Sci Monit. 2010;16:CR278–CR282
20. Massaccesi M, Dinapoli N, Fuga V, Rupe C, Panfili M, Calandrelli R. et. al. A predictive nomogram for trismus after radiotherapy for head and neck cancer. Radiother Oncol. 2022; 2: S0167–8140(22)04137–8
21. Cardoso RC, Kamal M, Zaveri J, Chambers MS, Gunn GB, Fuller CD, et al. Self-Reported trismus: prevalence, severity, and impact on quality of life in oropharyngeal cancer survivorship: a cross-sectional survey report from a comprehensive cancer center. Support Care Cancer. 2021;29:1825–35.
22. Sharma M, Radhakrishnan R. Limited mouth opening in oral submucous fibrosis: reasons, ramifications, and remedies. J Oral Pathol Med. 2017;46(6):424-30.
23. Yarnold J, Brotons MC. Pathogenetic mechanisms in radiation fibrosis. Radiother Oncol. 2010;97(1):149-61.
24. Kim PK, Deutschman CS. Inflammatory responses and mediators. Surg Clin North Am. 2000;80(3):885–94.
25. Yang JR, Xu JY, Chen GC, Yu N, Yang J, Zeng DX, et al. Post-diagnostic C-reactive protein and albumin predict survival in Chinese patients with non-small cell lung cancer: a prospective cohort study. Sci Rep. 2019;9(1):8143.
26. Zhou P, Shen Q, Zhou S, Ouyang X, Guo T, Song M, et. al. The prognostic role of C-reactive protein to albumin ratio and anti-MDA5 antibody-positive in idiopathic inflammatory myopathy: a retrospective study. Sci Rep. 2023;13(1):3863.

27. Luan YY, Yao YM. The clinical significance and potential role of c-reactive protein in chronic inflammatory and neurodegenerative diseases. Front Immunol. 2018;9:1302. Citations and References in Supplemental data are permitted provided that they also appear in the reference list here.

28.

TABLES AND FIGURES WITH LEGENDS

Table 1. Baseline and treatment characteristics of the whole study cohort per Global Immune-Nutrition-Inflammation Index Group.

Characteristics	All patients (N=230)	GINI-1 (<1424) (N=140)	GINI-2 (≥1424) (N=90)	P-value
Median age (years)	56 (18-76)	56 (20-76)	57.5(18-76)	0.06
Age group, N (%) > 56 years ≤ 56 years	 112 (48.7) 118 (51.3)	 66 (49.1) 74 (52.9)	 46 (48.9) 44 (51.1)	 0.6
Gender, N (%) Male Female	 158 (68.7) 72 (31.3)	 96 (68.6) 44 (31.4)	 62 68.9) 28 (31.1)	 1.0
Smoking status, N (%) Yes No	 146 (63.5) 84 (36.5)	 90 (64.3) 50 (35.7)	 56 (62.2) 34 (37.8)	 0.8
Alcohol consumption, N (%) Yes No	 74 (32.2) 156 (67.8)	 43 (30.7) 97 (69.3)	 31 (34.4) 59 (65.6)	 0.6
Median pre-CCRT MMO, mm (range)	41.4 (37.4-46.8)	41.6 (38.4-46.8)	41.0 (37.4-45.0)	0.2
Pre-C-CRT MMO group, N (%) < 41.4 mm ≥ 41.4 mm	 115 (50) 115 (50)	 65 (46.4) 75 (53.6)	 50 (55.6) 40 (44.4)	 0.22
T-stage, N (%) 1-2 3-4	 59 (25.7) 171 (74.3)	 38 (27.1) 102 (72.9)	 21 (23.3) 69 (76.7)	 0.54
N-stage, N (%) 0-1 2-3	 47 (20.4) 183 (79.6)	 29 (20.7) 111 (79.3)	 18 (20.0) 72 (80.0)	 0.89

GINI: Global Immune-Nutrition-Inflammation Index; pre: pretreatment; C-CRT: concurrent chemoradiotherapy; MMO: maximum mouth opening, mm: millimeter; T: tumor; N: node.

Table 2. Treatment characteristics of the entire study cohort per Global Immune-Nutrition-Inflammation Index Group.

Characteristics	All patients (N=230)	GINI-1 (<1424) (N=140)	GINI-2 (≥1424) (N=90)	P-value
Mean MAD, Gy (range)	37.2 (11.9–65.3)	38.3 (12.5–64.3)	36.7 (11.9–65.3)	0.46
Mean MAD group, N (%) < 37.2 Gy ≥ 37.2 Gy	 119 (51.7) 111 (48.3)	 74 (52.9) 66 (47.1)	 45 (50.0) 45 (50.0)	 0.67
MAD V53.2 Gy group, N (%) < 38.6% ≥ 38.6%	 98 (42.6) 132 (57.4)	 58 (41.4) 82 (58.6)	 40 (44.4) 50 (55.6)	 0.81
Median time from CCRT to RIT, months (range)	10 (6-18)	10 (7-13)	10 (6-18)	0.77
Median post-CCRT MMO, mm (range)	38.2 (25.9-44.0)	39.0 (28.3-44.0)	36.5 (25.9-43.2)	<0.001
Concurrent chemotherapy cycles, N (%) 1 2-3	 51 (22.2) 179 (77.8)	 32 (22.9) 108 (77.1)	 19 (21.1) 71 (78.9)	 0.73
Adjuvant chemotherapy cycles, N (%) 0 1-2	 59 (25.7) 171 (74.3)	 38 (27.1) 102 (72.9)	 21 (23.3) 69 (76.7)	 0.39
Post-CCRT RIT, N (%) Absent Present	 178 (77.4) 52 (22.6)	 127 (90.7) 13 (9.3)	 51 (56.7) 39 (43.3)	 <0.001

GINI: Global Immune-Nutrition-Inflammation Index, MAD: masticatory apparatus dose; Gy: gray; V: volume; post: postoperative; CCRT: concurrent chemoradiotherapy, mm: millimeter, RIT: radiation-induced trismus.

Table 3. Radiation-induced trismus outcomes of the entire study group

Characteristics	**All patients (N=230)**	**RIT (%) (N=52)**	**Univariate P-value**	**Multivariate P-value**	**HR (95% CI)**
Age group, years, N (%) ≤56 >56	112 (48.7) 118 (51.3)	27 (24.1) 25 (21.1)	0.64	-	-
Gender, N (%) Male Female	158 (68.7) 72 (31.3)	31 (19.6) 21 (29.2)	0.042	0.072	1.42 (0.96-2.14)
Smoking status, N (%) Yes No	146 (63.5) 84 (36.5)	32 (21.9) 20 (23.8)	0.55	-	-
Alcohol consumption, N (%)\ Yes No	74 (32.2) 156 (67.8)	13 (17.6) 39 (25.0)	0.24	-	-
Pre-CCRT MMO group, N (%) < 41.4 mm ≥ 41.4 mm	115 (50) 115 (50)	40 (34.8) 12 (10.4)	<0.001	<0.001	3.74 (2.12-5.81)
T-stage group, N (%) 1-2 3-4	59 (25.7) 171 (74.3)	8 (13.6) 44 (25.7)	0.007	0.009	1.73 (1.18-3.07)
N-stage group, N (%) 0-1 2-3	47 (20.4) 183 (79.6)	10 (21.3) 42 (23.0)	0.74	-	-
Pre-CCRT GINI group, N (%) < 1424 ≥ 1424	140 (60.9) 90 (39.1)	13 (9.3) 39 (43.3)	<0.001	<0.001	4.94 (2.07-7.81)
Concurrent chemotherapy cycles, N (%) 1 2-3	51 (22.2) 179 (77.8)	10 (19.6) 42 (23.5)	0.49	-	-
Adjuvant chemotherapy cycles, N (%) 0 1-2	59 (25.7) 171 (74.3)	13 (22.0) 39 (22.8)	0.88	-	-
Mean MAD group, N (%) < 37.2 Gy ≥ 37.2 Gy	119 (51.7) 111 (48.3)	10 (8.4) 42 (37.8)	<0.001	<0.001	4.76 (2.38-6.87)
MAD V53.2 Gy group, N (%) < 38.6% ≥ 38.6%	98 (42.6) 132 (57.4)	10 (10.2) 42 (31.8)	<0.001	<0.001	2.97 (1.91-4.86)

GINI: Global Immune-Nutrition-Inflammation Index; HR: Hazard Ratio; RIT: radiation-induced trismus; pre: pretreatment, C-CRT: concurrent chemoradiotherapy; MMO: maximum mouth opening; mm; millimeter, T: tumor; N: node; MAD: masticatory apparatus dose; Gy: gray; V: volume.

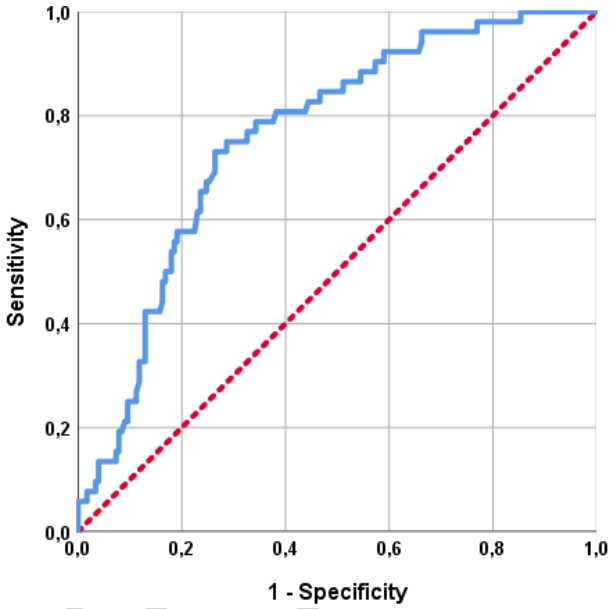

Figure 1. The outcomes of a receiver operating characteristic curve analysis examining the correlation between the Global Immune-Nutrition-Inflammation Index (GINI) and radiation-induced trismus rates (GINI cutoff: 1,424; Area under the curve: 76%; sensitivity: 75.0%; specificity: 71.7%, J-index: 0.463].

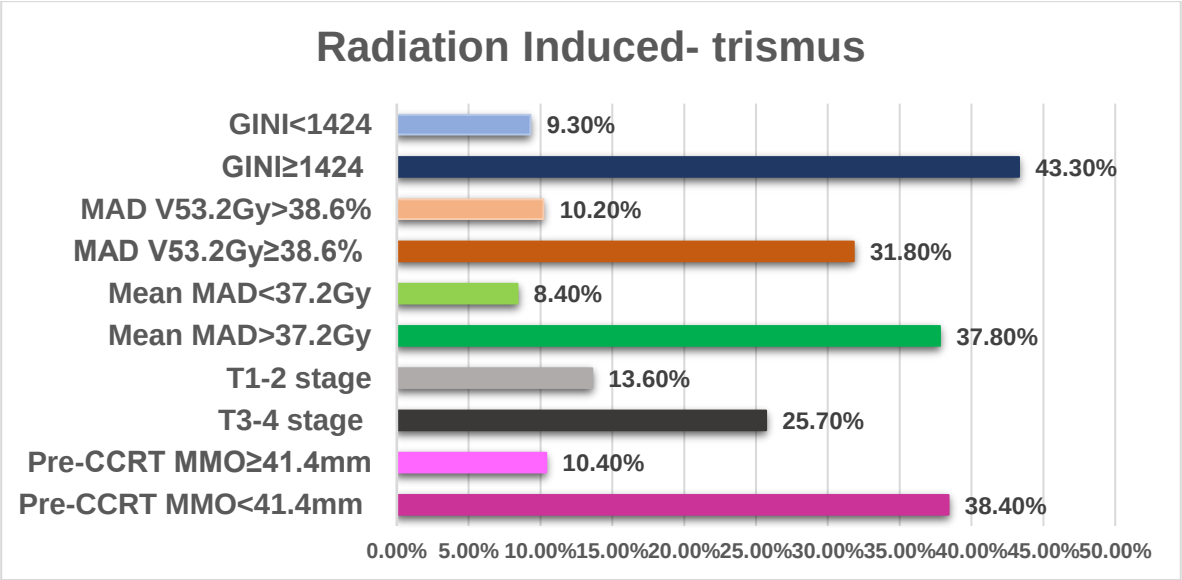

Figure 2. Bar graph displaying the frequency of radiation-induced trismus based on significant variables in multivariate analyses. MAD: mandibular apparatus dose; T: tumor; V: volume; CCRT: concurrent chemoradiotherapy; GINI: Global Immune-Nutrition-Inflammation Index; RIT: radiation-induced trismus.