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A Nomogram for Lateral Lymph Nodes that have Metastatic Cn0 Unifocal Papillary Thyroid Microcarcinoma

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Abstract

Background: The need for lateral neck dissection (LND) for papillary thyroid microcarcinoma (PTMC) can be better understood by identifying risk variables for occult lateral lymph node metastasis (LLNM). This study aimed to create a nomogram to predict the likelihood of LLNM in individuals with cN0 unifocal PTMC.

Methods: A total of 9744 patients with cN0 unifocal PTMC who were treated at our facility between February 2013 and April 2020 were included in our retrospective analysis. Risk variables for LLNM were identified using logistic regression analysis, and a nomogram was created based on these risk factors.

Results: In the study population, 3.2% had LLNM. Compared to tumors in the lower or middle lobe with a size less than or equal to 7 mm, tumors in the upper lobe had a substantially increased risk of LLNM (odds ratio [OR] = 2.56, 95% confidence interval [CI] 1.80–3.62; p 0.001) and OR = 2.59, 95% CI 1.85–3.62. ETE tumors had a significantly increased probability of developing LLNM (OR = 1.41, 95% CI 1.01–1.99; p = 0.044). One or two central lymph node metastases (CLNMs) or three or more of them (OR = 5.84, 95% CI 3.83-8.93; p 0.001) increased the probability of LLNM compared to those who did not (OR = 2.91, 95% CI 1.93-4.42; p 0.001). The receiver operating characteristic (ROC) curve of a nomogram considering these risk factors showed an area under the curve (AUC) of 0.777, indicating a good level of predictive accuracy.

Conclusion: Three or more CLNMs, especially three or more, and upper lobe tumors >7 mm in size were independent risk factors for LLNM in patients with cN0 unifocal PTMC. Based on these variables, the nomogram showed a good predictive value and consistency.

Keywords: Papillary thyroid microcarcinoma; Nomogram; Lymph node metastasis; Lateral neck dissection.

Introduction

Significantly increasing the frequency of PTC is papillary thyroid microcarcinoma (PTMC), which is defined as papillary thyroid carcinoma (PTC) with a maximum diameter of less than 1 cm [1]. PTMC patients often have a positive outlook, with a 10-year disease-specific survival rate as high as 99% and a low recurrence rate of 5% or less at the surgical site [3, 4]. However, lymph node metastases (LNM) in the cervical area occur in about 3.1-64% of cases [5-7]. Prophylactic central neck dissection (pCND) is recommended for patients with clinically negative cervical lymph nodes (cN0) who have

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advanced primary tumors (cT3/4) or clinically affected lateral neck nodes (cN1b) [8], according to recommendations from the American Thyroid Association (ATA)]. Risk factors for central LNM in cN0 PTMC have been extensively studied [9]. The ATA advises therapeutic lateral neck dissection (LND) for cN1b PTC of the lateral neck [8]. In earlier investigations, the prevalence of lateral LNM (LLNM) in PTMC ranged from 3.7 to 44.5% [6, 10-12]. When analyzing the incidence of lateral LNM, the majority of studies considered both palpable and nonpalpable lymph nodes [6]. However, to date, no study has been performed on the nomogram for LLNM in cN0 PTMC, especially with a large sample size. LNM in PTMC, particularly in the lateral neck region, is significantly associated with tumour recurrence and disease-free survival [13, 14]. Identifying LLNM risk factors, as well as other preventative measures, can help determine whether LND is required. This retrospective study aimed to identify clinicopathological risk factors for LLNM in cN0 unifocal PTMC and to create a useful nomogram for predicting the likelihood of LLNM, which will assist surgeons in making therapeutic decisions.

Materials and Methods

Patients

We retrospectively reviewed the medical records of 31,440 patients with papillary thyroid cancer (PTC) who underwent initial surgery at our facility between February 2013 and April 2020. Among these, 19858 patients had PTC with a pathological maximum diameter (PTMC) of ≤ 10 mm, and 1494 patients had clinically positive central or lateral cervical lymph nodes (cN1a/b). A total of 1,370 of 18,364 patients with cN0 PTMC who were not administered prophylactic central neck dissection (pCND) were included. We examined the data of 16,994 patients who underwent lateral neck dissection (LND) or unilateral or bilateral pCND. Finally, 9,744 patients with unifocal PTMC identified by postoperative pathology were included after eliminating 752 patients with incomplete clinicopathological data, and preoperative ultrasound (US) was used to determine the clinical lymph node (LN) status. When internal calcifications, cystic alterations, focal or diffuse hyperechogenicity, or a round shape could not be seen on ultrasound, cN0 was diagnosed [15].

Either total thyroidectomy with ipsilateral or bilateral pCND or lobectomy plus isthmectomy was performed during surgery. The retropharyngeal, paratracheal, and paratracheal lymph nodes were part of the ipsilateral CND. Intraoperative frozen pathological examination was performed when preoperative US revealed enlarged lateral lymph nodes, and LND was performed in patients with positive lymph nodes.

Data gathering

Sex, age, Hashimoto's thyroiditis (HT), multifocality, bilaterality, extrathyroidal extension (ETE), lymphovascular invasion (LVI), abnormal central lymph node (LN) status, and lateral LN status were among the information gathered. Age was dichotomized to 55 years using the stage norms in effect at that time. The receiver operating characteristic (ROC) curve showed a significant tumor size cut-off value of 7.5 mm (integrated area under the curve = 68.2%; p = 0.000, 95% CI = 0.640–0.724). The tumor size was measured based on the largest tumor dimensions. Tumor sizes (7 mm and > 7 mm) were used to separate patients into two groups. On the basis of the pathological findings, HT, multifocality, bilaterality, ETE, and LVI were diagnosed. Based on the intraoperative results, the location of the unifocal tumor was documented as higher, medium, or lower. The TNM Stage for Thyroid Cancer (8th Edition, 2017) of the American Joint Committee on Cancer was used for staging [16]. The initial risk stratification was performed according to the recommendations of the 2015 American Thyroid Association (ATA) recommendations [8].

Statistic evaluation

With the aid of the software SPSS v27.0 (SPSS Inc., Chicago, IL, USA), we carried out univariate and multivariate analyses. Intergroup variations in categorical variables were examined using Fisher's chi-squared test. Logistic regression tests were performed to identify variables associated with LLNM.

p-values of 0.05 were used to determine whether intergroup differences were statistically significant. To build the nomogram and use logistic regression to predict LLNM in patients with cN0 unifocal PTMC, we used the R package "rms" version 6.3. The contribution of each component to LLNM was indicated by the length of the line corresponding to that factor on the nomogram. R package "nomogram formula. Version 1.2, was used to determine the risk scores. Using the calibration curves, we examined the ability of LLNM to predict outcomes. R software 4.2.2 was used to analyze the data. The nomogram's prediction accuracy was assessed using receiver operating characteristic (ROC) curves, and cut-off values were established. Using the R package "ROCR" version 1.0–11, we determined the thresholds with the maximum sensitivity-specificity sum and plotted them on the ROC curve. Statistical significance was defined as $p < 0.05$.

Results

Clinical and pathological traits

9,744 patients made up the study population, and Table 1 summarizes their characteristics. The age range was 13–77 years, with a mean age of 43.46 ± 10.36. The range of tumor sizes was 1–10, with an average of 6.3–2.1 mm. Among the 9,744 patients, 1,636 (16.8%) underwent ipsilateral lobectomy + isthmectomy + contralateral partial thyroidectomy, 1,342 (65.1%) underwent ipsilateral lobectomy + isthmectomy

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alone, and 1,766 (18.1%) underwent total bilateral thyroidectomy. A total of 9,386 individuals (96.3%) had bilateral pCND, whereas 358 (3.7%) had ipsilateral pCND. 3,630 individuals (37.3%) had LNM in the ipsilateral central neck (CLNM). A total, 184 patients (0.6%) had bilateral CLNM. In the central neck, there were 2.50–2.04 positive LNs on average (range: 1–19). Overall, 157 patients (3.2 %) had lymph node metastases in the lateral neck 94 (1.6%) of the 6,054 individuals who did not have CLNM also had LLNM. In the lateral neck, there were 2.45 +/-1.74 positive LNs on average (range: 1–9). Levels II-V were present in 16 patients with LND, and levels II-IV were present in 150 patients. A total of 132 patients whose intraoperative frozen LN values were negative, but whose postoperative paraffin histology revealed positive LN results, did not undergo LND. Overall, 3,002 patients (30.8%) had tumors ≥7 mm, whereas 6,742 patients (69.2%) had smaller tumours. Of the 4,248 (43.6%) patients who had ETE, 4,024 (or micro-ETE) had the condition, while 224 (or macro-ETE) had the condition. There was no discernible difference between the rates of LLNM in patients with and without macro-ETE, which were 3.6% (8/224) and 3.2% (306/9,214), respectively (OR = 1.12, 95% CI 0.34-2.70; p = 0.833).

Table 1: Initial Clinicopathological Features

Characteristic		N=9,744
Sex	Female	3,668 (75.3%)
	Male	2,408(24.7%)
Age group	≥55 years	2,896 (14.9%)
	<55 years	8,296 (85.1%)
Tumor size	≤7 mm	6,742 (69.2%)
	>7 mm	3,002 (30.8%)
Tumor location	upper	2,286 (23.5%)
	middle	5,068 (52.0%)
	lower	2,390 (24.5%)
Hashimoto's thyroiditis		2,186 (22.4%)
LVI		62 (0.6%)
ETE		4,248 (43.6%)
ENE		350 (3.6%)
pT stage	1a	9,520 (97.7%)
	3b	180 (1.8%)
	4a	44 (0.5%)
pN stage	0	5,976 (61.3%)
	1a	3,454 (35.4%)
	1b	314 (3.2%)
pTNM stage	I	9,352 (96.0%)
	II	384 (3.9%)
	III	8 (0.1%)
ATA risk	low	5,284 (54.2%)
	intermediate	4,234 (43.5%)
	high	224 (2.3%)

LLNM risk factors in those with cN0 unifocal PTMC

Univariate analysis revealed that sex, tumor size, tumor location, ETE, and number of CLNMs were all significantly associated with LLNM (Table 2). Patients with tumors in the lower, middle, or higher lobes had LLNM rates of 2.5%, 2.7%, and 5.1%, respectively. There was no difference in the LLNM rate between patients with tumors in the middle and lower lobes (OR = 1.09, 95% CI 0.71-1.70; p = 0.706), but tumors in the upper lobe had a considerably higher risk of LLNM than tumors in the lower lobe (OR = 2.08, 95% CI 1.34-3.29; p = 0.001).

There were no differences between male and female patients in multivariate analysis (Table 2) (OR = 1.35, 95% CI 0.94–1.93; p = 0.102). The risk of LLNM was substantially higher for tumors in the upper lobe than for those in the lower and middle lobes (OR = 2.56, 95% CI 1.80–3.62; p 0.001). Comparing tumor sizes > 7 mm to 7 mm, a substantial increase in the incidence of LLNM was found (OR = 2.59, 95% CI 1.85–3.62; p 0.001). The incidence of LLNM metastases was higher in patients with ETE (OR = 1.41, 95% CI 1.01–1.99; p = 0.044). The risk of LLNM was substantially higher in those with three CLNMs (OR = 5.84, 95% CI 3.83–8.93; p 0.001) or 1-2 CLNMs (OR = 2.91, 95% CI 1.93–4.42; p 0.001) than in people without CLNMs.

Creation of nomograms

Using the four variables with non-zero coefficients (tumors location, tumors size, the existence of ETE, and the quantity of CLNMs), a nomogram was created to predict LLNM in patients with cN0 unifocal PTMC based on the findings of logistic regression analysis (see Figure 1). Notably, the greatest influence on the prediction model was due to the quantity of CLNMs. ROC curves were used to assess the accuracy of the nomogram; the AUC) was 0.777, and the 95% confidence interval (CI) ranged from 0.743 to 0.810 (Figure 2). The ideal cut-off score was 89.6110, with a sensitivity and specificity of 70.7% and 71.6%, respectively. Patients who received a total score of > 89.6110 and hadcN0 unifocal PTMC had a considerably increased chance of developing LLNM. As shown in Figure 3, the calibration curve shows outstanding consistency between the expected and actual probabilities.

Discussion

To the best of our knowledge, there have not been many studies on the risk factors for LLNM in cN0 PTMC patients, particularly those with sizable sample sizes from a single center [6, 10-12]. In this retrospective analysis, we examined the risk variables for LLNM using data from 4872 individuals with cN0 PTMC. According to earlier studies (ranging from 3.7 to 7.5%), the rate of occult LLNM was reported to be 3.2% [6, 12]. Multifocality has been identified in earlier research as

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Table 2: Logistic Regression Analysis of Risk Factors in Univariate and Multivariate Analysis

		LLNM		OR (95% CI, p-value)	
		no	yes	univariable	multivariable
Sex	Female	7,130 (97.2)	206 (2.8)	-	-
	Male	2300 (95.5)	108 (4.5)	1.63 (1.15–2.26, 0.005)	1.35 (0.94–1.93, 0.102)
Age group	≥ 55 years	1410 (97.4)	38 (2.6)	-	-
	<55 years	8,020 (96.7)	276 -3.3	1.28 (0.81–2.14, 0.324)	0.97 (0.60–1.65, 0.903)
Tumour upper location	no	7,260 (97.3)	198 (2.7)	-	-
	yes	2,170 (94.9)	116 (5.1)	1.96 (1.40–2.72,0.001)	2.56 (1.80–3.62,0.001)
Tumor size	≤7 mm	6,616 -98.1	126 (1.9)	-	-
	>7 mm	2,814 (93.7)	188 (6.3)	3.51 (2.54–4.87,0.001)	2.59 (1.85–3.65,0.001)
Hashimoto's thyroiditis	no	7,322 (96.9)	236 (3.1)	-	-
	yes	2,090 (96.4)	78 (3.6)	1.15 (0.78–1.64, 0.463)	1.27 (0.85–1.87, 0.224)
ETE	no	5,368 (97.7)	128 (2.3)	-	-
	yes	4,062 (95.6)	186 (4.4)	1.92 (1.39–2.66,0.001)	1.41 (1.01–1.99, 0.044)
LVI	no	9,372 (96.8)	310 (3.2)	-	-
	yes	58 (93.5)	4 (6.5)	2.08 (0.34-7.00, 0.318)	1.06 (0.16–3.85, 0.939)
CLNM	0	5,960 (98.4)	154 (1.6)	-	-
	1–2	2,284 (95.7)	102 (4.3)	2.83 (1.89–4.24,0.001)	2.91 (1.93–4.42,0.001)
	≥3	1,186 (91.0)	118 (9.0)	6.31 (4.26–9.38,0.001)	5.84 (3.83–8.93,0.001)

In light of the findings of the multivariate study, we suggested the following scoring formula: Location of the tumors: upper lobe; yes = 1, no = 0; Size of the tumor: >7 mm = 1, 7 mm = 0; ETE: "yes" = 1, "no" = 0; CLNMs present:3 = 2, 1-2 = 1, 0 = 0. Separate scores were summed to obtain the total score, following the aforementioned guidelines. 1102 patients received a total score of 0, 1533 patients received a total of 1, 1276 patients received a total of 2, 692 patients received a total of 3, 241 patients received a total of 4, and 28 patients received a total of 5. Patients with total scores of 0, 1, 2, 3, 4, and 5 had LLNM rates of 0.2%, 1.8%, 2.8%, 8.5%, 11.2%, and 21.4%, respectively.

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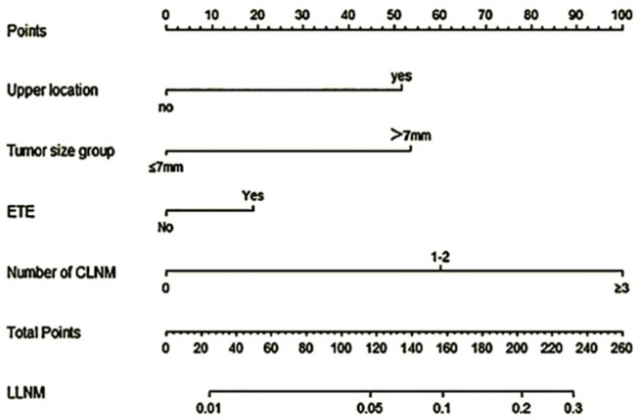

Figure 1: Nomogram for Predicting Lymph Node Metastasis in Patients with cN0 Unifocal Papillary Thyroid Microcarcinoma (PTMC)

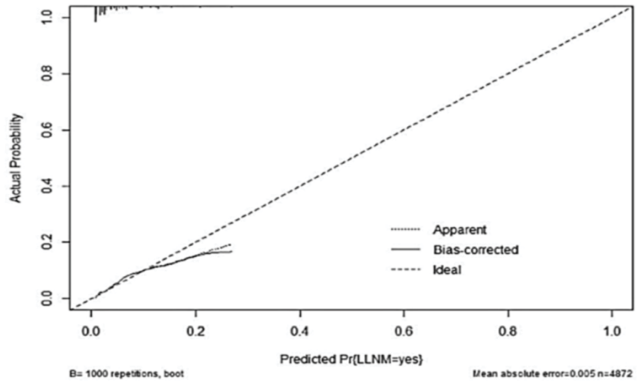

Figure 2: Curve of Receiver Operating Characteristics (ROC) for Prediction

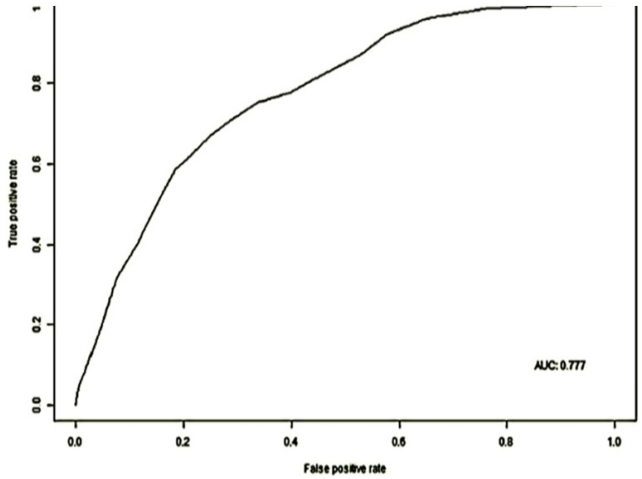

Figure 3: Shows the nomogram calibration curves for predicting lymph node metastasis in patients with cN0 unifocal PTMC.

a risk factor for LNM in PTMC [17, 18]. The LLNM rate was substantially higher (4.7%; 153/3249, p = 0.006) in patients with multifocal PTMC, according to our analysis of the relationship between multifocality and the LLNM rate. However, the multivariate analysis revealed that multifocality was a separate risk factor (data not shown). Subsequently, we included only patients with unifocal PTMC to examine the risk factors for LLNM. For differentiated thyroid carcinoma, the primary tumor size is a known prognostic factor [8], and earlier research has found a substantial link between a higher risk of LNM and greater tumor size [19]. Tumor size was revealed to be a significant factor related to LLNM by Yon et al. in their assessment of 490 individuals with PTMC [20]. The significant tumor size cutoff value in our study was determined by ROC curve analysis to be 7.5 mm, and patients were subsequently separated into two groups (7 mm and > 7 mm). Tumor size > 7 mm was found to be an independent risk factor for LLNM, and the rates of LLNM in these two groups were 1.9% and 6.3%, respectively, with significant differences in both univariate and multivariate analyses. While other studies revealed that tumor size > 5 mm was an independent predictor of the high prevalence of LLNM [17, 21], Zhang et al. [18] evaluated 1066 patients with PTMC and found that tumor size > 6 mm was substantially linked with LLNM. Different population demographics and sample sizes may be responsible for the heterogeneity in tumor size cutoff values among researchers. Additionally, all patients included in our analysis had unifocal tumors, which would have affected the determination of the cut-off value. It is well known that the location of tumors influences both the frequency and severity of lymph node metastasis. Tumors in the upper thyroid lobe frequently metastasize to the lateral neck [22, 23, 24], and tumor location in the upper third of the thyroid lobe has been found to be an independent risk factor for LLNM [22]. This is because the superior thyroid artery facilitates the flow of lymphatic fluid, which encourages the spread of tumor cells. In addition, we found that patients with tumors in the upper lobe had a considerably higher incidence of LLNM (5.1% vs. 2.7%) than those with tumors in the middle and lower lobes. Additionally, multivariate analysis supported prior research findings [18, 21, 25] that tumor site in the upper lobe was an independent risk factor for LLNM. Extrathyroidal extension (ETE) is a significant risk factor for LNM and one of the most important prognostic indicators for PTC [8, 10]. Tumors with macro-ETE that invade the strap muscles or organs are restaged as T3b or T4 in the eighth edition staging method (2017), whereas tumors with micro-ETE are staged as T1/2 (4 cm) or T3a (> 4 cm) [16]. According to previous studies, microscopic ETE remains a reliable indicator of LLNM [17, 25,30]. In our study, we analyzed both micro- and macro-ETEs. Patients of LLNM were a 4.4% incidence of LLNM, while patients without ETE had a 2.3% respectively. Univariate and multivariate analyses revealed that the differences were statistically significant. Patients with macro-ETE (3.6%) and those with micro-ETE or intrathyroidal tumors (3.2%, p = 0.832) did not differ significantly from one another. Similarly, Back discovered no correlation between macro-ETE and LLNM [21].

The small sample size of macro-ETE in individuals with cN0 PTMC may explain this finding. Recent research has shown that preoperative ultrasonography (US) examination-detected tumours close to the thyroid capsule and thyroid capsule discontinuity are separate risk factors for LLNM in PTMC patients [25, 26]. Tumords with ETE must be tightly associated with the thyroid capsule on US examination, although we did not analyze the preoperative US characteristics of the tumors. Therefore, based on the preoperative US scan, the link between the tumor and thyroid capsule, as well as the tumor location, as previously discussed, it is possible to determine the likelihood of LLNM. Previous studies have established CLNM as a significant risk factor for LLNM [17, 20, 25, 27]. According to Lim et al. LLNM is substantially related to the typical proportion of positive LNs in the central compartment [20, 30]. In the current investigation, we discovered that patients with 1-2 CLNMs or 3 CLNMs had a significantly higher risk of LLNM than patients without CLNMs (OR = 2.91, 95% CI 1.93-4.42; P 0.001). According to Bohec et al., patients with >5 positive CLNMs results had a greater risk of LLNM, [27]. A recent study at our center found that the number of CLNMs (> 3) was strongly associated with lateral neck recurrence in patients with pN1a PTC [29, 30]. CLNM was also found to be a predictor of lateral neck recurrence in patients [28]. Therefore, we believe that CLNM quantity is a useful indicator of the likelihood of LLNM. In the current cohort analysis, characteristics such as tumor location in the upper lobe, tumor size greater than 7 mm, ETE, and CLNM, particularly three3 positive LNs, were found to be independent risk factors for LLNM of cN0 unifocal PTMC. Based on these variables, we developed a nomogram with a high likelihood of LLNM (AUC = 89.611) and a high predictive value (AUC = 0.777). For patients with PTMC, this nomogram can help predict the likelihood of LLNM, select a personalized surgical approach, and direct surgeons to carefully assess the lateral neck during the follow-up. Our study has limitations, including the fact that it was a non-randomized, retrospective cohort study. To avoid missing cases of subclinical LLNM, LND was performed only in patients with enlarged LNs identified on preoperative ultrasonography and diagnosed as positive on frozen pathology. The strength of this study is that it was conducted in a single medical facility with a sizable sample size and stringent inclusion criteria, producing accurate results.

Conclusion

In conclusion, ETE, CLNMs (, particularly three or more), and upper lobe tumor sites and sizes >7 mm were independent risk factors for LLNM in cN0 unifocal PTMC. The likelihood of LLNM can be calculated and predicted by using a nomogram. Therefore, to reduce selection bias and to confirm our findings, a prospective multicenter investigation is required.

Acknowledgment: Not applicable

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author's request.

All authors approved and shared the database.

Funding: Non

Ethics declarations

Ethics approval and consent to participate

This study was conducted in accordance with the guidelines and regulations for human research (Declaration of Helsinki). The study was approved by the Ethics Committee of Zagzig University Hospital.

Written informed consent was obtained at the time of surgery for the general use of clinical information in future studies.

Consent for publication

Not applicable

Competing interests

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

Author's contributions

HAS, ME: contributed to conception and design of MR, AKE: organized the database and performed the statistical analysis. HAS, KS: wrote sections of the manuscript and prepared tables. MIF, AB: contributed to manuscript revision. All authors read, approved equally shared the submitted version.

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