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ORIGINAL RESEARCH

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Ki67 can be used as a predictive factor for the effectiveness of neoadjuvant chemotherapy in breast cancer patients

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Abstract

Cell proliferation, as measured by Ki67, is considered a significant predictive factor for the success of neoadjuvant chemotherapy (NACT) in breast cancer. However, its clinical utility remains debated. This study aimed to determine the optimal cut-off value for Ki67 and evaluate its predictive potential in this context. This study analyzed 74 patients with locally advanced breast cancer undergoing NACT. The response to NACT was assessed using the pathological complete response (pCR) rate and the neoadjuvant response index (NRI). All patients had centrally evaluated Ki67 levels alongside other tumor characteristics. The optimal cut-off value for Ki67 was determined using receiver operating characteristic (ROC) curve analysis, and its predictive potential was confirmed through univariate and multivariate analyses. A Ki67 cut-off value of 50% was identified as optimal for predicting both pCR rate and NRI. Patients with high Ki67 ($\geq$50%) achieved an NRI of 0.49, compared to 0.32 in patients with Ki67 $<$50% ($p < 0.01$). Similarly, the pCR rate was 19.4% in the high Ki67 group versus 5.3% in the low Ki67 group, although this difference did not reach statistical significance ($p = 0.06$). The independent predictive value of the Ki67 cut-off was confirmed through multivariate analysis. Cell proliferation measured by Ki67 serves as a critical predictor of response to NACT. A cut-off value of 50% can effectively identify patients more likely to achieve favorable outcomes and a higher probability of pCR.

Keywords

Breast cancer; Ki67; Neoadjuvant chemotherapy; Neoadjuvant response index; Pathological complete response

1. Introduction

Breast cancer is currently regarded as a systemic disease rather than a localized one. Consequently, there is increasing interest in the use of systemic preoperative therapies, such as neoadjuvant chemotherapy (NACT) and endocrine therapy, to treat the early systemic manifestations of the disease [1, 2]. Patients with locally advanced breast cancer (stages IIB or III) are optimally managed with a multimodality approach, incorporating both systemic and loco-regional therapies.

Cell proliferation has been extensively studied in various tumors. In breast cancer, a common method for measuring cell proliferation is the immunohistochemical detection of the Ki67 antigen. This method has proven to be very useful, although its application in clinical practice lacks general consensus [3]. Currently, Ki67 is primarily used as a predictive factor for the response to neoadjuvant hormonal therapy [4]. Several studies have shown its value in predicting the response to NACT, while other studies have failed to confirm these findings. This contradiction may be due to the lack of standardized procedures for Ki67 assessment and the wide range of cut-off values used across different studies, commonly ranging from 10% to 50%. Multiple studies have demonstrated a correlation between high levels of Ki67 antigen and higher rates of pathological complete response (pCR) [5, 6]. Even though not all studies have corroborated these results, Ki67 is currently being used routinely in clinical practice its clinical utility continues to be widely investigated [7, 8].

The approach to treating breast cancer has evolved significantly in recent years [9, 10]. Neoadjuvant chemotherapy (NACT) is increasingly becoming standard practice for treating locally advanced breast cancer. Selecting patients with the greatest potential to benefit from NACT is crucial for ensuring optimal results and patient well-being.

While most neoadjuvant chemotherapy studies focus on achieving pCR as their primary objective, the neoadjuvant response index (NRI) may offer a more precise method for evaluating the effectiveness of neoadjuvant therapy, as it considers any degree of downstaging, including pCR or near-pCR [11].

2. Materials and methods

2.1 Patients

We analyzed the data of 75 patients with primary invasive breast cancer who were treated with neoadjuvant chemotherapy (NACT) at the University Medical Centre Maribor between 2020 and 2022. Every single patient undergoing NACT for breast cancer was therefore included in the study. One patient was excluded from the study for not undergoing surgery. Patients were selected for NACT treatment if they were HER2-positive, had triple-negative breast cancer (TNBC), or were hormonally active with a large tumor or positive lymph nodes. All women with primary breast cancer underwent mammography and ultrasound evaluation. Definitive diagnosis was established using a large needle biopsy of the tumor, measuring hormonal receptor status, HER2 status and Ki67. Disease staging was performed by ultrasonically measuring the tumor size. Lymph nodes were evaluated clinically and ultrasonically, with aspiration biopsy conducted in suspicious cases. Women were stratified into different chemotherapy regimens based on tumor biology and intrinsic subtype. NACT regimens included 6 cycles of epirubicin and cyclophosphamide (EC), 6 cycles of docetaxel, carboplatin, and trastuzumab (TCH), or a combination of 3 cycles of each. Used schemes included EC + T (epirubicin plus cyclophosphamide followed by docetaxel), EC + DD (epirubicin plus dose-dense cyclophosphamide), EC + TH (epirubicin plus cyclophosphamide followed by docetaxel and Herceptin), EC + TC (epirubicin plus cyclophosphamide followed by docetaxel and carboplatin). In some cases, 4 cycles of chemotherapy were administered instead of 6. During NACT treatment, patients were monitored using ultrasound evaluation of tumor size.

After completing the planned treatment, patients underwent surgical intervention with either lumpectomy or mastectomy. Lymph nodes were managed with either sentinel node biopsy or axillary lymphadenectomy, as appropriate. Specimens were sent for histological evaluation, where tumor size and lymph node involvement were assessed histologically. Hormonal status and Ki67 were determined again in all samples.

2.2 pCR definition

Pathological complete response (pCR) was defined as the complete absence of invasive tumor cells in both the breast and the examined axillary lymph nodes [10].

2.3 Determination of Ki67, estrogen receptors (ER), progesterone receptors (PR) and HER2

Tissue microarrays were immunohistochemically stained using the Ventana BenchMark XT automated slide stainer (Ventana Medical Systems, Inc., Tucson, AZ, USA). The sections were deparaffinized, rehydrated and processed with the ultraView Universal DAB Detection Kit (Ventana Medical Systems, Inc., Tucson, AZ, USA) for Ki67. Sections underwent antigen retrieval in the automated slide stainer for 60 minutes with Cell Conditioning 1 (CC1; Ventana Medical Systems, Inc.). The slides were then incubated with an appropriately diluted primary antibody. Mouse anti-human monoclonal antibody to Ki67 (Mib-1, 1:100) (Dako Denmark A/S, Glostrup, Denmark) and rabbit antibodies to ER and PR (SP1 and 1E2 by Ventana Medical Systems, respectively) were used. Expressions of Ki67, ER and PR were evaluated by scoring the percentage of positively stained nuclei of malignant cells under a light microscope.

2.4 Neoadjuvant response index

Each patient was staged at the initial workup prior to NACT treatment based on ultrasound and clinical examination, with additional imaging studies performed if distant metastases were suspected. Ultrasound measurements of tumor changes during NACT were not included in the study; only post-surgery results were used for calculating cancer response. After obtaining histological results, the disease stage was reassessed. The neoadjuvant response index (NRI) was calculated based on a system described by Rodenhuis *et al*. [9]. The breast response score was calculated based on the reduction in T-stage, with one point assigned for every decrease in T-stage, except for a reduction from T1 to T0. One point was assigned for achieving a near-pCR and two points for a pCR. The axillary response score was calculated using a simple clinical staging system, with one point assigned for every decrease in axillary stage, including a point for reduction from N1 to N0. The NRI was defined as the sum of the breast response score and the axillary response score, divided by the sum of achievable points, resulting in a value between 0 and 1, where 0 indicates no change in stage and 1 indicates the maximum possible stage decrease [9].

2.5 Statistical analysis

For statistical analysis, IBM SPSS version 29.0.0 (IBM Corp, Armonk, NY, USA) was used. The optimal cut-off value for Ki67 was determined using receiver operating characteristics (ROC) curve analysis, considering combined sensitivity and specificity for cut-off values between 1 and 100 in steps of 10 units. The optimal cut-off value was confirmed using Youden's index. Univariate and multivariate logistic regression were employed to assess the association between predictive values and response to NACT. The model was evaluated by analyzing the area under the ROC curve (AUC) produced from predicted probabilities. Parametric and nonparametric tests (*t*-tests and Mann-Whitney) were used to compare different groups based on variable distribution. Pearson's test was used to evaluate the correlation of nominal variables. MedCalc version 22.023 (MedCalc Software, Ostend, Belgium) was used to produce the ROC curve with Youden's J index to determine the optimal cut-off value for Ki67 by applying sensitivity and specificity in correlation with NRI.

The aim of this study was to evaluate the potential predictive value of Ki67 on the success of neoadjuvant chemotherapy in breast cancer patients with either inoperable disease or those with operable disease who are not candidates for breast-conserving surgery. The effect of NACT was measured by both pCR and NRI, which includes assessments of both breast and axillary responses, providing a more precise evaluation system.

3. Results

3.1 Clinical and pathological characteristics

The study included 74 women with a mean age of 54 years (range: 30–81 years, standard deviation (SD) = 13). At diagnosis, most women were staged as T2 (N = 53), followed by T4 (N = 10), T1 (N = 6), and T3 (N = 5), with a median T stage of 2. Lymph node involvement was staged as N1 in 28 women, N2 in 26, N0 in 19 and N3 in 1, with a median N stage of 2. The mean tumor diameter prior to chemotherapy was 3.9 cm (range: 1.2–10 cm, SD = 2.1 cm).

Hormonal receptor status revealed that 69% of patients (N = 50) had hormone receptor-positive breast cancer. The mean percentage of positive estrogen receptors was 58% (range: 0–100%, SD = 48%), and the mean percentage of progesterone receptors was 46% (range: 0–100%, SD = 43%). The mean Ki67 status was 46% (range: 0–100%, SD = 43%). HER2 receptors were positive in 37% of cases (N = 27). Triple-negative breast cancer (TNBC) accounted for 27% of cases (N = 20). Tumor characteristics can be seen in Table 1.

Histologically, the majority of cancers were invasive ductal carcinoma (N = 72), with only 2 cases of invasive lobular carcinoma. Carcinomas were graded as grade 2 (50%, N = 37), grade 3 (33%, N = 33), and grade 1 (4%, N = 3).

Regarding treatment regimens, 50% of patients received the EC scheme (N = 37), 25% the TCH scheme (N = 18), 9% the EC + TH scheme (N = 7), 7% the EC + DD scheme (N = 5), 5% the EC + T scheme (N = 4), and 4% the EC + TC scheme (N = 3).

Following NACT, the mean tumor diameter reduced to 1.7 cm (SD = 1.43), which is less than half of the initial diameter (3.9 cm), a statistically significant reduction ($p < 0.01$). The mean neoadjuvant response index (NRI) was 0.42 (range: 0–1, SD = 0.34). Thirteen patients (17%) had an NRI of 0, and 9 patients (12%) achieved an NRI of 1 (pathological complete response).

In the TNBC group, the mean NRI was 0.34, which was not significantly different from the overall NRI ($p = 0.84$). When dividing the group into estrogen receptor-positive (NRI = 0.39) and estrogen receptor-negative cancers (NRI = 0.44), there was no significant difference in NRI ($p = 0.6$). The results can be seen in Table 2.

3.2 ROC curves and determining Ki67 cut-off value

An ROC curve analysis was performed to determine the sensitivity and specificity of Ki67 in predicting dichotomous NRI results, with NRI $\leq$0.4 indicating poor response and NRI $>$0.4 indicating a good response to NACT. The median NRI value was used as the cut-off.

The optimal Ki67 cut-off value was identified as 50%, with 70.4% sensitivity and 72.3% specificity (n = 74, AUC = 0.71, $p = 0.001$). Based on this cut-off value, 32 patients (43.2%) had high Ki67 levels. A similar analysis using pCR as an independent variable indicated an optimal Ki67 cut-off value of 55%, with 78% sensitivity and 62% specificity (n = 74, AUC = 0.69). The ROC curve used to calculate Ki67 cut-off is seen in Fig. 1.

3.3 Association between NRI, pCR and tumor characteristics

The mean NRI in the group with Ki67 $>$50% was 0.49, which was significantly higher than in the low Ki67 group (mean NRI = 0.32). pCR rates were 5.3% in the low Ki67 group and 19.4% in the high Ki67 group. The difference in NRI was statistically significant ($p < 0.01$), while the difference in pCR rates was near significant ($p = 0.06$).

Univariate analyses revealed significant associations between NACT response (measured by NRI and pCR) and HER2 positive status, with a 22.2% pCR rate in HER2-positive tumors versus 6.4% in HER2-negative tumors. However, there was no significant difference in NRI based on HER2 positive status ($p = 0.29$). Tumor stage also significantly influenced NRI, with T1 tumors responding better than higher stages ($p = 0.05$). Tumor grade was another important factor, with higher grade tumors showing better NACT response ($p = 0.01$).

3.4 Predictive value of Ki67, hormonal status and HER2 status

Multivariate logistic regression analysis (Table 3) confirmed that high Ki67 was an important predictive factor for NRI outcome ($p = 0.005$) with an odds ratio (OR) and confidence interval (CI) of 1.03 (95% CI: 1.01–1.05) as a continuous variable and an OR of 4.5 (95% CI: 1.6–12.9) considering the cut-off value of 50% (AUC = 0.779). Another significant predictive factor was TNBC status, with an OR of 4.03 (95% CI: 1.06–15.3), $p = 0.020$.

4. Discussion

Our study evaluates findings from a cohort of 74 patients, treated with NACT for locally advanced breast cancer with the aim of reducing tumor load prior to surgery. The mean tumor diameter prior to treatment was 3.9 cm $\pm$ 2.1 cm. We examined the predictive value of Ki67 expression levels along with other biomarkers (estrogen receptor (ER), progesterone receptor (PR) and HER2), clinico-pathologic parameters (including age, tumor size, clinical stage and tumor grade), and treatment factors (such as the number of chemotherapy cycles) in determining the response to neoadjuvant chemotherapy (NACT).

Response to NACT treatment was assessed both clinically and through imaging techniques. For the purposes of this study, the definitive post-NACT measurement was obtained through macroscopic and histological examination of the specimen. Initial tumor diameter was measured by an expert sonographer which differs from other studies that at our centre, expert ultrasound plays major role in tumor evaluation, while magnetic resonance imaging (MRI) is used more often in detection of early breast cancer and positron emission tomography/computed tomography (PET-CT) for identification of possible metastasis [12].

The overall NRI was 0.42 with 11% of patients achieving pCR, which is on the lower end in comparison with other studies [5, 11, 13–17]. There are very few studies evaluating NRI in addition to pCR alone. The lack of consensus on the definition of NACT response presents a great challenge. While

TABLE 1. Tumor characteristics.

	Number of cases (%)	NRI	pCR	*p* (NRI)	*p* (pCR)
Treatment					
EC	37 (50.0)	0.36	1 (2.7)	0.39	0.04
EC + T	4 (5.4)	0.23	0 (0)		
EC + DD	5 (6.8)	0.55	2 (40.0)		
EC + TH	7 (9.5)	0.34	1 (14.3)		
EC + TC	3 (4.1)	0.33	0 (0)		
TCH	18 (25.3)	0.55	5 (27.8)		
ER					
Positive	51 (68.9)	0.39	6 (11.8)	0.58	0.88
Negative	23 (31.1)	0.44	3 (13.0)		
PR					
Positive	50 (68.9)	0.39	7 (14.0)	0.40	0.49
Negative	24 (32.4)	0.44	2 (8.3)		
HER2					
Positive	27 (36.5)	0.47	6 (22.2)	0.29	0.05
Negative	47 (63.5)	0.37	3 (6.4)		
TNBC	20 (27.0)	0.41	1 (5.0)	0.84	0.25
T-stage					
T1	6 (8.1)	0.58	2 (33.3)	0.05	0.35
T2	53 (71.6)	0.38	6 (11.3)		
T3	5 (6.8)	0.21	0 (0)		
T4	10 (13.5)	0.54	1 (10.0)		
N-stage					
N0	19 (25.7)	0.49	4 (21.1)	0.68	0.34
N1	28 (37.8)	0.38	4 (14.3)		
N2	26 (35.1)	0.37	1 (3.8)		
N3	1 (1.4)	0.33	0 (0)		
Histologic grade					
G1	3 (4.1)	0.44	0 (0)	0.01	0.11
G2	37 (50.0)	0.30	2 (5.4)		
G3	33 (33.0)	0.53	7 (21.2)		
Gx	1 (1.4)	0.25	0 (0)		

Tumor, node, metastasis stage according to NCCN Clinical Practice Guidelines.
Abbreviations: EC: epirubicin plus cyclophosphamide; EC + T: epirubicin plus cyclophosphamide followed by docetaxel; EC + DD: epirubicin plus dose-dense cyclophosphamide; EC + TH: epirubicin plus cyclophosphamide followed by docetaxel and Herceptin; EC + TC: epirubicin plus cyclophosphamide followed by docetaxel and carboplatin; TCH: docetaxel, carboplatin and Herceptin; ER: estrogen receptors; PR: progesterone receptors; TNBC: triple negative breast cancer; HER2: human epidermal growth factor receptor 2; NRI: neoadjuvant response index; pCR: pathological complete response.

pCR is commonly reported, its definition can vary from the absence of invasive cancer in the breast only to the absence of both invasive and *in situ* components, with no disease in the axillary lymph nodes. As pCR rates are known to be related to tumor size, comparing NACT responses across different stages of the disease can be problematic. Moreover, the dichotomous classification of pCR and non-pCR does not distinguish between tumors that show no response and those that significantly reduce in size without achieving pCR. To address this issue, we implemented another grading system parallel to pCR. The system proposed by Rodenhuis *et al*. [9] includes tumor and lymph node downstaging along with pCR and is considered more sensitive to tumor load reduction.

When evaluating the predictive value of Ki67, we found that

TABLE 2. NACT response.

	Initial Tumor Diameter (cm)	Tumor Diameter After NACT (cm)	*p*	Mean (NRI)	NRI 0 (%)	NRI 1 (pCR) (%)
All	3.9	1.7		0.42	13 (17%)	9 (12%)
Estrogen positive	3.7	1.7	0.35	0.39	10 (24%)	6 (12%)
Estrogen negative	4.4	1.9	0.66	0.44	3 (9%)	3 (9%)
TNBC	3.7	1.8	0.63	0.34	2 (10%)	1 (5%)
Ki67 >50%	3.9	1.4	0.18	0.49	5 (14%)	7 (19%)
Ki67 <50%	3.8	1.9	0.18	0.32	8 (21%)	2 (5%)

NACT: neoadjuvant chemotherapy; NRI: neoadjuvant response index; pCR: pathological complete response; TNBC: triple-negative breast cancer.

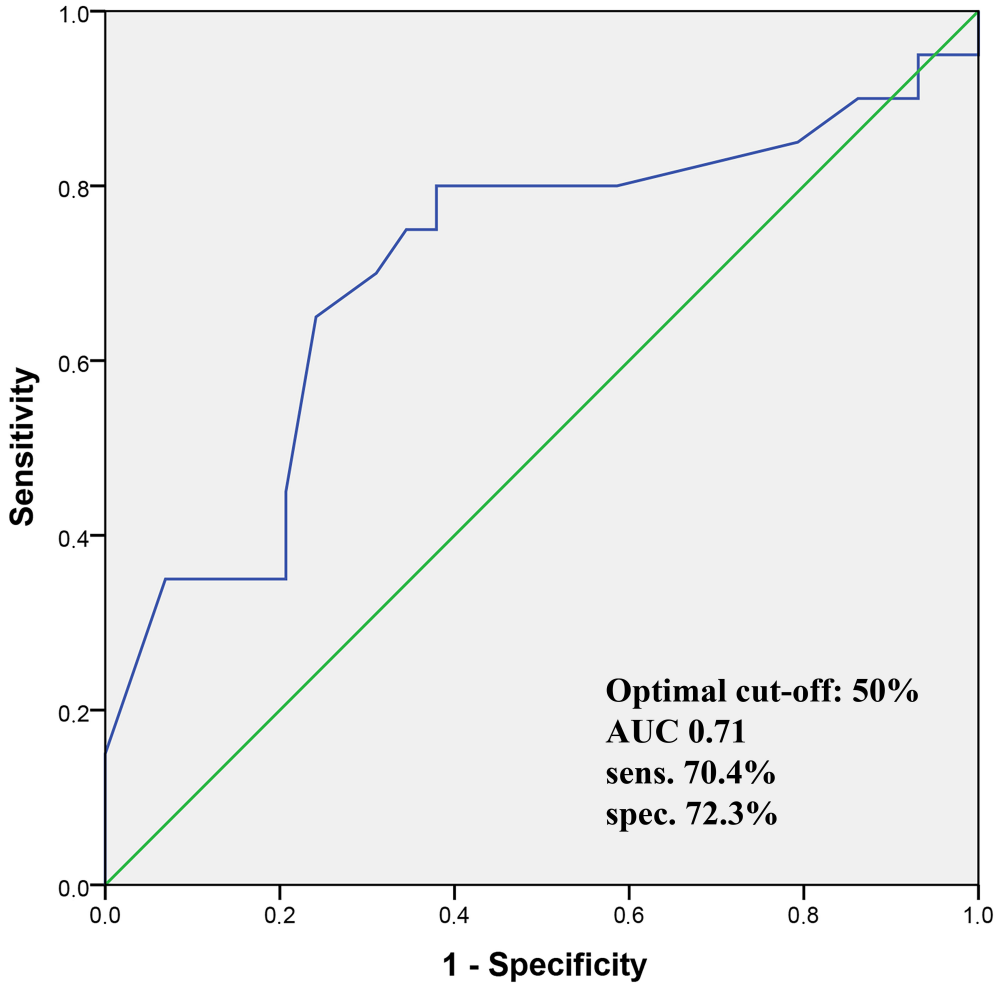

FIGURE 1. Receiver-operating characteristics curve for Ki67 and NRI. AUC: area under the curve; sens: sensitivity; spec: specificity.

high Ki67 group had significantly higher mean NRI and rate of pCR, which is consistent to the majority of studies [3–6, 8, 13, 15, 17, 18]. Additionally, we confirmed the Ki67 cut-off value to be independent of other factors using univariate and multivariate analysis. ROC curve was created and optimal cut-off value of Ki67 determined to be 50% by the use of Youden's index. Several studies have confirmed similar cut-off values even though ranges were as low as 20% as proposed by Acs [8, 17, 19]. In the newer studies evaluating automated Ki67 scoring, cut-off values were as low as 14% [11, 20]. Currently accepted thresholds according to St. Gallen consensus state high Ki67 as more than 30%, low below 5% while values in between do not have reliable predictive value [7]. However, not all studies have confirmed predictive value of Ki67 [21–24].

One major limitation of the routine determination of Ki67 is

TABLE 3. Multivariate analysis for predictive factors to NRI.

Parameter	OR (95% CI)	*p* value
Ki67 (continuous)	1.03 (1.01–1.05)	0.001
Ki67 (cut off 50%)	4.5 (1.6–12.9)	0.005
TNBC	4.03 (1.06–15.3)	0.020

Area under the curve = 0.779.
Abbreviations: TNBC: triple negative breast cancer; OR: odds ratio; CI: confidence interval.

the absence of standardized testing methodology, that was in some studies targeted by automated computer scoring [7, 11]. Ki67 is determined through immunohistochemical staining, and scoring is performed by the examiner, which leads to high interobserver variability, unless performed by computer vision that still does not by itself guarantee standardization, especially due to variability in equipment and algorithms [7].

Several studies and also meta analyses indeed indicate the predictive value of Ki67 and its correlation with response to NACT. However, these findings are predominantly from retrospective studies rather than randomized clinical trials [4, 15, 16].

Our study has limitations, including its retrospective design and the limited number of patients. Due to the small sample size, we could not perform a stratified analysis for the predictive value of Ki67 in each breast cancer subtype. Additionally, patients in the study were treated with various chemotherapy regimens, and due to the non-homogeneous groups with a low number of participants, analysis for respective regimens could not be conducted.

Despite these limitations, our findings suggest that Ki67 is a valuable predictive marker for NACT response, and a cut-off value of 50% may help identify patients more likely to benefit from this treatment. Further prospective studies with larger patient cohorts and standardized methodologies are necessary to validate these findings and integrate Ki67 into routine clinical practice.

5. Conclusions

This study shows that Ki67 can be used as a significant predictive marker for the response to NACT in breast cancer patients. An optimal cut-off value of 50% effectively predicts both pCR and the neoadjuvant response index (NRI). The independent predictive value of Ki67 was further validated through multivariate analysis. However, the study highlights the need for standardized testing methodologies for Ki67. Further prospective research with larger cohorts is recommended to validate Ki67's role in clinical practice.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the reported results are available upon request from the corresponding author.

AUTHOR CONTRIBUTIONS

NK and VGL—designed the research study. NK—performed the research. VGL—provided help and advice on the statistical analysis. Both authors analyzed the data and wrote the manuscript. Both authors read and approved the final manuscript. Both authors have contributed equally to the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

No ethics approval was required based on the retrospective audit design. All participants have signed an informed consent.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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