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Original Article

HER2 Reactivity Pattern and Its Association with Various Tumor Factors in Breast Cancer Patients

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Abstract

Background: Breast cancer prognosis and therapeutic strategies are strongly influenced by biomarker profiles, particularly HER2 reactivity, which impacts treatment selection and disease progression.

Objective: To study the HER2 reactivity pattern and identify the association of HER2 pattern with various tumor factors in patients with breast cancer.

Methods: This prospective study comprised of 150 surgically operated female cases of breast cancer admitted to the Department of Pathology for ER, PR, and HER2 testing between December 2015 and October 2017. Results: Of 150 cases, the mean age was 52 years (IQR, 41-63 years). This study showed that majority of tumors were IDC-NOS, grade 2, tumor size T2, and had negative lymph node status. HER2 negative cases were in the majority, as well as the ER/PR+ cases. Triple-negative cases were slightly higher (49 cases). When HER2 was correlated with tumor characteristics, younger patients with HER2-positive were in the majority, with the higher the tumor size is, the greater the chance for HER2 negativity. The majority of IDC cases and all ILC cases showed HER2 negativity. Both medullary cases showed HER2 positive, and one case of mucinous showed HER2 negativity with ER/PR positivity. Irrespective of ER/PR status, the majority of tumors had HER2 negativity.

Conclusion: HER2/neu positively correlates with increasing age, menstrual status, tumor size, and tumor grade. No association is found between histological type, lymph node status, and ER/PR. This study also reveals that patient with higher levels of HER2/NEU-overexpression had statistically significant lower levels of ER/PR-positive tumors. In addition, when HER2/neu is positive in tumors, along with ER and PR, it is mostly high-grade.

Keywords: Breast cancer, HER2, invasive carcinoma, triple negative

Introduction

Breast cancer is the most commonly diagnosed cancer worldwide and the second leading cause of cancer-related death among women.[1] Around 13.5% account for the new cancer cases and overall common cancer deaths.[2] Human epidermal growth factor receptor-2 (HER2) has emerged as a significant independent predictive marker in recent years. Additionally, the HER2 status has grown in importance as a prognostic indicator for evaluating patient response to Herceptin.

According to the literature, approximately 15% to 30% of breast cancers exhibit HER2 overexpression.[3] Several studies have identified HER2 overexpression in early breast cancer as a poor prognostic factor Several studies have identified HER2 overexpression in early breast cancer as a poor prognostic

factor.[4] Early and metastatic breast cancer patients now have a much better prognosis because of the discovery of trastuzumab.[5] Unfortunately, because trastuzumab is an expensive medication, most patients in developing countries cannot afford it.

This study aimed to evaluate the expression pattern of HER2 in the invasive component of breast carcinoma and to assess the association of HER2 status with various prognostic parameters, including menstrual status, tumor size, histologic grade, histologic type, regional lymph node involvement, and expression of estrogen receptor (ER) and progesterone receptor (PR). The study also aimed to explore a possible relationship between HER2 status and patient age.

Methods

This prospective study comprised 150 surgically operated female cases of breast cancer that were admitted to the Department of Pathology for ER (Estrogen Receptor), PR (Progesterone Receptor), and HER2 testing between December 2015 and October 2017 at a tertiary care Hospital in Aurangabad, Maharashtra, India.

Clinical data was obtained from the hospital records and requisition forms received in the department. Upon arrival, specimens were examined for gross features, routinely processed, and sectioned at 3–5 microns from paraffin-embedded blocks. These sections will be routinely stained with H and E and examined for invasive breast carcinoma presence. Nottingham Richardson classification was used for tumor grading and histological type.[6] The Allred scoring system was utilized to interpret ER and PR positive.[7] Reporting of ER, PR, and HER2/neu status followed the American Society of Clinical Oncology/ College of American Pathologists (ASCO/CAP) guidelines.[8,9] The study analyzed correlations between HER2, ER, and PR status and various histological and clinical parameters.

Ethical clearance for this study was obtained from the Mahatma Gandhi Mission's Ethics Committee for Research on Human Subjects, MGM Medical College and Hospital, Aurangabad, Maharashtra, under ethical approval number MGM-ECRHS/2017/26.

Data entry and statistical analysis were performed using IBM SPSS Statistics for Windows, Version 21. Descriptive statistics, including means, standard deviations, and percentages, were calculated.

Results

In this study, 150 women were diagnosed with invasive primary breast carcinoma with a mean age of 52 years± 11 years (IQR: 41–63 years). Breast cancer was most commonly seen in premenopausal women (58%). These results clearly show that most of the patients having breast cancer in India are younger and in the premenopausal menstrual stage. From a radiological perspective, the right breast appeared to be significantly more impacted.

Tumor sizes were classified into three categories. The tumor size of 2–5 cm2 was represented the highest [66%]. The various histological types found in this study were Invasive Duct Carcinoma [IDC] (123 cases), Invasive lobular carcinoma [ILC] (18 cases), medullary carcinoma (1 case), mucinous carcinoma (1 case), mixed (3 cases; 2 cases IDC with medullary and 1 case IDC with apocrine differentiation) and Paget's disease of the nipple (4 cases). Most of the cases (99 cases) were Modified radical mastectomy (MRM) specimens with the majority showing no lymph node involvement. A total of 150 cases of breast cancer were graded according to Modified Bloom Richardson Histologic Grade with the majority of them grade 2. One case could not be graded as no invasion was noted. Among 150 patients, 48% and 54% expressed ER, and PR respectively. Immunohistochemistry evaluation for HER2/ NEU was negative for 62% of cases whereas borderline or equivocal in 10%. The equivocal cases were advised fluorescent in-situ hybridization for confirmation. HER2/NEU was positive in 28% of cases. This study showed that the largest category of breast cancer was negative for HER2/NEU. Table 1 presents the clinicopathological characteristics of the study population.

The borderline HER2/NEU 2+ cases were not correlated as they could not be categorized in either positive or negative categories without further subjecting them to Fluorescent in-situ Hybridization (FISH). Table 2 shows the frequency of HER2 and clinicopathologic variables of the study population.

HER2-positive status was observed mostly in patients aged ≤50 years, and HER2 status was significantly associated with age (p=0.013) and menopausal status (p=0.009). In this study, it showed that, out of 150 cases, most tumors were T2 tumors, and out of these HER-2 negative cases were 63, positive were 30, and equivocal were 6 cases. A statistical significance was seen when the HER2/NEU

Table 1 Clinicopathological Characteristics of the Study Population (n 150)

Characteristic	Parameters	Number of Cases
Age	≤50 years	96
	>50 years	54
Menopausal status	Pre-menopausal	87
	Post-menopausal	63
Laterality	Right breast	77
	Left breast	72
	Bilateral	1
Tumor size	<2	9
	2–4	99
	>5	27
	Any size growing into the chest/ skin	15
Histology	Invasive ductal carcinoma (IDC)	123
	Invasive lobular carcinoma (ILC)	18
	Medullary carcinoma	1
	Mucinous carcinoma	1
	Mixed	3
	Paget's disease of nipple	4
Histologic grade	Grade 1 (low)	36
	Grade 2 (moderate)	59
	Grader 3 (high)	55
Axillary Node Status	Negative (0 nodes)	73
	Positive (1-3 nodes)	59
	Positive (4-9 nodes)	6
	Positive (> 9 nodes)	12
Estrogen Receptor (ER)	Positive	72
	Negative	78
Progesterone Receptor (PR)	Positive	81
	Negative	69
HER2/Neu Receptor	Positive	42
	Negative	93
	Equivocal	15
ER/PR	ER/PR+	84
	ER/PR-	66

** ER/PR=estrogen receptor/progesterone receptor; HER2=human epidermal growth factor receptor 2

expression profiles were correlated with tumor size (p=0.001). HER-2 receptor status in the cases of invasive carcinoma (no special type), showed that the maximum cases were of HER-2 negative status. All 18 cases of invasive lobular carcinoma were found to be HER2 negative. One case of medullary was HER-2 positive and one case of mucinous was HER-

Table 2 Frequency of HER2 Status by Clinicopathologic Variables

Variables	HER2 Positive		HER2 Negative		HER2 Equivocal		p-value
	(n=42)	%	(n=93)	%	(n=15)	%	
Age							
≤50 years	32	76	50	54	14	93	0.013
>50 years	10	24	43	46	1	7	
Menopausal Status							
Pre-menopausal	30	71	44	47	13	87	0.009
Post-menopausal	12	29	49	53	2	13	
Tumor size							
< 2cm	1	3	2	2	6	40	
2–5 cm	29	69	64	69	6	40	0.001
>5cm	3	7	24	26	0	0	
Any	9	21	3	3	3	20	
Histologic Type							
IDL	36	86	73	79	14	93	
ILC	0	0	18	19	0	0	0.324
Others	6	14	2	2	1	7	
Tumor Grade							
Grade 1	10	24	21	23	5	33	
Grade 2	23	56	29	31	6	40	0.007
Grade 3	8	20	43	46	4	27	
Lymph Node Status							
0 Nodes	25	60	45	48	3	20	
1-3 Nodes	17	40	39	42	3	20	0.526
4-9 Nodes	0	0	0	0	6	40	
>9 Nodes	0	0	9	10	3	20	
ER Status							
ER Positive	18	43	45	48	9	60	0.551
ER Negative	24	57	48	52	6	40	
PR Status							
PR Positive	24	57	47	51	10	67	0.476
PR Negative	18	43	46	59	5	33	

**HER2 = human epidermal growth factor receptor 2, ER = estrogen receptor, PR = progesterone receptor, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma

2 negative. Three out of four cases of Paget's disease were found to be HER-2 positive and one with HER-2 equivocal status. In the mixed carcinoma cases, both cases of IDC with medullary showed HER-2 status positive, and the case with IDC with apocrine showed HER-2 status negative. HER2 status was statistically not significantly associated with histologic type (p = 0.324).

The majority of HER2 negative cases were seen in grade 3 and HER2 positive cases were seen in grade 2 tumors. One case of Paget's disease of nipple with ductal carcinoma in situ did not show invasion and could not be graded.

Table 3 Hormone Receptor Status by Histologic Type

Histologic Type	ER/PR+(Luminal A/B)	HER2 Equivocal	HER2-rich	Triple-Negative
Invasive Ductal Carcinoma (IDC)	67	3	14	39
Invasive Lobular Carcinoma (ILC)	12	0	0	6
Medullary Carcinoma	1	0	0	0
Mucinous Carcinoma	1	0	0	0
Paget's Disease	0	1	0	3
Mixed	2	0	0	1

However, the HER2 positivity was closely related to grade (p = 0.007). The majority of HER2 negative receptors were seen when lymph node status was negative (no nodes seen). No significant association was noted (p=0.526).

Association of HER2 with ER (p = 0.551) and PR status (p = 0.476) did not show much difference and was not statistically significant. HER2/NEU profiles were correlated with ER, PR expression profiles, it derived into an inverse correlation (p value < 0.05). The HER2/NEU positive tumors have less chance of having expression of ER PR.

Hormone receptor status with histologic types showed that 67 cases of IDC were ER/PR+, 3 cases were equivocal, 14 cases were HER2 rich (ER-/PR-) and 39 cases were triple negative. In the case of ILC, 12 cases were ER/PR positive, and 6 cases were triple negative. All the cases of medullary and 1 case of mucinous showed ER/PR positive, however, both the cases of medullary were HER2 positive and 1 case of mucinous was HER2 negative. In the case of 4 Paget's disease, 1 case was excluded for IHC as there was no invasion, 1 case showed HER2 equivocal and 3 cases showed Triple negative. In total,49 cases of triple-negative breast cancer were seen in this study. Table 3 shows hormone receptor status with histologic type.

Discussion

This study found that 28% of breast cancer cases were HER2-positive and showed statistically significant associations with age, menstrual status, tumor size, and tumor grade. No significant associations were observed with histologic type or lymph node status. An inverse association was seen between HER2 and hormone receptors ER/PR.

The HER2-positivity rate in this study (28%) is consistent with previous Asian data, such as the study by Mudduwa *et al.*[10] in Sri Lanka, which reported 19.1% HER2-positivity among breast carcinoma cases. However, the frequency of HER2/NEU positivity varies among Indian studies.

The mean age of patients included in this study was 52 years. The results are in concordance with the study conducted by Mudduwa *et al.*[10] in which the mean age was 52.5 years and 85.7% of the patients were more than 40 years. Similar to other studies, (Gullick *et al.*[11]; Amirifard *et al.*[12]) a statistically significant correlation between age and HER2-neu overexpression was seen in this study. Premenopausal women overexpressed more HER2 than postmenopausal women. Similar results were observed by several authors.

HER-2 receptor negativity was seen in the majority of T2 tumors and this was in concordance with the study done by Bergeron *et al.*[13] in which the majority of HER-2 receptor negativity was present in 31 out of 139 (31.2%) stage II lesions.

HER-2 receptor status in the cases of invasive carcinoma (no special type), showed that the maximum cases were of HER-2 negative status. This was in discordance with the study done by Bergeron *et al.*[13] which showed 68 out of 185 cases of invasive carcinoma to have HER2 overexpression.

HER-2 neu expression was correlated in high-grade tumors, whereas grade I tumors were expressing higher ER&PR, which was comparable to a study done by Onitilo *et al.*[14] In this study, the majority of HER2-negative cases were seen in grade 3 tumors. This finding was also seen in the study done by Arafah *et al.*[15] in which the majority of HER2 negative cases were seen in the grade 3 tumor The majority of HER2 negative cases were

seen in negative lymph node status. This was also in concordance with the study done by Englander *et al*.[15] in which around 72 patients were seen to have HER2 negative status in negative lymph node status.

This study shows that most of the patients who had Her-2/neu protein over-expression were ER-/PR- and this was in concordance with the study done by Ariga *et al*.[17] Notably, a relatively high number of triple-negative breast cancer (TNBC) cases (n=49) was identified in this cohort. While higher than commonly reported in literature, this finding was in agreement with observations by Ahmed *et al*.[18]

The proportions of ER-positive and ER-negative, cases did not differ much. Also, PR positive and PR negative cases also did not differ much, although both ER and PR negative cases were slightly higher than ER/PR positive cases. Also, the proportion of ER+/PR+/HER2+ and ER-/PR-/HER2 cases did not differ much, although ER+/- and PR+/- with HER2 negative cases were much higher. And this was in concordance with the study done by Onitilo *et al*.[14] in which there were 65% of HER2 negative tumors.

Out of 150 malignant cases, an intriguing finding was that: only two cases had ER-/PR+. This was a controversial finding in terms of clinical significance. Some reports claim that this subtype represents a distinct, clinically useful entity, while others pose this to be a technical artefact and not very clinically significant. PR has no independent prognostic value in patients with ER-.[19] PR expression is a respective marker of a functional ER pathway. Hence patients with ER(-)/PR(+) subtype can still have survival benefits from hormone therapy. This phenotype has been described by Shen *et al*.[20]

The majority of invasive carcinoma (NST), were ER/PR+. This contradicted the findings of Devi *et al*. study.[21] The literature states that medullary cancer expresses no HER2/neu; nevertheless, two medullary instances expressed ER, PR and HER2/neu, which is consistent with the findings of Devi *et al*. study.[21] Due to funding limitations, the cases of HER2 equivocal could not be confirmed with Fluorescent in-situ Hybridization (FISH).

In conclusion, immunohistochemical analysis of ER, PR, and HER2 receptors is widely accessible and cost-effective, providing critical prognostic, predictive, and therapeutic guidance. Despite heterogeneity in hormone receptor expression patterns, routine testing for HER2 along with ER and PR status is essential for optimal clinical management. Further research should be carried out to understand the various trends and relationships between different variables associated with breast cancer for better prognosis of breast cancer patients in order to obtain better clinical outcomes with improved survival.

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Original Article

AI-powered Somatic Cancer Cell Analysis for Early Detection of Metastasis: The 62 Principal Cancer Types

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Abstract

Background: Early detection of metastasis is critical in improving survival outcomes in cancer patients, with artificial intelligence offering advanced tools for predictive analytics.

Objective: To emphasize the importance of early metastasis detection in improving cancer patient outcomes, and to highlight that recent advancements in AI-powered somatic cancer cell analysis may enhance early detection and personalize treatment strategies.

Methods: This study leveraged a comprehensive survival and artificial intelligence (AI) powered analysis to identify key genomic and clinical factors influencing cancer prognosis, with a focus on early metastatic detection. The AI algorithms explored the possibility of detecting tumors with a high spread risk. The study underscored the critical role of AI-powered analysis in the early detection of metastasis and the personalization of treatment strategies in cancer care.

Results: By leveraging advanced AI algorithms, key predictors of cancer prognosis such as fraction genome alteration, primary tumor site, and smoking history, all of which significantly influence metastasis outcomes, were identified. Furthermore, the models demonstrated exceptional predictive accuracy, with XGBoost and Support Vector Machines achieving an accuracy of 0.95.

Conclusion: Integrating AI capabilities into clinical workflows holds the promise of significantly enhancing early detection and treatment of metastatic cancer, thereby improving patient outcomes and optimizing therapeutic interventions.

Keywords: Cancer, early detection, machine learning, metastasis

Introduction

Metastasis is the hallmark of cancer growth and is responsible for the majority of cancer-related fatalities. However, it requires earlier detection and better understanding. The rapid growth of cancer biology research and the rise of new paradigms in the study of metastasis have revealed some of the molecular underpinnings of this spreading process.[1] Cancer emerges from a series of molecular events that fundamentally alter the standard properties of cells. The mutated cells divide and grow in the presence of signals that generally inhibit average cell growth.

The growing mutated cells develop new characteristics, including changes in cell structure, decreased cell adhesion, and production of new enzymes.[2] Metastatic cancer growth occurs when cancer cells break from the primary tumor, spread through the body's circulation or lymph vessels, and form new

tumors. This process can occur in three ways: cells can move through the circulation system to distant areas, grow into the surrounding tissue, or travel through the lymph system to nearby or removed lymph nodes.[3]

Martin et al.[4] emphasized that metastasis remains a leading cause of cancer mortality and is increasingly the focus of scientific and clinical investigations. However, the mechanisms remain inadequately understood and strategies in combatting metastasis stay constrained. Yang et al.[5] discovered a new migration mechanism called collective cell migration in many cancers, which can occur as clusters with the tight cell-cell junction in the tumor microenvironments. This migration has been shown to have higher invasive capacity and resistance to clinical treatments than single tumor cell migration. Collective cell migration has been detected in the early stages of cancer patients, highlighting the importance of early disease screenings.

The classical view of tumor metastasis suggests that tumor cell migration begins with a single cell and progresses through various methods before reaching distant tissues and organs. Zhang et al.[6] found that cancer cell collective invasion is regulated by the energetic states of leader-follower cells. Leader cells require more energy than follower cells, and forward invasion consumes and depletes their available energy. A follower cell then takes over the leader position to sustain invasion. This suggests that metabolic pathways can also be repressed by focusing on metabolic pathways, which is a major clinical interest in treating malignant growth. Even though discoveries have been made, Huang[7] stated that the complexity of the metastatic process has made it difficult to gain a full comprehension of the origins of this most lethal aspect of cancer.

Yu et al.[8] further stressed that early metastasis is often misdiagnosed, contributing to poor prognosis and reduced survival. They highlighted the need for improved detection techniques and predictive models to identify early-onset metastatic disease, emphasizing the role of clinicopathological and molecular profiling in achieving this goal.

This study aims to identify and evaluate the most significant factors contributing to cancer metastasis by integrating classical statistical methods with advanced machine learning algorithms. By analyzing 62 principal cancer types, the objective is to develop a superior predictive model that enhances accuracy and precision in forecasting metastatic outcomes.

Methods

This study utilizes a dataset from a clinical study on 62 metastatic cancer types, derived from Zehir et al.,[9] encompassing genomic alterations in 5,193 female and 5,143 male patients, covering 361 distinct tumor types. The data was collected as part of the MSK-IMPACT initiative at Memorial Sloan Kettering Cancer Center (MSKCC), New York, in June 2017. TMSK-IMPACT is a large-scale, prospective clinical sequencing program that combines clinical, genomic, and pathological information. Data preprocessing and analysis were performed using Python. As part of the data preprocessing pipeline, missing values were handled using mean/median imputation, ensuring a consistent and unbiased representation of the feature set prior to normalization and modeling.

For statistical analysis, the Cox Proportional Hazards (CPH) model was employed to assess survival outcomes across the 62 cancer types. The CPH model assumes proportional hazard functions and a linear relationship between the logarithm of the hazard and the covariates.[10] It was used to identify key prognostic factors and to quantify the impact of various biomarkers on patient survival. Feature Selection (FS) was employed to reducing data dimensionality to enhance Machine Learning (ML) algorithms performance This technique detects attribute dependencies and provides a unified view of attribute estimation in regression and classification.[11] A hybrid method was developed by combining FS with ML. Model training used a 70:30 train-test split, and a confusion matrix was used to evaluate performance.

AI-powered algorithms such as Random Forest (RF), Extreme Gradient Boosting (XGBoost), Neural Networks (NN), and Support Vector Machines (SVMs) are used to analyze complex data patterns, improve predictive accuracy, and classify cancerous cells. RF enhances cancer diagnosis accuracy by constructing ensembles of decision trees trained on various datasets, capturing complex features, and enhancing robustness against outliers and noise.[12] XGBoost enhances predictive accuracy by iteratively boosting decision trees, capturing complex interactions and non-linear relationships, optimizing FS, improving model performance, and identifying early metastasis indicators.[13] NN are used to learn complex patterns in high-dimensional cancer data, improving predictive accuracy for early intervention strategies. The

NN consist of three layers: input, hidden, and output, with performance influenced by their structure.[14] SVMs are advanced predictive modelling algorithms that classify complex data, improve metastasis prediction accuracy, and identify biomarkers in oncology, focusing on Structural Risk Minimization (SRM) and higher-dimensional space mapping.[15]

The confusion matrix (CM) is used to measure method performance in classification. It compares the system's classification results with true results. Four conditions are included: True Positive (TP), False Positive (FP), True Negative (TN), and False Negative (FN). Accuracy, precision, and recall are estimated based on these conditions. Accuracy measures the accuracy of the framework in classifying data, precision reflects the degree of accuracy between data and the framework's response, and recall measures the framework's speed in recovering data.

Accuracy in ML and predictive modelling is the proportion of correctly classified instances, crucial for assessing model performance, such as cancer detection algorithms.

$$\text{Accuracy} = \frac{TP+TN}{TP+TN+FP+FN} * 100\%$$

Precision is a metric evaluating the accuracy of a model's positive predictions, calculated as the ratio of true positives to the total number of positive predictions.

$$\text{Precision} = \frac{TP}{TP+FP} * 100\%$$

Recall, or sensitivity, measures the percentage of positive cases correctly identified by a model, with high recall indicating its effectiveness in detecting all relevant instances.

$$\text{Recall} = \frac{TP}{TP+FN} * 100\%$$

The F-measure, or F1 score, is a harmonic mean of precision and recall, providing a comprehensive evaluation of a model's performance, particularly in imbalanced datasets.

$$\text{F-measures} = \frac{2*\text{Recall}*\text{Precision}}{\text{Recall} + \text{Precision}}$$

Results

In Table 1 analysis reveals notable sex-specific differences in tumor genomics and patient outcomes. Female patients exhibit a higher fraction of their genome altered (0.207488) compared to male patients (0.181764), indicating more extensive genomic changes in female tumors. Conversely, male patients present with a higher mutation count (7.435573) and a higher nonsynonymous tumor mutation burden (TMB) (7.305357) than female patients (6.846098 and 6.790197, respectively). Despite these differences, overall survival is similar between the sexes, with female patients showing a marginally longer survival (12.505943 months) compared to male patients (12.406399 months). Tumor purity is nearly identical, with female and male patients having values of 45.528834 and 45.726689, respectively.

Table 2 examines tumor genomic characteristics and survival based on smoking history. Never-smokers have a fraction of genome altered of 0.197811, a mutation count of 6.076468, and a nonsynonymous tumor mutation burden (TMB) of 5.981001. In contrast, previous or current smokers have a slightly lower fraction of genome altered (0.191291) but a significantly higher mutation count (8.144559) and TMB (8.067902). Those with unknown smoking history have intermediate values, with a fraction of genome altered at 0.194683, mutation count of 7.489166, and TMB of 7.364490. Overall survival is highest among never-smokers (13.418332 months), followed by previous or current smokers (12.821535 months), and lowest for patients with unknown.

Table 3 results provide insights into the significance and impact of various predictors on the outcome variable (metastasis). The coefficients (coef) and their exponential values (exp(coef)) indicate the direction and magnitude of the relationship between each predictor and the outcome. Among the predictors, Smoking History and Fraction Genome Altered emerged as significant factors. Smoking History has a positive coefficient of 0.13 with an associated z-value of 5.18 and a p-value less than 0.005, indicating a strong positive association with the outcome, as those with a history of smoking have an estimated 14% increase in the odds of the outcome occurring. Fraction Genome Altered shows a substantial positive coefficient of 0.85, with an exp(coef) of 2.34, suggesting that higher genomic alterations are associated

Table 1 Sex-Specific Differences in Tumor Genomics and Clinical Outcomes

Sex	Fraction Genome Altered	Mutation Count	Overall Survival (Months)	TMB (nonsynonymous)	Tumor Purity
Female	0.207488	6.846098	12.505943	6.790197	45.528834
Male	0.181764	7.435573	12.406399	7.305357	45.726689

TMB=tumor mutation burden

Table 2 Differences in Tumor Genomics and Clinical Outcomes by Smoking History

Smoking History	Fraction Genome Altered	Mutation Count	Overall Survival (Months)	TMB (nonsynonymous)	Tumor Purity
Never	0.197811	6.076468	13.418332	5.981001	46.680397
Prev/Curr Smoker	0.191291	8.144559	12.821535	8.067902	43.823368
Unknown	0.194683	7.489166	9.126138	7.364490	47.192308

TMB=tumor mutation burden

with significantly increased odds (2.34 times) of the outcome, supported by a high z-value of 9.66 and a $p < 0.005$.

In contrast, cancer type, cancer type detailed, and primary tumor site had minimal impact, with coefficients near zero. While the primary tumor site had a statistically significant z-value (−2.56), its effect size was negligible (coef ≈ −0.00). Sex and mutation count were not significant predictors (p=0.45 and 0.74, respectively), indicating limited influence on metastatic outcomes.

Table 3 Significance and Impact of Predictors on Cancer Metastasis (Cox Proportional Hazards Model)

	coef	Exp (coef)	SE (coef)	Coef 95% CI Lower	Coef 95% CI Upper	Exp (Coef) 95% CI Lower	Exp (Coef) 95% CI Upper	cmp to	z	p	$-\log_2$ (p)
Cancer Type	0.00	1.00	0.00	-0.00	0.00	1.00	1.00	0.00	1.57	0.12	3.10
Cancer Type Detailed	0.00	1.00	0.00	0.00	0.00	1.00	1.00	0.00	2.47	0.01	6.22
Primary Tumor Site	-0.00	1.00	0.00	-0.00	-0.00	1.00	1.00	0.00	-2.56	0.01	6.57
Sex	-0.03	0.97	0.04	-0.10	0.04	0.90	1.05	0.00	-0.76	0.45	1.16
Smoking History	0.13	1.14	0.03	0.08	0.19	1.09	1.20	0.00	5.18	<0.005	22.14
Fraction Genome Altered	0.85	2.34	0.09	0.68	1.02	1.97	2.77	0.00	9.66	<0.005	70.95
Mutation Count	0.00	1.00	0.00	-0.00	0.00	1.00	1.00	0.00	0.34	0.74	0.44

Table 4 Feature Importance in Predicting Cancer Metastasis (Feature Selection Analysis)

Features	Score	Percentage (%)
Cancer Type Detailed	0.135	13.5
Fraction Genome Altered	0.447	44.7
Mutation Count	0.183	18.3
Sex	0.030	3.0
Smoking History	0.045	4.5
Cancer Type	0.068	6.8

These findings underscore the importance of smoking history and the extent of genomic alterations as key factors in the model, while other variables appear to have limited or no significant impact.

Table 4 analysis revealed pivotal insights into the predictors influencing cancer metastasis. Among the examined factors, genomic alterations emerged as the most influential predictor, exhibiting a substantial importance score of 0.447. This underscores the significance of genomic instability in driving cancer progression and metastasis, aligning with existing literature emphasizing the role of genomic alterations in tumor development and spread. Following closely behind, mutation count also demonstrated notable importance (0.183), emphasizing its relevance in predicting metastatic potential. These findings highlight the centrality of genomic instability and mutational burden in dictating cancer progression, offering potential avenues for targeted therapeutic interventions aimed at mitigating metastatic risks.

Additionally, the analysis shed light on the predictive value of specific tumor characteristics. Detailed cancer type information and primary tumor site displayed moderate importance scores (0.135 and 0.089, respectively), suggesting their contributions to metastasis prediction. Broad cancer-type categorizations and smoking history exhibited lower importance scores and still contributed significantly to the predictive model. Conversely, sex emerged as the least influential factor, with minimal impact on metastasis prediction. These results emphasize the multifactorial nature of cancer metastasis, implicating a combination of genetic, environmental, and clinical factors in driving disease progression. Overall, the findings underscore the complexity of metastatic processes and offer valuable insights into potential targets for therapeutic intervention and personalized treatment strategies aimed at mitigating cancer metastasis.

Table 5 Performance of AI-ML Algorithms in Predicting Cancer Metastasis

AI-ML Algorithm	Accuracy Score	Train-Test Split
XGBoost	0.95	70:30
SVM	0.95	70:30
Random Forest (RF)	0.90	70:30
Neural Network (NN)	0.80	70:30

Table 5 compares the performance of four AI/ML models in predicting metastasis. XGBoost and Support Vector Machine (SVM) achieved the highest classification accuracy (0.95) using a 70:30 train-test split, indicating excellent predictive ability. These results indicate robust predictive capabilities for both algorithms, suggesting their effectiveness in accurately classifying metastatic outcomes based on the provided features. Following closely behind, the Random Forest algorithm achieved an accuracy score of 0.90 with the same train-test split ratio. While slightly lower

Table 6 Predictive Accuracy of AI-ML Models Based on Confusion Matrix Analysis

Metastasis Type	Precision	Recall	F1-score	Support
Primary	1.00	0.92	0.96	13
Secondary	8.00	1.00	0.93	7
Accuracy			0.95	20
Macro Avg	0.94	0.96	0.95	20
Weighted Avg	0.96	9.95	0.95	20

than XGBoost and SVM, this score still signifies strong predictive performance, highlighting the efficacy of ensemble learning methods in cancer metastasis prediction tasks. In contrast, Neural Networks demonstrated comparatively lower performance, achieving an accuracy score of 0.80. Despite its neural architecture's complexity and potential for learning intricate patterns, Neural Networks may require further optimization or feature engineering to enhance its predictive capabilities for this specific task.

Overall, the results underscore the effectiveness of XGBoost, SVM, and Random Forest algorithms in accurately predicting cancer metastasis based on the provided features. These findings offer valuable insights into selecting appropriate machine learning models for cancer prognosis and personalized treatment planning, ultimately contributing to improved patient outcomes in clinical settings.

Table 6 provides a classification report, detailing precision, recall, and F1-score for predicting primary and secondary metastases. For the primary metastasis class, the model achieved a precision of 1.00, indicating that when it predicts an instance as primary metastasis, it is almost always correct. The recall, which measures the ability to correctly identify all instances of primary metastasis, is 0.92, suggesting that the model successfully captures a high proportion of actual primary metastasis cases. The F1-score, which balances precision and recall, is 0.96, reflecting overall good performance in predicting primary metastasis. The support value indicates that there are 13 instances of primary metastasis in the dataset.

For the secondary metastasis class, precision was 0.88, implying that there may be some false positive predictions. However, the recall is 1.00, indicating that the model correctly identifies all instances of secondary metastasis. The F1-score for secondary metastasis is 0.93, suggesting a reasonably balanced performance between precision and recall. The support value indicates that there are 7 instances of secondary metastasis. Overall, the model achieves an accuracy of 0.95, meaning that it correctly predicts the metastasis type for 95% of the instances in the dataset.

Discussion

This study provides a comprehensive evaluation of the performance of various AI-ML algorithms in predicting cancer metastasis. XGBoost and Support Vector Machine (SVM) demonstrated the highest accuracy scores of 0.95 in a 70:30 train-test split, indicating their effectiveness in distinguishing between primary and secondary metastasis. These algorithms outperformed RF and NN, which achieved accuracy scores of 0.90 and 0.80, respectively. While XGBoost and SVM showcased superior predictive capabilities, RF, despite slightly lower accuracy, still performed reasonably well. NN, although the least accurate among the models evaluated, might have potential for improvement through hyperparameter tuning or additional data preprocessing. These results are consistent with Tapak at el.[16] who found SVM to outperform other machine learning models—including Naïve Bayes, RF, AdaBoost, Logistic Regression, and Linear Discriminant Analysis—in predicting breast cancer outcomes.

The study also reveals that smoking history significantly impacts tumor genomics and patient outcomes. Patients without smoking have a higher mutation count and TMB, while those with a history of smoking have a lower fraction of genome alteration. Overall survival is highest among people who have never smoked. Sex-specific differences in tumor genomics and patient outcomes shows female patients more extensive genomic changes and higher mutation counts. Despite these differences, overall survival is similar, with female patients having a marginally longer survival time. Tumor purity is nearly identical. Furthermore, the study reveals that smoking history and genomic alterations are significant predictors of metastasis. Smoking history increases the odds of the outcome by 14%, while genomic alterations increase the odds by 2.34 times. This analysis was further done on AI-powered algorithms and results revealed that genomic alterations and mutation count are the most influential predictors of cancer metastasis, with genomic instability driving progression and metastasis. Specific tumor characteristics, such as cancer type and primary tumor site, also contribute to metastasis prediction. However, sex is the least influential factor, compared to smoking history, primary tumor site and fraction genome alteration. These findings highlight the multifactorial nature of cancer metastasis, highlighting the need for targeted therapeutic interventions and personalized treatment strategies to mitigate metastatic risks.

These findings underscore the multifactorial nature of metastasis. Chakraborty et al.[17]

previously demonstrated that prostate cancer patients with a high FGA (>6%) but low mutation count (<30 mutations/case) had shorter disease-free survival. In conclusion, cases with a high fraction of genome altered are related to aggressive illness, and those with lower mutational counts might be related to diminished immune responsiveness. Genomic Alterations add to bigger tumor size, higher tumor evaluation, and receptor pessimism. Unmistakable gatherings of genomic changes were seen as related to various evaluations of Invasive Ductal Carcinomas (IDCs). TP53 change was found to assume a significant job in characterizing high tumor grade and is related to a mutation phenotype.[18]

The clinical implications of mutation count have also been explored in prior studies. Bettegowda et al.[19] identified a circulating tumor DNA (ctDNA)-based model showing that lower mutation counts were associated with better prognosis in late-stage lung adenocarcinoma patients treated with chemoradiation. Furthermore, smoking has been implicated in increased metastatic potential in lung and colorectal cancers. Tseng et al.[20] further alluded that there appears to be a link between cigarette smoking and the development of lung metastatic illness in breast cancer patients. This is also highlighted by Makino et al.[21] that cigarette smoking may contribute to the pathophysiology and development of lung metastasis in CRC by increasing adhesion and inflammation.

In summary, the findings emphasize the critical role of genomic alterations (Fraction Genome Altered) and mutation count, smoking history in predicting cancer metastasis. Detailed cancer type information and the primary tumor site also contribute to the prediction. Sex appears to have the least impact on metastasis, but further studies should be done to further assist in identifying key insights into these variables and interventions in managing cancer metastasis.

The study underscores the pivotal role of AI-powered analysis in enhancing early detection of metastasis and personalizing treatment strategies in cancer care. Utilizing a comprehensive dataset of genomic and clinical factors, the AI algorithms identified key predictors of cancer prognosis, particularly focusing on early metastatic detection. The survival analyses pinpointed fraction genome altered (coef= 0.77, $p<0.005$), primary tumor site (coef=0.00, $p<0.005$), and smoking history (coef=0.14, $p<0.005$) as significant factors influencing metastasis. Among these, fraction genome altered exhibited the highest impact on outcomes (Exp(coef)=2.17), followed by smoking history (Exp(coef) = 1.15), highlighting their critical roles in disease progression. The AI-powered models demonstrated high predictive accuracy, with XGBoost and SVM achieving a predictive power accuracy score of 0.95. These models effectively utilized the detailed cancer type, primary tumor site, fraction genome alteration, and mutation count to predict metastasis rates. RF and NN also showed notable performances, with accuracy scores of 0.90 and 0.80, respectively. These findings reinforce the potential of integrating AI in clinical workflows to improve the early detection and treatment of metastatic cancer.

To enhance early metastatic detection and personalize treatment, integration of high-impact predictors such as FGA, primary tumor site, and smoking history into routine clinical workflows is recommended. Given their high accuracy, AI models like XGBoost and SVM should be prioritized in predictive oncology. Genomic testing to assess FGA and mutation burden can help stratify patients by risk. In parallel, implementing effective smoking cessation programs may reduce metastasis risk and improve outcomes.

In conclusiom, this study highlights the significant role of genomic alterations and mutation counts, along with smoking history, in predicting cancer metastasis. AI-powered algorithms, especially XGBoost and SVM, exhibited high accuracy and offer promise in clinical application. Tumor type and primary site further enhance predictive capability, while sex showed minimal influence. These findings emphasize the multifactorial nature of metastasis and suggest that personalized treatment strategies, based on genomic testing and lifestyle factors such as smoking history, are crucial for improving patient outcomes. The integration of AI-powered models in clinical workflows could greatly enhance early metastatic detection and guide targeted therapeutic interventions, reinforcing the importance of continuous research and collaboration to refine predictive models and enhance cancer care.

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Role of Osteopontin in Hypothyroid Anemic Woman and Their Association with Oxidative Stress

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Abstract

Background: Hypothyroidism is frequently associated with anemia and oxidative stress, necessitating exploration of biomarkers like Osteopontin to better understand disease mechanisms.

Objective: To explore the association between Osteopontin, oxidative stress, and antioxidant capacity in hypothyroid woman with or without anemia.

Methods: The study was conducted at the Santosh Medical College Department of Biochemistry in Ghaziabad, India, from September 2019 to October 2021. This study was cross-sectional and recruited 360 female subjects, divided into three groups: hypothyroidism with anemia, hypothyroidism without anemia, and normal healthy controls. Osteopontin, thyroid profile, malondialdehyde (MDA) and total antioxidant capacity were measured.

Results: Osteopontin, T3, T4, and total antioxidant capacity levels were significantly lower ($p<0.001$), and the TSH and MDA levels significantly increased ($p<0.001$) in female subjects experiencing hypothyroidism, with or without anemia, as compared to normal healthy female control groups. Osteopontin demonstrated significant negative relationship with TSH and MDA, while showing a significant positive relationship with T3, T4, and total antioxidant status in both studied groups.

Conclusion: Osteopontin and oxidative stress/antioxidant status significantly correlate in female subjects experiencing hypothyroidism, with or without anemia. In these patients, Osteopontin might be a useful biomarker for evaluating antioxidant levels and oxidative stress.

Keywords: Antioxidant, hypothyroidism, osteopontin, oxidative stress

Introduction

Hypothyroidism is a clinical condition marked by elevated levels of thyroid stimulating hormone (TSH) and lower levels of triiodothyronine (T3) and thyroxine (T4).[1] Hypothyroidism and subclinical hypothyroidism were more prevalent in women than in men, with prevalence's of 4.1% and 5.4% respectively. In India, 200 million individuals are susceptible to iodine deficiency disorders, while 42 million are affected by thyroid conditions.[2]

Osteopontin (OPN), a glycoprotein was first discovered in 1986 in osteoblasts and is made up of 300 amino acids. It is downregulated in people with hypothyroidism and is found on the long arm of chromosome 4 region 13 (4q13). Osteopontin overexpression in thyroid cancers links to its role in immune cell

movement and promoting malignant tumor development.[3] Osteopontin has significant role in both normal physiological & pathological processes and Numerous diseases including obesity, atherosclerosis, cardiac fibrosis, immune system disorders like Graves' disease, chronic inflammation, and several forms of cancer.[4]

Anemia is a clinical condition, occurs when the blood's hemoglobin or red blood cell count is below normal and has been prevalent in patients with hypothyroidism by 20 to 60%. Hypothyroidism is related to development and severity of anemia.[5] Results from previous studies indicated that iron deficiency anemia causes minor abnormalities without any significant changes in thyroid function. However, studies in animals have shown iron deficiency anemia to be associated with thyroid metabolism and Iron deficiency are more serious for women.[6]

Oxidative stress, defined as an imbalance between pro-oxidants and antioxidants, leads to molecular damage, including oxidative DNA damage and lipid peroxidation.[7] Free radical production decreases due to lowered thyroid hormone levels and metabolic suppression in hypothyroidism.[8] Malondialdehyde (MDA), a byproduct of lipid peroxidation, serves as a key biomarker of oxidative stress, particularly in the context of polyunsaturated fatty acid oxidation, such as linoleic and linolenic acids.[9] A reduced total antioxidant capacity may suggest the presence of oxidative stress or a heightened vulnerability to oxidative damage.[10]

This present study aimed to assess OPN, MDA, and total antioxidant capacity levels and to investigate the correlation between OPN, MDA, and total antioxidant capacity in subjects with hypothyroidism, with or without anemia subjects.

Methods

This case-control study was conducted from September 2019 to 2021 in the Department of Biochemistry at Santosh Medical College & Hospital, Ghaziabad, Uttar Pradesh, India. The study was approved by the Institutional Ethical Committee (F. No. SU/2018/528(33), dated May 25, 2018), and all patients provided informed permission prior to the study. A total of 360 subjects aged 30 to 60 years were enrolled in the study. The participants were divided into three groups: 120 hypothyroid subjects with anemia, 120 hypothyroid subjects without anemia, and 120 healthy controls within the same age range. The hypothyroid and anemic subjects were taken from the Department of Medicine and had previously been diagnosed by a physician based on a complete history, thyroid profile testing, and hemoglobin test.

The current study included all hypothyroid subject aged between 30–60 years who were willing to provide informed consent. The study excluded patients with type 2 diabetes mellitus, asthma, COPD, cancer, sexually transmitted disease, cardiac disease, renal disease, hepatic disease, gout and arthritis, pregnancy, on thyroid medication, and refuse to provide prior permission.

A 5 mL of venous blood sample were collected from their medial cubital vein into a plain vial. The serum was tested after 3 minutes of centrifugation at 1500 rpm. All parameters were determined using the enzymatic technique and an automated analyzer (Beckman Coulter-AU-480). Satoh *et al*. established a method for determining malondialdehyde (MDA) in serum samples that employs thiobarbituric acid reactive material. The ferric reducing antioxidant power (FRAP) method was used to calculate total antioxidant capacity using tripyridyl triazine (TPTZ). Serum Osteopontin was measured using the Sandwich-ELISA method with a commercially available kit from Elabscience, USA (Catalogue Number: E-EL-H1347).

Descriptive data were presented as the mean with its standard deviation. Normality test, specifically the Kolmogorov-Smirnov test, was used. The student's t-test was used to compare the outcomes of two groups across all parameters. Pearson's correlation analysis was used to determine any potential relationships between the analyzed parameters. A p-value of less than 0.05 was considered statistically significant. Statistical analysis was carried out using IBM SPSS Statistics for Mac, Version 25.0 (IBM Corp., Chicago, IL, USA).

Results

Table 1 presents the biochemical parameters of the studied subjects. Serum TSH and malondialdehyde (MDA) levels were significantly increased in hypothyroid subjects, both with and without anemia, compared to healthy controls. Similarly, Decreased T3, T4, Total antioxidant capacity and Osteopontin levels were observed in hypothyroid subjects with or without anemia as compared to controls.

Table 2 shows the correlation analysis of the

Table 1 Biochemical Parameters of the Studied Subjects (mean ± SD)

Parameters	Controls	Hypothyroidism with Anemia	Hypothyroidism without Anemia
TSH (µIU/mL)	4.91 ± 0.56	33.43 ± 4.61 *	25.08 ± 1.53 *
T3 (ng/mL)	1.45 ± 0.30	0.41 ± 0.08 *	0.63 ± 0.09 *
T4 (µg/dL)	9.16 ± 1.10	2.72 ± 0.51 *	3.39 ± 0.55 *
MDA (nmol/mL)	1.50 ± 0.41	4.42 ± 1.16 *	3.45 ± 0.75 *
TAC (mmol/L)	1.99 ± 0.45	1.11 ± 0.22 *	1.49 ± 0.30 *
OPN (ng/mL)	7.22 ± 1.53	4.02 ± 0.56 *	4.45 ± 0.39 *

Table 2 Correlation of Studied Parameters with Osteopontin (OPN) in Hypothyroid Subjects with Anemia

Variables	TSH	T3	T4	MDA	TAC
OPN	r = -0.625	r = 0.439	r = 0.491	r = -0.426	r = 0.415
	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001

studied parameters in hypothyroid subjects with anemia. Osteopontin was significantly & negatively correlated with TSH & MDA and positively & significantly correlated with T3, T4 and TAC in hypothyroidism with anemia subjects.

Table 3 presents the correlation of the studied parameters in hypothyroid subjects without anemia. OPN was negatively and significantly correlated with TSH & MDA and positively and significantly correlated with T3, T4 and total antioxidant capacity in hypothyroid subjects without anemia.

Discussion

Hypothyroidism is the most prevalent among endocrine disorders. Variation in the measures of thyroid hormone leads to hypothyroidism. Thyroid hormones regulate the ferritin expression and decreases the levels of irons which can affect the metabolism of thyroid hormone.

In this study, A significant variation was recorded in the thyroid profile (TSH, T3 & T4) showing increased levels of TSH and decreased levels of T3 and T4. A decreased levels of T3 and T4 may be due the reduced TPO activity and reduced thyroid hormone production. Thyroid hormones promote erythrocyte precursor proliferation as well as erythropoietin synthesis and is dependent on iron levels for TPO activity. iron deficiency anemia has a negative impact on thyroid hormone status.[11] This is consistent with study by Sahana KR *et al*., reported increased level of TSH and decreased level of T3 and T4 in hypothyroidism subjects as compared to controls subjects. This may be the result of the body not making enough thyroid hormone, which is sometimes associated with a lack of iodine.[12]

Malonaldehyde is an oxidative stress marker and TAC reflects antioxidant status in this study. This study revealed significant changes in oxidative stress and antioxidant

Table 3 Correlation of Studied Parameters with Osteopontin (OPN) in Hypothyroid Subjects without Anemia

Variables	TSH	T3	T4	MDA	TAC
OPN	-0.397	0.562	0.474	-0.501	0.659
	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001

levels in the body. A significant low level of total antioxidant capacity and significant increase level of MDA were observed in hypothyroid subjects with anemia as compared to hypothyroid subjects without anemia**.** This alteration may be explained on both of increased levels of reactive oxygen species (ROS) that is associated in a variety of physiological and pathological conditions.[13] The oxidation of lipids by an increased MDA levels in hypothyroid subjects that may be aided by the increase in lipid level and caused by free radicals generated during oxidative stress. To neutralize ROS and minimize oxidative stress, healthy cells utilize a wide range of antioxidant defense mechanisms. These mechanisms play an important role in scavenging and converting ROS into less reactive or non-reactive molecules.[14]

Hypothyroidism has been associated with an increased oxidative stress and lipid peroxidation, which was believed to contribute to the development and progression of atherosclerosis and cardiovascular diseases. Highly increased production of ROS and oxidative stress in hypothyroidism subjects is might be due to the increased lipid peroxidation and failure of the antioxidant defense mechanism.

In the present study, serum total antioxidant capacity was decreased significantly in hypothyroid patients compared to control. These findings are consistent with the study done by Kalaivanam KN *et al*.[15] Kochman J *et al*. discussed the correlation between hypothyroidism and a decrease in the activity of antioxidant system components, indicating that thyroid hormones have an impact on oxidative stress and antioxidant systems. Oxidative stress is caused by an increase in oxidant levels and/or a decrease in antioxidant enzyme activity in iron deficiency anaemia. [8]

Osteopontin (OPN) is a glycoprotein that has been linked to bone growth and calcification, as well as processes such as inflammation, adhesion of cells and migration, and apoptosis prevention, due to its expression in a variety of body tissues. In this study, the level of OPN was significantly decrease in hypothyroid with anemic subjects compared to hypothyroid without anemic subjects. This is consistent with studies done by EL-Zawaw HT *et al*.[16] Sawaki D *et al*. studied Grave's disease patients and discovered elevated serum OPN levels, which were associated with an increase in OPN receptor co-expression and proinflammatory cytokine and chemokine production.

Osteopontin may be downregulated in hypothyroidism because of oxidative stress and a reduction of antioxidant defenses in the mitochondrial inner membrane, resulting in increased free radical production.[17] Numerous studies have suggested that OPN could be a useful predictive biomarker in patients with impaired thyroid function.

Serum OPN level was found decreased in hypothyroidism with or without anemic patients due to iodine deficiency.[18] The reduction in OPN levels might be attributed to various cellular processes occurring in the thyroid gland influenced by Osteopontin but exact mechanism of Osteopontin in iron deficiency anemia subjects is not known. However, this may be related to regulation at the level of Osteopontin gene expression.

The present study found that TSH & MDA levels increased significantly while T3, T4, total antioxidant capacity and Osteopontin levels decreased significantly. Results of the present study are in accordance with many previous studies conducted separately in hypothyroid subjects.[19] There was a significant reduction in Osteopontin in the hypothyroidism with or without anemia. This was further confirmed by correlation studies between the different parameters in all the studied groups. Correlation studies have found that OPN was positively and significantly correlated with T_3, T_4, and total antioxidant capacity whereas significantly negatively correlated with TSH and Malondialdehyde in hypothyroid subjects with or without anemia. The present study suggests a positive association between hypothyroidism and Osteopontin. However, there is negative correlation between TSH and Osteopontin. In associated condition of iron deficiency anemia, oxidative stress is increased causing a further decrease in the levels of Osteopontin.

In the present study, it was observed that hypothyroidism is negatively associated with Osteopontin. However, there is negative correlation between TSH and Osteopontin. Osteopontin, reflected that it could be used as prognostic biomarkers for the diagnosis of hypothyroidism. Osteopontin was Significantly negatively correlated with Malondialdehyde levels as well as positively correlated with total antioxidant capacity in both hypothyroid with or without anemic female subjects.

In conclusion, OPN appears to play a key role in modulating oxidative stress and antioxidant defenses in hypothyroid patients, with the condition exacerbated by anemia. The results highlight the potential use of OPN as a

biomarker for assessing oxidative imbalance in female hypothyroid patients. However, the study's limitations include a restricted sample size and the exclusive inclusion of female subjects, necessitating further research to validate these findings across broader populations.

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Original Article

Impact of Chronic Smoking on Choroidal Thickness: A Comparative Analysis Using Optical Coherence Tomography

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Abstract

Background: Chronic smoking has systemic vascular effects, including alterations in ocular blood flow and choroidal thickness, impacting visual health.

Objective: To compare choroidal thickness (CT) in chronic smokers and nonsmokers using optical coherence tomography and to evaluate the effect of smoking duration on CT based on pack-year quartiles (PYQ).

Methods: This was a case-control study conducted at the Regional Institute of Ophthalmology, Medical College, Kolkata, India between January 2023 and June 2024. Choroidal thickness was assessed in 120 cases (60 smokers and 60 nonsmokers) over a period of 18 months. Choroidal thickness was measured using Enhanced Depth Imaging Spectral-Domain Optical Coherence Tomography (EDI SD-OCT) at the sub foveal region and 1.5 mm away in the superior, inferior, nasal, and temporal directions. CT between smokers and nonsmokers was compared. Statistical analysis was performed using the SPSS 23.0 software and a p-value of less than 0.05 was taken as statistically significant.

Results: The study analyzed age distribution, ocular parameters, and choroidal thickness in 60 smokers and 60 nonsmokers. The mean age in smokers and nonsmokers was found to be 43.1 ± 7.2 and 40.8 ± 11.4 years respectively. Smokers were found to have a significantly lower sub foveal CT compared to nonsmokers (272.42 ± 13.57 µm vs. 284.94 ± 14.15 µm, $p<0.05$). Increased smoking exposure significantly correlated with progressive choroidal thinning ($p<0.05$). Other ocular parameters, such as intraocular pressure ($p=0.235$) and axial length ($p=1.0$), were found to be comparable in both groups ($p>0.05$).

Conclusion: There significant choroidal thinning in chronic smokers as compared to nonsmokers with a dose-dependent effect linked to higher smoking exposure. These findings suggest a smoking-induced vascular compromise in the choroid.

Keywords: Choroidal thickness, smoking, optical coherence tomography, vascular compromise

Introduction

The choroid is a highly vascularized ocular structure located between the retina and the sclera, essential for maintaining retinal function by supplying oxygen and nutrients to the outer retinal layers. Anatomically, the choroid is composed of multiple layers, including Bruch's membrane, the choriocapillaris, Sattler's layer (medium-sized vessels) and Haller's layer

(large-caliber vessels). The choriocapillaris is a specialized network which is responsible for metabolic exchange between the retinal pigment epithelium and systemic circulation. On the other hand, Larger vessels regulate choroidal blood flow. The choroid is highly susceptible to systemic and ocular pathologies and its thickness is an important parameter for assessing ocular and systemic health. Conditions like hypertension, diabetes, and dyslipidemia may affect choroidal thickness.[1]

Choroidal thickness varies between individuals and is influenced by several physiological and demographic factors. In healthy adults, the sub foveal choroidal thickness (SFCT) generally ranges from 250 to 350 microns, though this can fluctuate based on age, axial length, refractive status, and diurnal variation. The choroid is typically thickest at the sub foveal region and gradually tapers toward the periphery. Age-related decline in choroidal thickness is a well-known phenomenon and progressive vascular atrophy is known to contribute to reduced choroidal perfusion. Myopia, hypermetropia, hydration status, systemic blood pressure, intraocular pressure and environmental conditions such as altitude and temperature are known to influence choroidal thickness.[2]

Many systemic and ocular conditions can lead to changes in choroidal thickness. Hypertension diabetes mellitus, Autoimmune diseases (systemic lupus erythematosus and rheumatoid arthritis) and endocrine disorders (hypothyroidism and hyperthyroidism) may impact CT as well as choroidal circulation. Ocular conditions like central serous chorioretinopathy are characterized by choroidal hyperpermeability and increased thickness. In contrast, the atrophic form of age-related macular degeneration leads to significant choroidal thinning due to the progressive degeneration of the choriocapillaris.[3]

Substance abuse, including alcohol consumption, illicit drug use and tobacco smoking significantly affect choroidal circulation and thickness. Chronic alcohol intake is associated with retinal and choroidal microvascular alterations leading to fluctuating choroidal thickness due to dehydration and vasodilatory effects. Cannabis is known to influence intraocular pressure and blood flow. Stimulants such as cocaine and amphetamines cause acute vasoconstriction thereby reducing choroidal perfusion and leading to transient thinning. Among these substances, tobacco smoking has the most extensively studied effects on choroidal thickness.[4] Chronic smoking introduces thousands of toxic chemicals into the bloodstream, including nicotine, carbon monoxide, and reactive oxygen species (ROS). These substances collectively contribute to endothelial dysfunction and microvascular damage..[5]

Assessing choroidal thickness in chronic smokers is important for assessment of smoking-induced ocular damage and systemic microvascular dysfunction. CT may serve as an early biomarker for various ocular pathologies.[6] Optical coherence tomography provides a non-invasive and highly sensitive method to evaluate these changes allowing for risk stratification and potential early interventions.[7] This study aims to perform a comparative analysis of choroidal thickness in chronic smokers versus nonsmokers using OCT and to assess the impact of smoking duration based on pack-year quartiles (PYQ).

Methods

This case-control study was conducted at the Regional Institute of Ophthalmology, Medical College, Kolkata, India, over an 18-month period from January 2023 to June 2024. Approval was obtained from the Institutional Ethics Committee, and informed written consent was secured from all participants prior to inclusion. Based on the findings of a previous study Sigler where a difference of 33 micrometers in the mean sub foveal thickness was found, keeping Alpha at 0.05 and Beta at 0.20, a sample size of 60 subjects in each group was calculated.

The study included male participants aged 25–50 years with best-corrected visual acuity of 6/6 (±2.0 diopters), near vision of N6, and normal intraocular pressure in both eyes. Cases comprised of chronic smokers with a history of smoking at least one pack (20 cigarettes) per day for 10 or more years, while controls included nonsmokers who met the same ocular criteria. Subjects with any ocular disease, previous eye surgery, or a history of drug intake known to affect ocular structures, particularly the choroid, retina, and retinal nerve fibers, were excluded from both groups.

The smokers (cases) were selected from the friends and relatives of out-patients. The nonsmokers were recruited from the in-patients and staff of the institution. All the subjects were counselled and an informed consent was taken. A personal interview was conducted and a detailed history was done

before going to ocular examination of both eyes and general check-up. Visual acuity of each eye with and without correction was taken. Refraction was carried out manually using Streak retinoscope followed by subjective correction.

Slit-lamp examination detailed examination was done to note the status of cornea, conjunctiva, anterior chamber, iris and the lens. Tonometry the cornea was anaesthetized using 0.5% proparacaine eye drop. The tear film was stained with sodium fluorescein 2% and intra ocular pressure was then measured using an Applanation Tonometer (Goldman).Fundus Examination- Optic disc was examined after dilating each pupil with one drop of a mixture of tropicamide 0.8% and phenylephrine 5%. A +90D lens (VOLK) was used at the slit-lamp for fundus examination.

All the subjects underwent EDI SD-OCT using the Spectralis Heidelberg apparatus. In each subject, two horizontal and vertical OCT EDI B –scans averaged 100 times, were taken centering on the fovea. In the horizontal and vertical scans, measurement of choroidal thickness was performed manually using the calipers provided by the Spectralis Heidelberg software on the center of fovea and 1.5 mm away from the fovea in the cardinal directions (superior, inferior, nasal and temporal). Choroidal thickness was measured from the outer limit of the retinal pigment epithelium to the choroidal-scleral junction. Comparison of choroidal thickness was done between smokers (cases) and nonsmokers (controls). Also, comparison of CT within smokers was done on the basis of pack-year quartiles (PYQ).

Statistical analyses were conducted using SPSS version 23.0. Foveal thickness, as measured using Enhanced Depth Imaging Spectral-Domain Optical Coherence Tomography (EDI SD-OCT), was analyzed as a continuous variable and presented as mean ± standard deviation (SD). Categorical data, including the proportion of subjects with reduced foveal thickness among smokers and nonsmokers, were expressed as frequency and percentage. The Chi-square test was used to evaluate associations between categorical variables. A p-value of less than 0.05 was considered statistically significant.

Results

The age distribution analysis revealed that the most common age group among smokers was 35–39 years (23.3%), followed by 30–34 years (20.0%). Among nonsmokers, the highest proportion also fell within the 35–39 years range (21.7%), followed by 30–34 years (18.3%) (Table 1).

All participants in both the smoker and nonsmoker groups were male (p=1.00). The mean pack-years among smokers was 20.2 ± 11.8, while it was 0 in the control group, and this difference was statistically significant ($p<0.05$). The intraocular pressure (IOP) was slightly lower in smokers (17.8 ±3.5 mmHg) compared to controls (18.5 ±2.9 mmHg), but this difference was not statistically significant (p=0.38). Similarly, the axial length (AL) was nearly identical between the two groups, with smokers having a mean AL of 22.9 ± 0.8 mm and controls at 22.9±1.0 mm (p=1.0) (p=1.0) (Table 2).

The comparison of choroidal thickness between smokers and nonsmokers showed significant thinning in several regions among smokers. In the sub foveal region, smokers had lower thickness in both the right eye (272.42 ± 13.57 µm vs. 284.94 ± 14.15 µm, $p<0.05$) and left eye (271.47 ± 15.27 µm vs. 285.38 ± 13.25 µm, $p<0.05$). Similarly, the superior parafoveal and nasal parafoveal regions showed significantly reduced thickness in smokers in both eyes ($p<0.05$). Overall smokers exhibited

Table 1 Age Distribution of Studied Subjects

Age Group (years)	Smokers (n=60)	Nonsmokers (n=60)	p-Value
25 to 29	8 (13.3%)	10 (16.7%)	
30 to 34	12 (20.0%)	11 (18.3%)	
35 to 39	14 (23.3%)	13 (21.7%)	
40 to 44	10 (16.7%)	9 (15.0%)	0.1890 (Not Significant)
45 to 49	9 (15.0%)	8 (13.3%)	
50	7 (11.7%)	9 (15.0%)	
Mean Age ± SD	43.1±7.2	40.8±11.4	

Table 2 Comparison of Clinical and Ocular Parameters Between Smokers and Controls

Variable	Smokers (n=60)	Controls (n=60)	p-Value
Age (years, mean ± SD)	43.1 ± 7.2	40.8 ± 11.4	0.18
Males (n)	60	60	1.00
Pack-years*	20.2 ± 11.8	0	<0.05
Intraocular Pressure (mmHg)	17.8 ± 3.5	18.5 ± 2.9	0.235
Axial Length (mm)	22.9 ± 0.8	22.9 ± 1.0	1.0

notable choroidal thinning particularly in the sub foveal and superior parafoveal regions (Table 3).

The distribution of smokers based on pack-year quartiles (PYQ) revealed that the Q3 (16-25 pack-years) had the highest number of cases, comprising 18 individuals (30%). The Q1 (1-5 pack-years) and Q4 (>25 pack-years) each included 15 individuals (25%), while the Q2 (6-15 pack-years) had the lowest proportion, with 12 individuals (20%). The analysis of retinal thickness across quartiles of PY (pack-years) showed a decreasing trend in most regions of both eyes. In the right eye, sub foveal thickness was highest in the 1st quartile (283.00 ± 11.78) and progressively declined to the 4th quartile (261.00 ± 7.58). A similar trend was observed in the superior parafoveal (276.00 ± 14.04 to 252.93 ± 8.97) and inferior parafoveal regions (269.53 ± 12.48 to 249.80 ± 8.94). The left eye also demonstrated a reduction in sub foveal thickness from 280.13 ± 16.29 in the 1st quartile to 265.73 ± 12.65 in the 4th quartile, with a comparable decline in superior parafoveal (276.33 ± 17.24 to 261.80 ± 12.53) and inferior parafoveal thickness (268.53 ± 15.95 to 257.40 ± 12.57) (Table 4).

The analysis of choroidal thickness across different pack-year quartiles (PYQ) demonstrated a significant decrease in thickness with increasing smoking exposure ($p<0.05$) in all choroidal regions. Both sub foveal and superior parafoveal regions showed a consistent decline in thickness in both eyes ($p<0.05$). Similarly, the nasal and temporal parafoveal regions exhibited a significant

Table 3 Comparison of Choroidal Thickness (CT) in Smokers vs Nonsmokers

Choroidal Thickness (in µm)	Variable	Smokers (n=60)	Nonsmokers (n=60)	p-Value
Right Eye	Sub foveal	272.42 ± 13.57	284.94 ± 14.15	<0.05
	Superior Parafoveal	264.78 ± 14.58	276.17 ± 14.68	<0.05
	Inferior Parafoveal	260.57 ± 14.14	271.82 ± 14.33	<0.05
	Nasal Parafoveal	264.53 ± 13.22	277.02 ± 13.59	<0.05
	Temporal Parafoveal	262.90 ± 13.32	277.87 ± 13.67	<0.05
Left Eye	Sub foveal	271.47 ± 15.27	285.38 ± 13.25	<0.05
	Superior Parafoveal	264.16 ± 15.16	276.10 ± 14.45	<0.05
	Inferior Parafoveal	261.78 ± 13.91	272.73 ± 14.07	<0.05
	Nasal Parafoveal	264.88 ± 14.87	277.87 ± 13.67	<0.05
	Temporal Parafoveal	261.18 ± 15.03	274.82 ± 14.71	<0.05

Table 4 Comparison of Choroidal Thickness in Individuals with Different Pack-Year Quartiles (PYQ)

Eye	Region	Q1 (1-5 pack-years) (n=15)	Q2 (6-15 pack-years) (n=12)	Q3 (16-25 pack-years) (n=18)	Q4 (>25 pack-years) (n=15)
Right Eye	Sub foveal	283.00 ± 11.78	277.17 ± 11.05	266.33 ± 11.81	261.00 ± 7.58
	Superior Parafoveal	276.00 ± 14.04	269.33 ± 11.79	258.75 ± 11.66	252.93 ± 8.97
	Inferior Parafoveal	269.53 ± 12.48	266.56 ± 12.57	253.83 ± 12.39	249.80 ± 8.94
	Nasal Parafoveal	275.53 ± 10.98	266.83 ± 11.67	258.42 ± 10.74	255.67 ± 10.37
	Temporal Parafoveal	272.53 ± 11.76	266.22 ± 12.45	255.00 ± 10.38	255.60 ± 10.61
Left Eye	Sub foveal	280.13 ± 16.29	275.22 ± 15.56	262.17 ± 8.45	265.73 ± 12.65
	Superior Parafoveal	276.33 ± 17.24	267.83 ± 14.57	257.08 ± 8.08	261.80 ± 12.53
	Inferior Parafoveal	268.53 ± 15.95	265.22 ± 13.05	253.67 ± 8.38	257.40 ± 12.57
	Nasal Parafoveal	275.80 ± 13.40	269.22 ± 13.91	255.17 ± 9.28	256.53 ± 11.98
	Temporal Parafoveal	272.07 ± 12.45	263.72 ± 14.75	251.58 ± 12.33	254.93 ± 12.55

Table 5 Correlation Between Choroidal Thickness and Pack-Year Quartiles (PYQ)

Choroidal Region	Finding
Sub foveal (Right & Left)	Significant decrease in thickness with increasing PYQ ($p<0.05$)
Inferior Parafoveal (Right & Left)	Significant decrease in thickness with increasing PYQ ($p<0.05$), except left inferior region (NS)
Superior Parafoveal (Right & Left)	Significant decrease in thickness with increasing PYQ ($p<0.05$)
Nasal Parafoveal (Right & Left)	Significant decrease in thickness with increasing PYQ ($p<0.05$)
Temporal Parafoveal (Right & Left)	Significant decrease in thickness with increasing PYQ ($p<0.05$)

reduction in thickness with increasing PYQ ($p<0.05$). These findings support a dose-dependent effect of chronic smoking on choroidal thinning, with certain regions being more vulnerable than others (Table 5).

Discussion

The choroid is a vital vascular structure that plays an essential role in ocular physiology by supplying oxygen and nutrients to the retinal pigment epithelium and photoreceptors. Choroidal thickness is an essential parameter that reflects choroidal vascular health and it can be affected by various ocular and systemic conditions.[8] A decrease in choroidal thickness has been implicated in the pathogenesis of retinal diseases such as age-related macular degeneration (AMD), diabetic retinopathy, and central serous chorioretinopathy (CSCR).[9] Studies using enhanced depth imaging optical coherence tomography (EDI-OCT) have demonstrated that choroidal thinning is an early marker of systemic vascular dysfunction and could predict the progression of ischemic and degenerative conditions.[10] Various Researchers including Abouammoh MA reported a significant reduction in

choroidal thickness in patients with chronic CSCR.[11] Similarly Gattoussi S demonstrated a strong correlation between reduced choroidal thickness and AMD.[12] Since choroid predominantly vascular in nature any systemic factor that alters vascular tone and perfusion may contribute to choroidal thinning and subsequent visual impairment.

The cause of reduced choroidal thickness in individuals having history of chronic smoking is multifactorial and includes factors such as vasoconstriction and oxidative stress. Nicotine present in tobacco is known to cause release of catecholamines which cause vasoconstriction of the choroidal vasculature. This vasoconstriction is responsible for reducing perfusion and nutrient delivery.[13] In a study by Teberik *et al.*[14] smokers were found to have significantly reduced sub foveal choroidal thickness as compared to nonsmokers.Additionally oxidative stress from smoking is known to cause endothelial dysfunction by reducing nitric oxide (NO) bioavailability, Reduced NO bioavailability leads to impaired vasodilation and promoting vascular inflammation.[15] This mechanism was supported by the findings of El-Mahdy *et al.*[16] who reported that chronic exposure to cigarette smoke resulted in increased oxidative damage to the choroidal endothelium.

In this study, smokers demonstrated significantly decreased sub foveal and parafoveal choroidal thickness as compared to nonsmokers. This finding is consistent with previous research. Quiroz-Reyes, M.A found that chronic smokers had reduced sub foveal choroidal thickness as compared to healthy controls thereby suggesting a direct relationship between smoking and choroidal thinning.[17] Furthermore, Yuan *et al.*[18] observed a reduction in choroidal thickness even in children exposed to second hand smoke.These findings align with this study where smokers exhibited a notable decrease in choroidal thickness particularly in the sub foveal and superior parafoveal regions. The regional differences in choroid thinning may be attributed to variations in choroidal vascular density and susceptibility to nicotine-induced vasoconstriction.

The relationship between smoking duration and choroidal thinning is another important area of investigation. This study demonstrated a progressive decrease in choroidal thickness with increasing pack-years of smoking which suggests that a there is a cumulative effect of smoking on choroidal vasculature. This finding is also supported by Moschos *et al.*[19] who reported that smokers with more than 20 pack-years had significantly thinner choroids compared to those with lower cumulative exposure. The dose-dependent association between smoking and choroidal thinning highlights the importance of early smoking cessation to preserve choroidal and retinal health. Given that choroidal atrophy is associated with retinal degenerative diseases the reduction in choroidal thickness seen in chronic smokers can be used as a biomarker for early vascular dysfunction as well as susceptibility to visual impairment.[20]

The limitations of this study included a relatively small sample size which may limit the applicability of findings of this study to a broader population. Additionally smoking history was assessed on the basis of self-reported pack-years making the data collection susceptible to recall bias. Lastly vascular risk factors such as hypertension, diabetes and lipid profile which could introduce confounding effects and influence the observed results, were not extensively analyzed. These were the major limitations of this study.

This study found a significantly reduced choroidal thickness among chronic smokers as compared to nonsmokers. Moreover, there was a dose-dependent relationship between smoking and choroidal thinning and increased smoking exposure (higher pack-year quartiles) was associated with progressive choroidal thinning. These structural changes suggest a possible smoking-induced vascular compromise in the choroid.

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Original Article

Role of High-Resolution CT Thorax in Interstitial Lung Disease Evaluation

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Abstract

Background: High-Resolution Computed Tomography (HRCT) plays a crucial role in the evaluation of interstitial lung diseases, offering detailed imaging for accurate diagnosis.

Objective: To evaluate diagnostic precision and clinical relevance of HRCT in evaluating Interstitial Lung Diseases (ILDs).

Methods: This observational study analyzed HRCT images from 30 patients using a multi-detector CT scanner. The study was conducted at the Department of Radiodiagnosis of Gian Sagar Medical College and Hospital, India, in a period of one year (January 2024 to December 2024). Images were reviewed by two radiologists for various features, including ground-glass opacities, reticulations, honeycombing, and traction bronchiectasis. The patterns were classified as definite UIP, probable UIP, or suggestive of chronic HP or NSIP.

Results: Eighteen patients (60%) showed basal-predominant honeycombing, reticulations, and traction bronchiectasis consistent with definite UIP. Six of these also exhibited upper lobar emphysema, categorized as Combined Pulmonary Emphysema and Fibrosis (CPFE). Another six patients with NSIP displayed subpleural curvilinear opacities, fine reticulations, and ground-glass abnormalities. Six (20%) patients with chronic HP showed diffuse ground-glass opacities and traction bronchiectasis, primarily in the upper lobes with air trapping on expiratory scans.

Conclusion: This case series demonstrates the diverse HRCT findings in ILD, underscoring the importance of HRCT in diagnosis and prognosis. Larger studies with histopathological confirmations are needed to refine these diagnostic insights.

Keywords: HRCT, hypersensitivity pneumonitis, interstitial lung disease, NSIP, usual interstitial pneumonia

Introduction

Interstitial lung diseases (ILDs) represent a broad and heterogeneous group of pulmonary disorders. These disorders are marked by varying degrees of inflammation, fibrosis as well as distortion of the lung's interstitial architecture.[1] This vast spectrum includes conditions associated with autoimmune reactions, environmental exposures and drug-induced toxicity. Idiopathic cases, where no attributable cause can be identified, are also common. The complexity of ILDs is compounded by their overlapping clinical presentations and radiological features. These overlapping clinical features make precise diagnosis and appropriate management a significant clinical challenge.[2] High-resolution

computed tomography (HRCT) of the thorax is increasingly becoming an indispensable imaging modality in the assessment of cases of ILD. It provides details of lung parenchyma that are critical for the accurate assessment of these diseases.[3]

HRCT provides detailed images of the lung tissue by using thin-section imaging and have high spatial resolution reconstructions which allow identification of subtle parenchymal abnormalities. HRCT demonstrates key radiological features such as ground-glass opacities, reticulations, honeycombing, and architectural distortion in great detail.[4] These findings are important in distinguishing different ILD subtypes. For instance, the presence of peripheral, subpleural reticulations with honeycombing is highly suggestive of idiopathic pulmonary fibrosis (IPF) whereas a more diffuse pattern of ground-glass opacities may point toward non-specific interstitial pneumonia (NSIP) or hypersensitivity pneumonitis (HP).[5] Such precise imaging not only narrows the differential diagnosis but also directs the subsequent need for invasive procedures such as lung biopsies when the clinical picture remains ambiguous.[6]

Moreover, HRCT plays a critical role beyond mere diagnosis. It provides baseline data of disease severity and extent facilitating the assessment of progression of disease over time.[7] Serial HRCT scans can help treating physician evaluate the effectiveness of therapeutic interventions thereby guiding modifications in management strategies.[8] This aspect is important in ILDs where the progression from inflammation to irreversible fibrosis can significantly alter patient outcomes. The ability of HRCT to capture even minute changes in the lung architecture makes it an essential tool in patient management.[9]

The integration of HRCT findings with clinical and histopathological data is important for comprehensive management of ILDs.[10] HRCT not only assists in differential diagnosis but also can be used in monitoring disease progression and evaluating treatment response.

While HRCT offers assessment of severity of the disease process, histopathological examination provides definitive tissue characterization. Histopathology also helps in differentiating between various ILD subtypes and helps in identifying coexistent pathologies such as inflammation, fibrosis, or granulomatous changes. Histopathology also remains the gold standard for accurate diagnosis particularly in cases where HRCT findings are inconclusive or overlap between patterns.[11] This multidisciplinary approach ensures that patients receive individualized management.

The present study examines diverse HRCT patterns observed in ILDs, including IPF, NSIP, and HP. By analyzing these imaging characteristics, the study aims to highlight the diagnostic precision and clinical relevance of HRCT in the evaluation and management of ILDs.

Methods

This prospective observational study was conducted in the Department of Radiology at Gian Sagar Medical College and Hospital, Rajpura, Patiala, India, with the aim of evaluating the spectrum of high-resolution computed tomography (HRCT) thorax findings in patients with interstitial lung diseases (ILDs). The study was designed to assess HRCT imaging characteristics and correlate them with clinical and functional parameters. The study duration was one year, from January 2024 to December 2024. Since it was a purely observational study where CT images were analyzed (and no ethical issues were involved) hence ethical clearance was waivered. A total of 30 patients clinically suspected of having ILDs and referred for HRCT thorax as part of their diagnostic evaluation were included. The diagnosis of ILDs was established through a multidisciplinary approach, incorporating clinical evaluation, laboratory investigations and imaging findings. Patients with incomplete imaging or clinical data and those with poor-quality CT scans due to motion artifacts were excluded from the study.

The sample size was calculated based on a pilot study evaluating the prevalence of ILD patterns on HRCT. Using OpenEpi software (version 3) and assuming a 95% confidence interval and 90% power, the minimum required sample size was estimated to be 27 patients. To account for potential dropouts or exclusions due to incomplete data, a final sample of 30 patients was included in the study.

Demographic and clinical data—including age, sex, and comorbidities—were recorded at the time of enrollment. The HRCT findings were correlated with clinical and functional data to evaluate disease severity and distribution. HRCT scans were performed using a multi-detector CT scanner (Somatom go. UP, Siemens, Munich, Germany) with patients positioned supine during full inspiration. Non-contrast

HRCT imaging was conducted to assess lung parenchyma. Thin-section images (1 mm slice thickness) were obtained and reconstructed in axial, coronal, and sagittal planes using a high spatial resolution algorithm. The standardized scan parameters included a tube voltage of 130 kVp, an auto-adjusted tube current based on patient body habitus, collimation of 32 × 0.7 mm, and a reconstruction kernel optimized for lung parenchyma. The matrix size was set at 512 × 512 to ensure high-resolution imaging.

HRCT images were independently reviewed in real time by two experienced radiologists. The following imaging features were systematically assessed: ground-glass opacities, mosaic attenuation, reticulations, honeycombing, emphysema, and traction bronchiectasis. In instances of disagreement between radiologists a consensus was reached through joint discussion. However, formal statistical analysis of interobserver agreement was not performed at the time of data analysis.

Based on imaging characteristics, cases were categorized as definite usual interstitial pneumonia (UIP), probable UIP, or suggestive of alternative diagnoses such as chronic hypersensitivity pneumonitis (HP) or nonspecific interstitial pneumonia (NSIP). The extent of parenchymal involvement was visually assessed and categorized as mild (<25%), moderate (25–50%), or severe (>50%). The distribution pattern of lung involvement was also documented in terms of zonal predominance (upper, middle, or lower lobes) and axial distribution (central, peripheral/subpleural, or diffuse).

Data were recorded in Microsoft Excel and analyzed using SPSS software (version 23.0). Quantitative variables, such as age and percentage of lung involvement, were expressed as mean ± standard deviation (SD). Categorical variables, including specific HRCT patterns and distribution features, were reported as frequencies and percentages. A p-value of <0.05 was considered statistically significant.

Results

Among the 30 patients included in the study, 19 (63.33%) were male and 11 (36.67%) were female, yielding a male-to-female ratio of 1:0.57. The analysis of the age distribution among the studied cases showed that the most common age group was 51–60 years, comprising 30.0% of the total patients (31.6% of males and 27.3% of females). This was followed by the 61–70 years age group, accounting for 26.7% of all patients (26.3% of males and 27.3% of females). The 41-50 years category made up 20.0% of cases, while patients aged 71 years and above constituted 13.3%. The least common group was 19-40 years, contributing only 10.0% of the total cases. The mean age of male patients was 59.1 ± 9.8 years, while for females, it was 56.8 ± 11.2 years, with an overall mean age of 57.95 ± 10.5 years. The p-value for age distribution was 0.561, indicating that the difference in age between males and females was not statistically significant (Table 1).

The analysis of the HRCT patterns in studied cases revealed that reticulations were present in all cases (100 %), followed closely by traction bronchiectasis, which was observed in 24 patients (80%). Honeycombing was noted in 24 cases (80 %) as well, while ground-glass opacities (GGO) were seen in 12 patients (40 %). Air trapping and emphysema were seen in 6 (20 %) cases. The CT images were analyzed for presence of UIP, NSIP and Chronic HP patterns.

HRCT Thorax of 18 patients (60%) demonstrated basal-predominant

Table 1 Gender-wise Distribution of Studied Cases by Age Group

Age Group	Males (n)	Males (%)	Females (n)	Females (%)	Total Patients	Total (%)	p-value
19–40 years	2	10.5	1	9.1	3	10	
41–50 years	4	21.1	2	18.2	6	20	
51–60 years	6	31.6	3	27.3	9	30	
61–70 years	5	26.3	3	27.3	8	26.7	0.561
71+ years	2	10.5	2	18.2	4	13.3	
Total	19	100	11	100	30	100	
Mean Age	59.1 ± 9.8 years		56.8 ± 11.2 years		57.95 ± 10.5 years		

Table 2 HRCT Patterns Observed in Studied Cases (n = 30)

HRCT Pattern	Present		Absent		Total	
	Number of cases	Percentage (%)	Number of cases	Percentage (%)	Number of cases	Percentage (%)
Honeycombing	24	80	6	20	30	100
Reticulations	30	100	0	0	30	100
Traction Bronchiectasis	24	80	6	20	30	100
GGO	12	40	18	60	30	100
Air Trapping	6	20	24	80	30	100
Emphysema	6	20	24	80	30	100

Table 3 Severity of Lung Parenchymal Involvement on HRCT (n=30)

Severity of Involvement	Number of cases	Percentage (%)
Mild (< 25)	6	20
Moderate (25–50)	12	40
Severe (>50)	12	40
Total	30	100

honeycombing of various degrees. This was accompanied by fine reticulations and traction bronchiectasis. In 6 of these cases (20%), more than 50% of the lung parenchyma was affected, while the remaining 12 cases (40%) exhibited 25–50% involvement. Among these UIP cases, 5 patients (16.7%) also demonstrated upper lobe-predominant paraseptal emphysema, consistent with combined pulmonary fibrosis and emphysema (CPFE). NSIP-like changes were observed in 6 patients (20%), showing subpleural curvilinear opacities, bilateral

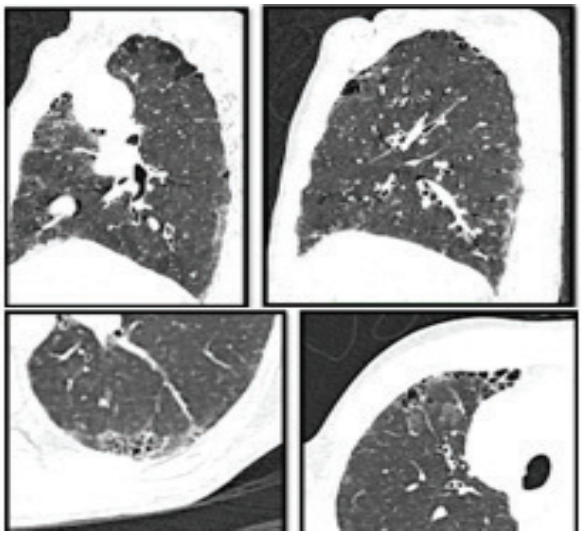

Fig. 1 Combined Pulmonary Fibrosis and Emphysema (CPFE)
Sagittal HRCT images demonstrate apical paraseptal emphysema and basal predominant fibrosis. Axial images in lung window reveal subpleural areas of honeycombing and fine reticulations

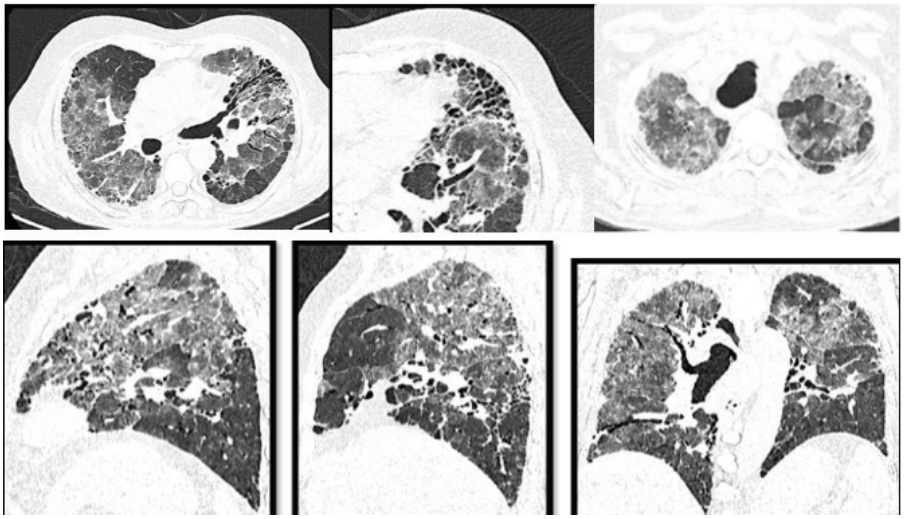

Fig. 2 Non-Specific Interstitial Pneumonia (NSIP)
Axial HRCT lung window images reveal subpleural curvilinear opacities and reticulations. Mild tubular bronchiectasis (white arrow) is also seen

symmetrical ground-glass opacities, fine reticulations with basal predominance, and relative sparing of the immediate subpleural region. The absence of honeycombing, architectural distortion, and significant traction bronchiectasis further supports the NSIP pattern.

Diffuse areas of ground glass opacification with associated traction bronchiectasis were seen in both lungs of 6 (20 %) patients. These were more predominant in upper lobes. There was ancillary irregular interstitial septal thickening and architectural distortion due to fibrosis. More than 80 percent of the lung parenchyma was affected. Subpleural areas of honeycombing were seen in both lungs, showing predominance in their upper portions. The diffuse ground glass abnormality also revealed interspersed areas of normal and hypoattenuating lung parenchyma on expiratory scan. Hypoattenuating areas were possibly due to air trapping (Table 2).

The analysis of lung parenchymal involvement severity on HRCT among the studied cases showed that moderate (25-50 %) and severe (>50 %) involvement were the most common, each observed in 40 % of the patients. Mild involvement (<25 %) was seen in 20 % of the cases (Table 3).

Discussion

In this study involving 30 patients, 63.33% were male and 36.67% were female, with a

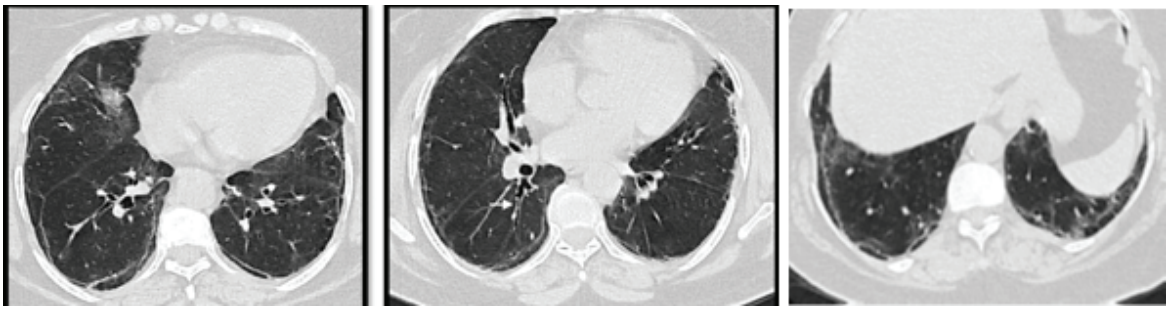

Fig. 3 Chronic Hypersensitivity Pneumonitis (CHP)
Axial CT images reveal extensive ground glass opacities, interstitial septal thickening, traction bronchiectasis, honeycombing and mosaic attenuation. Sagittal and coronal images display predominant upper lobe involvement

male-to-female ratio of 1:0.57. The mean age of male patients was 59.1±9.8 years, while for females, it was 56.8±11.2 years, with an overall mean age of 57.95±10.5 years. Balas Z C *et al* conducted a prospective observational study to compare spirometry findings in ILD patients with their radiological and clinical features.[12] For this purpose, the authors undertook a study comprising of 50 ILD patients who were diagnosed based on clinical and radiological criteria. A detailed history was obtained, and all patients underwent clinical examination and basic investigations. The study found that idiopathic pulmonary fibrosis was the most common ILD, accounting for 32 (64 %) patients. The average duration of symptoms was 5.46±5.49 months, and the mean age of patients was 61.58±12.92 years, ranging from 27 to 88 years. There were 27 (54 %) males and 23 (46 %) females. Chest X-ray findings showed reticular opacities in 24 (48 %) patients, while HRCT revealed ground-glass opacity in 33 (66 %) patients. Male gender predominance as well as mean age of cases with ILD seen in this study was similar to this study. Similar male preponderance in cases of ILD was also reported by the authors such as Ozaki *et al*[13] and Kawano-Dourado *et al*.[14]

A definite UIP pattern was identified in 60 % of patients, characterized by basal-predominant honeycombing with accompanying fine reticulations and traction bronchiectasis. Among these, one-third of cases demonstrated extensive involvement (>50 % of lung parenchyma), while two-thirds exhibited an intermediate degree (25 % –50 %) of fibrosis. Notably, air trapping was absent in all cases, suggesting that small airway involvement was not a predominant feature in this cohort. Interestingly, 16.7% of UIP cases also displayed upper-lobe predominant paraseptal emphysema, fulfilling the criteria for combined pulmonary fibrosis and emphysema (CPFE). These findings align with prior studies, such as those by Douglas D *et al*. who reported that CPFE is a distinct radiological entity within the fibrotic ILD spectrum, associated with a high prevalence of smoking history and a worse prognosis due to coexisting airway destruction and vascular abnormalities.[15] Similarly, Amariei *et al*. demonstrated that CPFE patients often exhibit preserved lung volumes with severely impaired diffusion capacity, reinforcing the complex interplay between emphysematous and fibrotic changes.[16]

A nonspecific interstitial pneumonia (NSIP) pattern was identified in 20 % of cases, demonstrating subpleural curvilinear opacities with fine reticulations and relative subpleural sparing, a hallmark feature differentiating NSIP from UIP. Additionally, scattered GGO was present, with less than 25 % lung involvement in all cases. These findings are in concordance with the study by Teoh AKY *et al* which described NSIP as a histologically distinct entity often associated with autoimmune diseases, particularly systemic sclerosis.[17] Furthermore, Hobbs S reported that the presence of scattered GGO and subpleural sparing on HRCT is a key differentiator of NSIP from UIP, aiding in noninvasive diagnosis.[18]

Chronic hypersensitivity pneumonitis (HP) was identified in 20% of cases, exhibiting a pattern of diffuse GGO with associated traction bronchiectasis, predominantly affecting the upper lobes. Additional findings included interstitial septal thickening, architectural distortion, and subpleural honeycombing, with over 80 % of lung parenchyma involved. These findings are consistent with those reported by Salisbury *et al*., who highlighted that chronic HP is often characterized by upper-lobe predominant fibrosis with mosaic attenuation on expiratory imaging, a key distinguishing feature from UIP and NSIP.[19] More recently, Calaras D *et al*. demonstrated that air trapping in chronic HP is a critical predictor of disease chronicity and progression, supporting the importance of expiratory-phase imaging in the diagnostic evaluation.[20]

The predominance of UIP in this study aligns with existing literature, reinforcing its role as the most common fibrotic ILD pattern. The coexistence of CPFE in a subset of patients further highlights the heterogeneous nature of ILD and its overlap with smoking-related lung diseases. The identification of NSIP and chronic HP in a significant proportion of cases emphasizes the necessity of meticulous HRCT interpretation to ensure accurate classification, as misdiagnosis can have significant therapeutic implications. Furthermore, the absence of air trapping in non-HP cases underscores the importance of expiratory-phase imaging in differentiating various ILD subtypes.

A key limitation of this study is the absence of detailed smoking history, which is particularly important in cases demonstrating combined pulmonary fibrosis and emphysema (CPFE). Since the study was primarily conducted in the radiology department clinical history including occupational and environmental exposures could not be comprehensively

documented. Another key limitation of this study is the absence of formal interobserver agreement analysis using statistical methods such as Cohen's kappa. Although HRCT images were independently reviewed by two radiologists and consensus was reached in cases of discrepancy, the lack of quantified agreement may introduce subjectivity in imaging interpretation.

In conclusion, HRCT plays a crucial role in evaluation of ILD. The predominant pattern in this study was UIP. The presence of CPFE in a subset of patients underlines the importance of clinical correlation particularly in smokers. Differentiating NSIP and chronic HP on imaging carries important prognostic and therapeutic implications. Histopathological correlation is warranted to further refine the radiological classification of ILD and its subtypes.

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Original Article

Assessment of Disease Progression in Idiopathic and Collagen Vascular ILDs Using Spirometry, DLCO, and 6 Minute-Walk-Test

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Abstract

Background: Monitoring progression in interstitial lung diseases is essential for timely intervention, with spirometry, DLCO, and 6MWT serving as key functional tests.

Objectives: To evaluate disease progression in idiopathic and collagen vascular interstitial lung diseases (ILD) using pulmonary function parameters, including spirometry, DCLO (Diffusing Capacity of the Lungs for Carbon Monoxide), and the six-minute walk test.

Methods: This prospective observational study was performed from January 2023 to December 2024 at Shadan Institute of Medical Sciences , Hyderabad, India. In this study, the pulmonary function in 51 ILD patients were assessed using spirometry, DLCO, and the six-minute walk test. Patients underwent detailed clinical evaluation, routine investigations, chest X-ray, ABG analysis, and HRCT to confirm ILD. Those suspected of CTD-ILD had RF and ANA testing, with a complete ANA profile if positive. Subjects were categorized into IPF and CTD-ILD groups. Pulmonary parameters were compared, and standard treatments were administered. Six deaths occurred during follow up period. For statistical purposes p value less than 0.05 was taken as statistically significant.

Results: Fifty-one patients with diffuse parenchymal lung disease were included, with idiopathic pulmonary fibrosis (IPF) (46.4%) and connective tissue disease-associated ILD (CTD-ILD) (44.6%) as the main types. The CTD-ILD patients were younger (mean age 48.64 vs. 61.80 years, p=0.0006) and predominantly female. IPF patients had lower six-minute walk distance (239.73 vs. 312.60 meters, p=0.0066) and SpO2. Strong correlations were observed between lung function parameters in both groups. However, 6MWT showed no correlation in CTD-ILD.

Conclusion: In ILD patients, FVC and DLCO were found to be reliable for disease monitoring, while simpler tests like 6MWT and FVC proved to be useful in resource-limited settings. Further research is needed to confirm their role in tracking IPF progression and treatment response.

Keywords: Connective tissue disease-associated interstitial lung disease, Idiopathic pulmonary fibrosis, pulmonary function test, six-minute walk test

Introduction

Interstitial lung diseases (ILDs) are a heterogeneous group of diffuse parenchymal lung disorders characterized by varying degrees of inflammation, fibrosis and impaired gas exchange.[1] These diseases primarily affect the lung parenchyma leading to progressive respiratory failure and reduced quality of life. ILDs encompass several distinct conditions that include conditions such as idiopathic pulmonary fibrosis (IPF), hypersensitivity pneumonitis (HP), sarcoidosis and connective tissue disease-associated ILD (CTD-ILD). The global prevalence of ILDs is difficult to estimate because of variations in diagnostic criteria and registry-based data collection. Some estimates suggest a prevalence of approximately 80–100 cases per 100,000 population globally. In India ILDs have gained increasing recognition with the establishment of Indian Registry of Interstitial Lung Diseases (ILD-India). ILD-India has reported a significant burden of these conditions in Indian population.[2]

ILDs can arise from a variety of etiologies that include environmental, occupational, drug-induced, infectious as well as autoimmune causes. Broadly, they are classified into idiopathic interstitial pneumonias (IIPs) and secondary ILDs associated with known triggers such as connective tissue diseases (CTDs), environmental exposures, or infections. Idiopathic interstitial lung diseases, particularly idiopathic pulmonary fibrosis (IPF) is characterized by progressive fibrosis of unknown origin. IPF is associated with a poor prognosis and limited therapeutic options with a median survival of 3–5 years post-diagnosis.[3] Another crucial category is collagen vascular disease-associated interstitial lung disease which includes ILDs secondary to autoimmune disorders such as rheumatoid arthritis (RA), systemic sclerosis (SSc), systemic lupus erythematosus (SLE), polymyositis/dermatomyositis (PM/DM), and Sjögren's syndrome. Among these, systemic sclerosis-associated ILD (SSc-ILD) and rheumatoid arthritis-associated ILD (RA-ILD) are among the most common. While idiopathic ILDs such as IPF typically demonstrate a usual interstitial pneumonia (UIP) pattern, CTD-ILDs may exhibit nonspecific interstitial pneumonia (NSIP) or organizing pneumonia (OP) patterns with better prognostic outcomes compared to IPF. Given the progressive and often irreversible nature of these diseases, accurate diagnosis and regular monitoring using pulmonary function parameters are imperative for optimizing clinical management.[4]

HRCT has made it possible to characterize ILD with great precision. As a result, the defining features of nearly all ILDs are well described which has helped to predict outcome and decide on an appropriate management plan.[5] While HRCT is important in initial diagnosis of ILD Pulmonary function testing (PFT) plays an important role in prognostication and monitoring of ILDs. ILDs typically present with restrictive lung physiology, leading to reduced lung volumes and impaired gas exchange. Pulmonary function parameters serve as objective markers to evaluate disease severity, functional impairment, and response to therapy.[6] Among the various PFT parameters, forced vital capacity (FVC), diffusing capacity of the lung for carbon monoxide (DLCO), and exercise capacity (assessed via the six-minute walk test [6MWT]) are widely utilized in both clinical and research settings. Serial assessment of these parameters provides critical insights into disease progression and helps guide therapeutic decisions including the initiation of antifibrotic or immunosuppressive therapy.

A decline in pulmonary function parameters over time correlates with increased mortality in ILD patients.[7] For instance, a decrease in FVC by ≥10% over six months is a strong predictor of poor prognosis in IPF. Similarly, DLCO reduction is associated with worsening pulmonary vascular involvement and gas exchange impairment. The six-minute walk test, an essential measure of functional status, reflects exercise-induced oxygen desaturation, an early indicator of ILD progression. Given these associations, periodic assessment of pulmonary function tests is critical in the comprehensive management of ILD patients.[8]

While individual pulmonary function parameters such as FVC and DLCO have been extensively studied in IPF, their predictive value in CTD-ILD and other idiopathic forms of ILD remains underexplored. The integration of 6MWT as a functional marker alongside spirometry and DLCO could provide a more holistic assessment of disease trajectory. This study aims to bridge these gaps by systematically evaluating the progression of idiopathic and collagen vascular ILDs using spirometry, DLCO and the six-minute walk test.

Methods

This prospective observational study was conducted in the Department of Pulmonary

Medicine at Shadan Institute of Medical Sciences, Hyderabad, Telangana, India, over a 23-month period from January 2023 to December 2024. The Institutional Ethics Committee approved the study, and informed written consent was obtained from all participants. Ethical guidelines were followed per international standards, including those from the American Thoracic Society (ATS) and the FDA (USA). No invasive procedures or experimental treatments were involved.

A total of 51 subjects with interstitial lung disease (ILD) of idiopathic and collagen vascular etiology were included in the study. The study aimed to assess pulmonary function status using spirometry, diffusing capacity of lung for carbon monoxide (DLCO), and the six-minute walk test (6MWT).

The study included subjects aged 30 years and above with respiratory symptoms such as cough and shortness of breath for more than three months, bilateral abnormalities on chest X-ray or high-resolution computed tomography (HRCT) scan of the thorax consistent with an interstitial pattern, and restrictive or mixed defects on spirometry. ATS/ERS classification was used for categorizing the cases into different ILDs. Patients with a history of smear-positive tuberculosis, infectious diseases, or malignancy were excluded.

All participants underwent a detailed clinical evaluation and routine investigations, including complete blood picture, blood chemistry, chest X-ray, and arterial blood gas (ABG) analysis. High-resolution computed tomography (HRCT) of the chest was performed to confirm ILD. Spirometry, DLCO (using the EASY PRO, Switzerland) and the six-minute walk test (6MWT) were conducted following ATS guidelines.

Patients suspected of having collagen vascular disease (CTD-ILD) underwent rheumatoid factor (RF) and antinuclear antibody (ANA) testing. If either was positive, a complete ANA profile was done. Additional investigations were conducted as required. Subjects were categorized into idiopathic pulmonary fibrosis (IPF) and connective tissue disease-associated interstitial lung disease (CTD-ILD) groups. Pulmonary function parameters, including forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio, DLCO, carbon monoxide transfer coefficient (KCO), initial and final SpO2, and six-minute walk distance (6MWD) were recorded. These parameters were analyzed and compared between the IPF and CTD-ILD groups.

All subjects received standard treatment, including oxygen therapy, antioxidants and antifibrotic agents (Pirfenidone). Some patients were also prescribed N-acetylcysteine. Patients were followed up every 6 months till the end of study period. They were encouraged to report earlier in case of disease exacerbation or medication side effects. The follow up was mainly for knowing mortality during study period. During the study period 50 patients completed one-year follow-up. Six deaths were recorded—five in the IPF group and one in the CTD-ILD group.

Statistical analysis was performed using Windostat Version 9.2 software. Continuous variables were expressed as mean ± standard deviation (SD). The Fisher's exact test was applied for categorical data, while the Student's t-test was used for continuous variables. Pearson's correlation was applied to examine associations between variables. A p-value of less than 0.05 was considered statistically significant.

Results

In this study, a total of 51 consecutive patients with diffuse parenchymal lung disease were included. Idiopathic pulmonary fibrosis (IPF) was found to be the most common variety (n=26, 46.4%) followed by CTD (n=25, 44.6%). Of the 25 cases of CTD, rheumatoid arthritis (RA) (n=16, 64%) and systemic lupus erythematosus (SLE) (n=5, 20%), were the most common followed by systemic sclerosis (n=4, 16%) .A majority of patents of CTD–DPLD

Table 1 Comparison of Demographics Between Patients with CTD-ILD and IPF

Demographics	CTD-ILD (n=25)	IPF (n=26)	p-value
Mean age (years)	48.64 ± 15.98	61.80 ± 9.01	0.00065
Sex ratio (male: female)	1:4 (5:20)	1:1 (13:13)	0.02492
Smoking, n (%)	2 (8%)	5 (19.2%)	0.45315
Body Mass Index (BMI)	24.74 ± 4.59	25.56 ± 4.59	0.46904

Table 2 Comparison of Physiological Parameters Between CTD-ILD and IPF Groups

Physiological Parameter	CTD-ILD (n=25)	IPF (n=26)	p-value
FVC (% predicted)	58.2 ± 17.39	57.42 ± 18.03	0.8762
FEV1 (% predicted)	55.56 ± 17.67	57.34 ± 16.98	0.7143
FEV1/FVC	96.84 ± 14.7	101.23 ± 15.37	0.3040
DLCO (% predicted)	40.76 ± 18.61	34.57 ± 17.20	0.2235
KCO (% predicted)	73.64 ± 22.84	70.80 ± 29.33	0.7029
Initial SpO_2 (%)	96.5 ± 2.4	94.7±2.9	0.0198
Final SpO_2 (%)	88.2 ± 7.5	85.8±7.1	0.2461
6MWT (meters)	312.60 ± 108.11	239.73 ± 72.60	0.0066

Table 3 Comparison of Various Parameters in CTD-ILD Group

Parameter 1	Parameter 2	Correlation Coefficient (r)	p-value
FVC	FEV1	0.8928	<0.0001*
FVC	DLCO	0.5773	0.002*
DLCO	KCO	0.79676	<0.0001*
KCO	FVC	0.3975	<0.0001*

Notes: 6MWT was an independent parameter showing no correlation with other physiological parameters

belonged to a younger age group than IPF. The mean age for CTD-ILD and IPF was 48.64 ±15.98 years, 61.80 ± 9.01 years respectively, with a significant p value(0.0006). A significant difference was found in the male to female ratio between two groups (p=0.02) (Table 1).

In CTD-ILD group (n=25), spirometry abnormalities were observed in 22(88%) patients, 20(80%) had restrictive defects and 2(8%) had obstructive defects. Mean FVC (% predicted) ,DLCO (% of predicted) was 58.2±17.39, 40.76±18.61 respectively. A DLCO below 25% of predicted was measured in 7 (28%) patients. Mean KCO (% pred) was 73.64±22.84. In IPF group (n=26), spirometry abnormalities were observed in 21 (81%) patients, 19(73%) had restrictive defects and 2 (8%) had obstructive defects. Mean FVC (%pred), DLCO(%pred) in this group was 57.42 ± 18.03, 34.57 ± 17.20 respectively. A DLCO below 25% predicted was observed in 9 (35%) patients. Mean KCO (% predicted) in this group was 70.80 ± 29.33. Baseline 6MWT of CTD-ILD and IPF were 312.60 ± 108.11 meters and 239.73 ± 72.60 meters respectively. Initial spo2 (%) in CTD-ILD group was 96.5 ± 2.4 and in IPF group it was 94.7±2.9 %. Compared to CTD–DPLD,

Table 4 Comparison of Various Parameters in IPF Group Top of Form Bottom of Form

Parameter 1	Parameter 2	Correlation Coefficient (r)	p-value
FVC	DLCO	0.2816	0.163
DLCO	KCO	0.7263	<0.0001*
6MWT	FVC	0.54004	0.004*
6MWT	FEV1	0.41846	0.03*
6MWT	KCO	0.41846	0.03*
6MWT	DLCO	0.45673	0.01*

IPF patients had significantly less baseline six-minute walk distance (p=0.00663). No significant difference was found among other parameters. However, the IPF patients had a significantly lower initial and final SpO2 during the 6MWT compared with the CTD-ILD patients (P=0.0198 and P=0.2461 respectively) (Table 2).

In the CTD-ILD group, FVC and FEV1 exhibited a strong positive correlation (r =0.8928, p<0.0001). FVC and DLCO showed a moderate positive correlation (r = 0.5773, p =0.002). DLCO and KCO demonstrated a strong positive correlation (r=0.79676, p< 0.0001). KCO and FVC had statistically significant positive correlation (r=0.3975, p< 0.0001) suggesting that lung volume and gas exchange efficiency are related to some extent. 6MWT did not show any correlation with other physiological parameters (Table 3).

In the IPF group FVC and DLCO showed a weak positive correlation (r=0.2816, p= 0.163), which was statistically not significant. DLCO and KCO demonstrated a strong positive correlation (r=0.7263, p<0.0001). 6MWT and FVC exhibited a moderate positive correlation (=0.54004, p=0.004), suggesting a relationship between six-minute walk distance and forced vital capacity. 6MWT and FEV1 had a weaker but statistically significant positive correlation (r=0.41846, p=0.03), indicating an association between exercise capacity and forced expiratory volume in the first second. Additionally, 6MWT showed moderate correlations with both KCO (r=0.41846, p=0.03) and DLCO (r=0.45673, p=0.01), as detailed in Table 4.

Discussion

This study compared demographic and physiological parameters between IPF and CTD-ILD groups. Fifty-one DPLD cases were studied over a period of two years in the present study. Twenty-six patients were IPF and twenty-five were CTD-ILD. This study showed that, IPF was the more common entity (46.4%) among DPLD cases followed by CTD–DPLD (44.6%). The mean age of IPF cases in the present study was 61.80± 9.01 years. Koo *et al.* conducted a national survey to evaluate whether age affects the survival of patients with idiopathic pulmonary fibrosis (IPF). For this purpose, the authors undertook a study comprising 1,663 patients with IPF. The mean age of cases with IPF in this study was found to be 67.9 years (range, 30–94 years).[9] Similar mean age of cases of IPF was also seen in this study.

The preponderance of males and smokers in the IPF group in this study was similar to the Indian and western literature.[10] Significant difference in age and sex ratio was found between the two groups in this study whereas mean BMI values were found to be comparable in both the groups. CTD-ILD patients were more likely to be young (mean age 48.64 ±15.98 years), female (80%) and non-smokers (8%) compared with IPF group in the present study. similar demographic parameters were found in studies done by Jeganathan *et al.*[11] and Leuschner *et al.*[12] The mean age of CTD-ILD was 57.24 ± 1.55 years which was significantly less than patients with IPF (p<0.05). The percentage of male patients was 31.7% in the CTD-ILD group which was significantly lower than IPF group (69.3%). Percentage of smokers was significantly lower in CTD-ILD group than in the IPF group which indicates that young female ILD patients were more prone to be CTD-ILD patients while older male ILD patients with smoking history were more prone to develop IPF. The present study was supported by a similar study conducted by Margaritopoulos.[13]

In the present study, pulmonary function abnormalities mostly restrictive were observed in 80% patients of CTD-ILD group and 73% patients in IPF group. It is important to note that no significant difference was found in FVC, DLCO and KCO between IPF and CTD-ILD groups of the present study. The observations of authors such as 14. Ciancio *et al.*[14] were similar. In the present study, a positive correlation between FVC and DLCO (r=0.5773, p=0.005) was found in CTD-ILD group which means both the above variables move in same direction in this group of subjects. No positive correlation was found between FVC and DLCO(r=0.2816) in IPF group. A disproportionate reduction in DLCO in IPF group may probably signify coexistent CPFE or pulmonary hypertension in this group.

In IPF group, 6MWT was correlated with FVC, FEV1, KCO and DLCO. Strong positive correlation was found between FVC and 6MWT. These findings suggest that the 6-minute-walk test is a valid, and responsive measure of exercise tolerance in patients with idiopathic pulmonary fibrosis. Hu *et al*.[15] conducted a study to explore the correlation between 6MWT and traditional measures such as pulmonary function and chest computed tomography (CT) and to find out factors that influence the 6-minute walk distance (6MWD).

For this purpose, the authors undertook a study of 73 patients with ILD. All patients underwent 6MWT, pulmonary CT, and pulmonary function tests and their correlations were analyzed. The study found that 6MWD was correlated with forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), total lung capacity (TLC), diffusing capacity for carbon monoxide (DLCO) and DLCO % pred. The decrease in oxygen saturation (SpO_2) after the test was correlated with FEV1%pred, FVC%pred, TLC, TLC% pred, DLCO, DLCO% pred and the percentage of normal lung calculated by quantitative CT. On the basis of these findings the authors concluded that The 6MWT results were closely correlated with pulmonary function and quantitative CT in patients with ILD.[15]

However, despite its usefulness in global evaluation of exercise capacity in ILD patients 6 MWT does not provide diagnostic information regarding specific causes for dyspnea or exercise limitation, which can only be obtained through more formal cardiopulmonary exercise testing (CPET).

One of the limitations of this study was a small sample size. Larger prospective epidemiological studies are necessary for a better understanding of the spectrum of diffuse parenchymal lung disorders and role of pulmonary function tests in evaluation of disease progression. Additionally, selection bias also cannot be excluded as cases with milder symptoms may not have undergone further investigations for diagnosis of ILD.

In conclusion, this study demonstrated significant demographic differences between IPF and CTD-ILD patients. The 6-minute walk test (6MWT) emerged as an independent functional marker though its prognostic value remains uncertain due to a lack of standardization. FVC and DLCO were found to be most reliable measures for disease monitoring. Simpler tests like 6MWT and FVC were found to be useful in resource-limited settings. However further research is needed to confirm their role in tracking IPF progression and treatment response.

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Original Article

Correlation between TSH, Prolactin, LH, FSH, Estrogen, and Progesterone in Women with Infertility

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Abstract

Background: Hormonal imbalances play a pivotal role in female infertility, affecting various endocrine pathways that warrant comprehensive evaluation.

Objective: To analyze correlations between thyroid-stimulating hormone (TSH), prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estrogen, and progesterone in women with infertility.

Methods: This retrospective observational study was conducted at the Department of Obstetrics and Gynecology of Prakash institute of Medical Sciences, India, between January 2024 and December 2024. Medical records of 140 women (90 with primary infertility and 50 with secondary infertility) aged 19–45 years were analyzed over a one-year period. Hormonal profiles including TSH, prolactin, LH, FSH, estrogen, and progesterone were analyzed. Statistical analyses were performed using the SPSS 23.0 software and a p-value of less than 0.05 was considered statistically significant.

Results: Women with primary infertility were younger and had a shorter duration since marriage compared to those with secondary infertility ($p<0.001$). Irregular menstrual cycles were significantly more common in primary infertility cases ($p=0.002$). Thyroid dysfunction was seen in 25% of cases, with hypothyroidism as the most common thyroid function abnormality (14.9%). A strong positive correlation was found between TSH and prolactin levels ($r=0.821$, $p<0.05$), whereas a significant negative correlation was present between TSH and LH ($r=-0.73$, $p<0.05$) and FSH ($r=-0.41$, $p<0.05$). Correlations between TSH and estrogen or progesterone was not found to be statistically significant ($P>0.05$).

Conclusion: TSH levels significantly correlate with prolactin, LH, and FSH levels in women with infertility. These findings underscore the importance of comprehensive endocrine evaluation of women with infertility to optimize diagnosis and management strategies.

Keywords: Hormonal imbalance, infertility, prolactin, thyroid-stimulating hormone

Introduction

Infertility is usually defined as failure to conceive even after 12 months of regular and unprotected sexual intercourse. It is a significant global health issue that affects approximately 8–12% of the couples worldwide.[1] The burden of infertility is significant in developing countries where infertility not only is a medical issue but also has serious social and psychological consequences. In India the prevalence of infertility is estimated to be around 10–14%, with variations based on socio-demographic

factors. Since female infertility accounts for approximately 40-50% of all infertility cases it is important to have an in-depth understanding of the etiological factors and underlying mechanisms involved in female's infertility.[2]

Female infertility is multifactorial and its causes ranges from anatomical, genetic, environmental, and lifestyle factors to endocrine and metabolic dysfunctions. Structural abnormalities (tubal blockage, congenital uterine anomalies and uterine fibroids) can interfere with fertilization and implantation.[3] Genetic disorders (chromosomal abnormalities and mutations affecting ovarian function) can lead to primary ovarian insufficiency. Lifestyle factors such as obesity, stress, smoking and exposure to environmental toxins also affect fertility in women. However, one of the most common yet underdiagnosed causes of infertility in women is hormonal imbalances particularly involving thyroid hormones, gonadotropins, and prolactin.[4] Thyroid dysfunction can result in altered sex hormone-binding globulin (SHBG) levels, abnormal follicular development and luteal phase defects.[5]

Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are key gonadotropins that are known to regulate follicular maturation and ovulation. Disturbances in their secretion can lead to ovulatory dysfunction which is a leading cause of infertility in women.[6] Elevated FSH levels is suggestive of diminished ovarian reserve. Altered LH secretion patterns are commonly seen in polycystic ovary syndrome (PCOS) which is a major cause of anovulatory cycles leading to infertility. Prolactin is involved in the regulation of the HPO axis. Hyperprolactinemia is known to suppress gonadotropin-releasing hormone (GnRH) secretion thereby causing decreased FSH and LH levels resulting in anovulation and menstrual irregularities.[7]

The relationship between thyroid hormones, FSH, LH and prolactin is complex. Thyroid dysfunction can significantly affect the secretion of gonadotropins as well as prolactin.[8] In women with hypothyroidism elevated thyrotropin-releasing hormone (TRH) levels stimulate prolactin secretion which in turn inhibits FSH and LH release. All these hormonal changes impair follicular development and ovulation. Hyperthyroidism has been associated with suppressed TSH and alterations in gonadotropin dynamics causing menstrual disturbances and infertility. Additionally, estrogen metabolism and SHBG levels are influenced by thyroid hormones further affecting reproductive hormone levels.[9]

Despite growing interest in the hormonal mechanisms underlying infertility, few studies have systematically explored the correlations between thyroid hormones, prolactin, FSH, LH, estrogen, and progesterone in women with infertility. A better understanding of these hormonal interactions can lead to improved clinical outcomes in affected women.

Methods

This retrospective observational study was conducted in the Department of Obstetrics and Gynecology of Prakash institute of medical sciences, India. The study period extended over one year, from January 2024 to December 2024. In this study medical records of total 140 women diagnosed with infertility were analyzed. These cases were categorized into two groups based on the type of infertility: primary infertility (n=90) and secondary infertility (n=50). All women included in the study were aged between 19 and 45 years. Since the study was retrospective and observational no ethical issues were involved and hence no ethical committee clearance was required. Patients' data was anonymized prior to analysis to maintain confidentiality. The study adhered to institutional norms regarding the use of medical records for research.

The minimum sample size was determined to be 120 cases based on previous pilot studies evaluating thyroid and other hormonal profiles among infertile women. Aiming for a statistical power of 90% and a 95% confidence interval. Therefore, 140 infertile women were included in this study to ensure adequate statistical power.

Data were collected retrospectively from patient records and included demographic details, menstrual history, obstetric history, medication use, and addiction history. Women with known male factor infertility were excluded, as were those taking medications known to interfere with thyroid function (e.g., amiodarone, phenytoin, lithium). Women diagnosed with tubal factor infertility, congenital uterine anomalies, large fibroids or history of thyroid disease and significant psychiatric illnesses were also excluded from the study. Patients in whom complete hormonal profile (Thyroid-Stimulating Hormone (TSH), Serum Follicle-Stimulating Hormone (FSH), Serum Luteinizing Hormone (LH), Serum

Prolactin, Serum Free Triiodothyronine (FT3), and Serum Free Thyroxine (FT4) and prolactin) was available for review were included and those with incomplete hormonal profile were excluded from study. Data about various hormonal levels was collected from hospital records. It was made sure to only include those patients whose fasting venous blood samples were drawn during the early follicular phase (between days 3 to 5) of the menstrual cycle.

Hormonal measurements were performed using the chemiluminescence immunoassay (CLIA) method, as documented in the hospital records. Reference ranges for each hormone were noted according to standard laboratory guidelines. Based on available thyroid function test results and corresponding clinical features noted in the records participants were retrospectively classified into categories including euthyroid, subclinical hypothyroidism, clinical hypothyroidism, subclinical hyperthyroidism, and clinical hyperthyroidism.

Statistical analysis was performed using SPSS version 23.0. Descriptive statistics were used to summarize demographic and clinical variables. Comparative and correlational analyses were conducted to assess associations between TSH, FSH, LH, prolactin, and infertility type. A p-value <0.05 was considered statistically significant.

Results

The analysis of demographic and clinical characteristics between primary and secondary infertility cases revealed statistically significant differences. Women with primary infertility were predominantly younger, with nearly half (47.78%) in the 18–25 years age group, whereas secondary infertility was more common in the 26–30

Table 1 Comparison of Age, Duration Since Marriage, and History of Menstrual Irregularity Between Primary and Secondary Infertility Groups

Parameters		Primary Infertility (n=90)		Secondary Infertility (n=50)		p-value
		Number of cases	%	Number of cases	%	
Age Group (years)	18–25	43	47.78	8	16	p<0.001*
	26–30	22	24.44	21	42	
	31–35	11	12.22	13	26	
	36–45	14	15.56	8	16	
	Total	90	100	50	100	
	Mean Age	24.12 +/- 5.4 years		29.32 +/- 7.68 years		
Duration Since Marriage	1-3 years	38	42.22	0	0	p<0.001*
	4-6 years	31	34.44	6	6.67	
	7-10 years	11	12.22	30	33.33	
	> 10 years	10	11.11	15	16.67	
	Total	90	100.0	50	100	
	Mean	4.94 ± 3.12 years		9.20 ± 2.16 years		
History Of Irregular Menstrual Cycles	Yes	52	58.75	15	32.50	0.002*
	No	38	41.25	35	67.50	
	Total	90	100	50	100	

*Statistically significant (p<0.05)

Table 2 Thyroid Function Test Results in Studied Cases

Hormonal Parameters	Euthyroid (n=105)	Hyperthyroid (n=15)	Hypothyroid (n=20)
FT3 (pg/mL)	2.28 ± 0.48	3.9 ± 0.76	1.12 ± 0.56
FT4 (ng/dL)	8.10 ± 2.50	16.20 ± 3.40	3.20 ± 1.25
TSH (mIU/L)	2.85 ± 1.50	0.18 ± 0.06	9.25 ± 1.10

Table 3 TSH, Prolactin, FSH,LH, Estrogen and Progesterone in Studied Cases

Variables	Mean	Standard Deviation
TSH (mIU/L)	4.09	0.88
Prolactin (ng/mL)	43.90	19.85
FSH (mIU/L)	3.82	1.72
LH (mIU/L)	12.05	10.58
Estrogen (ng/mL)	82.40	44.60
Progesterone (ng/mL)	14.10	4.55

years group (42.00%). The mean age was significantly lower in primary infertility cases (24.12 ± 5.4 years) as compared to secondary infertility cases (29.32±7.68 years) ($p<0.001$). The mean duration since marriage was significantly longer in secondary infertility cases (9.20 ± 2.16 years) as compared to primary infertility cases (4.94 ± 3.12 years) ($p<0.001$). Additionally, a history of irregular menstrual cycles was more prevalent among women with primary infertility (58.75%) than those with secondary infertility (32.50%), and this difference was statistically significant ($p=0.002$) (Table 1).

The analysis of hormonal parameters among studied cases showed significant differences in thyroid function markers. 105 (75%) patients were euthyroid whereas 15 (10.71%) cases were found to be hyperthyroid whereas hypothyroidism was seen in 20 (14.9%) cases. As expected TSH levels were markedly reduced in hyperthyroid women (0.18 ± 0.06 mIU/L) and significantly elevated in hypothyroid cases (9.25 ± 1.10 mIU/L) compared to euthyroid women (2.85 ± 1.50 mIU/L) (Table 2).

The analysis of various hormones in studied cases showed that the mean TSH and prolactin levels were 4.09 ± 0.88 mIU/L and 43.90 ± 19.85 ng/mL respectively. FSH levels averaged 3.82 ± 1.72 mIU/mL, while LH showed mean of 12.05 ± 10.58 mIU/mL. Estrogen and progesterone levels were 82.40 ± 44.60 pg/mL and 14.10 ± 4.55 ng/mL respectively (Table 3).

The analysis of the correlation between TSH and various reproductive hormones showed significant associations with prolactin, LH and FSH. A strong positive correlation was found between TSH and prolactin (Spearman's correlation coefficient =0.82143, $p<0.05$). On the other hand, TSH exhibited a significant negative correlation with LH (-0.73, $p<0.05$) and FSH (-0.41,

Table 4 Correlation of TSH with Prolactin, LH, FSH, Estrogen, and Progesterone

Hormones	Spearman's Correlation Coefficient	p-value
Prolactin (ng/mL)	0.82143	<0.05*
LH (mIU/L)	- 0.73	<0.05*
FSH (mIU/L)	-0.41	<0.05*
Estrogen (ng/mL)	- 0.201	>0.05
Progesterone (ng/mL)	-0.174	>0.05

p<0.05). However, the correlations between TSH and estrogen (-0.201, p>0.05) as well as progesterone (-0.174, p>0.05) were not statistically significant (Table 4).

Discussion

The current study evaluated the correlation between thyroid-stimulating hormone (TSH) and various reproductive hormones (prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estrogen, and progesterone) in women presenting with primary as well as secondary infertility. In this study out of 120 studied cases 105 (75%) patients were euthyroid. Hypothyroidism and hyperthyroidism were seen in 20 (14.9%) and 15 (10.71%) cases respectively. In a similar study Keerthana a *et al* reported hypothyroidism in 23.5% and hyperprolactinemia in 31% women presenting with infertility.[10] There was a significant positive correlation between TSH and prolactin levels in women presenting with infertility whereas negative correlations were found between TSH and LH, as well as between TSH and FSH. However, no significant correlations were observed between TSH and estrogen as well as progesterone.

Various previously done studies have reported elevated prolactin levels in hypothyroid patients to be secondary to increased thyrotropin-releasing hormone (TRH) stimulation. Fupare *et al* conducted a study to correlate thyroid hormones with FSH, LH and prolactin in infertility in the reproductive age group women.[11] For this purpose, the authors undertook a study comprising 120 women (80 were of primary infertility and 40 of secondary infertility) with infertility. The study found that Prolactin and TSH were positively correlated with each other. They were also negatively correlated with LH, FSH & T3 in infertile groups. The incidence of hypothyroidism in women with hyperprolactinemia was 25.5%. The mean serum prolactin concentration in the infertile cases with normal thyroid function was significantly higher (p<0.001) than the control group with normal thyroid function. The infertile women with hypothyroidism were found to have higher prolactin levels than the other three groups (the controls and the infertile subjects with euthyroid and hyperthyroidism) (p<0.001).The findings of this study reinforces the hypothesis that elevated TRH levels stimulate prolactin secretion consequently affecting reproductive function. Furthermore, Valvekar *et al*.[12] demonstrated a significant association between hypothyroidism-induced hyperprolactinemia and ovulatory dysfunction suggesting that routine screening for thyroid dysfunction could be beneficial in managing infertility.

This study found that there was a negative correlation of TSH and with LH and FSH. This reflects impaired gonadotropin release with increasing TSH levels. This inverse relationship may be secondary consequence of hyperprolactinemia as elevated prolactin suppresses gonadotropin-releasing hormone (GnRH) secretion thereby reducing LH and FSH levels.[13] Similar findings were reported by Sharma *et al*[14] who conducted a study of 150 infertile women. Serum LH, FSH, and estradiol were measured in all cases. The authors found a significant positive correlation between TSH and prolactin (p-value <0.05), whereas TSH showed a significant negative correlation with FSH and LH (p-value <0.05). There was an insignificant negative correlation between TSH and estrogen (D2) and progesterone (D21). The findings of this study confirmed the inhibitory effects of elevated prolactin secondary to hypothyroidism as reported by Sharma *et al*.[14] Similar negative correlation of TSH with FSH and LH has also been reported by the authors such as Conforti *et al*.[15] and Li *et al*.[16]

Interestingly, this study identified an insignificant correlation between TSH levels and estrogen and progesterone levels. This observation aligns with the study of Sharma S *et al* who demonstrated that direct correlations between TSH levels and estrogen or progesterone were relatively weak and inconsistent.[14] This inconsistent correlation of TSH with estrogen and progesterone may be due to multiple physiological mechanisms that override the isolated effects of TSH fluctuations.

This study also found substantial variability in hormone levels among infertile women notably elevated prolactin and LH concentrations. These variations underscore the importance of personalized diagnostic evaluations for management of women presenting with infertility. The elevated prolactin levels observed corroborate studies by Dhabe *et al*. who also reported prolactin's significant role in infertility.[17] In their study the authors found that Serum prolactin and hCG levels in infertile females were 33.96±11.46 ng/mL and 86.38±12.45 IU/L respectively . These values were statistically significantly high (p<0.05) as compared to prolactin and hCG levels in healthy controls. Similar higher

prolactin levels in cases of infertility have also been reported by the authors such as Lancu *et al*.[18] and Maiter *et al*.[19]

Given the substantial associations identified in this study, routine thyroid function screening, including TSH and prolactin assessments, appears indicated in infertile women. Recommendations by the American Thyroid Association also advocate evaluating thyroid status in infertility workups, supporting the clinical utility of findings of this study.[20]

Limitations of this study include its retrospective design and potential selection bias. Future prospective studies with larger sample size would enhance understanding of these hormonal interactions and further improve the understanding with respect to clinical management of infertility.

In conclusion, this study found a significant correlation between TSH and reproductive hormones in infertile women. A strong positive correlation existed between TSH and prolactin and negative correlation was found between TSH and LH/FSH. These findings suggest that even subclinical thyroid dysfunction may contribute to infertility, particularly through prolactin-mediated suppression of gonadotropins. Comprehensive endocrine evaluation should be considered essential in the diagnostic approach to female infertility.

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Anemia and Aggression Among Patients with Schizophrenia in Amino Gondohutomo A Hospital

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Abstract

Background: Anemia has been identified as a potential modifiable factor influencing aggression levels in individuals with schizophrenia.

Objective: To investigate the association between anemia and incidence of aggression in patients with schizophrenia in Amino Gondohutomo Psychiatric Hospital, Semarang, Indonesia.

Methods: A cross-sectional study was conducted between January 2022 and December 2023 on patients with schizophrenia in Amino Gondohutomo Psychiatric Hospital, Semarang, Indonesia. Subjects were selected using consecutive sampling technique, and individuals with affective mood disorder and lost to follow-up were excluded from the study. Data were obtained through patients' medical records, PANSS-EC scores, and hemoglobin measuring devices. Chi-square test and logistic regression were applied for statistical analyses.

Results: Of 100 participants, patients with schizophrenia presented with aggression were predominantly above 40 years old (26 patients, 81.3%), women (17 patients, 51.1%), and non-anemic (17 patients, 57.1%). Gender and anemia were significantly associated with aggression in patients with schizophrenia ($p<0.05$). Schizophrenic patients with anemia had a 7.68-fold greater risk (95% CI: 2.70–21.8) of aggression. Men with schizophrenia was associated with a 2.37-fold greater risk (95% CI: 1.00–5.60) of aggression.

Conclusion: Anemia and men seems to be risk factors of aggression in patients with schizophrenia. Further multicenter studies with larger sample size is needed to support this finding.

Keywords: Aggression, anemia, schizophrenia

Introduction

Schizophrenia is a severe psychiatric disorder characterized by symptoms such as delusions and hallucinations, affecting approximately 1% of the global population.[1] According to the 2018 Indonesian Basic Health Research, the prevalence of schizophrenia in Indonesia increased by 1.7 per million compared to the 2013 data.[2] During the acute phase, schizophrenia patients had either positive symptoms or negative symptoms. Positive symptoms such as delusions and auditory or visual hallucinations. As the symptoms begin to worsen, the patient's coping also becomes progressively worse. Anger and aggression made their delusions and hallucinations start to overtake their thinking and functioning. Patients become aggressive and threaten themselves and others. At this stage, inpatient care is often necessary to ensure stabilization and safety for both the patient and others.[3,4]

The patient with schizophrenia at the acute phase had increased dopaminergic activity but decreased serum iron. The BBB (Blood-brain barrier) is impermeable to iron. There is slow bidirectional transport of iron across the BBB. In schizophrenic patients, there is increased BBB permeability and decreased serum iron.[5] Iron deficiency anemia can affect dopamine receptor levels and disrupt sensitivity functions of brain regions leading to psychosis.[6] Poor perfusion caused by anemia also may lead to fatigue, decrease in stamina, dizziness, dyspnea, or syncope.[7] Megaloblastic anemia due to vitamin B12 deficiency can manifest with psychosis through mechanisms related to one-carbon metabolism and neurotransmitter synthesis.[8]

Jiang *et al*. found no significant association between anemia and cognitive function in schizophrenia patients.[9] A previous study conducted by Lee *et al*.[10] showed that iron deficiency anemia subjects had a significantly increased risk of psychiatric disorders, including panic disorder, sleep disorder, and psychosis. However, data on the association between anemia and aggression in patients with schizophrenia are scarce. The purpose of this study was to investigate the association between anemia and the incidence of aggression in patients with schizophrenia.

Methods

This observational analytic study with a cross-sectional design was conducted at Dr. Amino Gondohutomo Psychiatric Hospital in Semarang between January 2022 and December 2023. A total of 100 inpatients diagnosed with schizophrenia were included using a consecutive sampling method. The inclusion criteria were patients admitted with a diagnosis of schizophrenia during the study period who had experienced psychiatric symptoms for at least two years. Patients with affective mood disorders or those lost to follow-up were excluded from the study.

The target population for this study was all individuals diagnosed with schizophrenia, while the accessible population comprised schizophrenic inpatients at Dr. Amino Gondohutomo Psychiatric Hospital within the defined period. The sample size of 100 was obtained through consecutive sampling based on the specified inclusion and exclusion criteria.

Data were obtained through interviews, patients' medical records, hemoglobin measuring devices, and PANSS-EC. Each subject's hemoglobin level was examined using a hemoglobin measuring device. Patients were categorized into two groups: those with anemia (hemoglobin <11 g/dL) and those without anemia (hemoglobin ≥11 g/dL). PANSS-EC scores were used by evaluating each sign on a scale from 1 to 7. Participants were categorized into schizophrenia patients with aggression (PANSS-EC score ≥20) and without aggression (PANSS-EC score <20).

Data were analyzed using descriptive analysis and presented in frequency and percentages. Hypothesis test was performed to determine the *p* value using chi-square test and logistic regression. Ethical clearance was obtained from the This study received ethical approval from the Health Research Ethics Committee of Dr. Amino Gondohutomo Psychiatric Hospital, Semarang (Reference number: 420/1116).

Results

Table 1 summarizes the demographic and clinical characteristics of the study participants. Among patients with schizophrenia who exhibited aggression, the majority were over 40 years old (26 patients, 81.3%), female (17 patients, 51.1%), and non-anemic (17 patients, 57.1%). Comparable results were found regardless of the marital and occupational status (16 patients, 50.0%).

Table 2 presents the association between participant characteristics and no aggression, as measured by the PANSS-EC score. A chi-square test with continuity correction was used to calculate the prevalence ratio (PR), confidence intervals (CI), and identify variables with statistically significant associations to be included in the logistic regression model. Gender (PR 2.37, 95% CI [1.00–5.60]; p= 0.047), marital status (PR 2.57, 95% CI [1.07–6.16]; p=0.031), and anemia (PR 7.68, 95% CI [2.70–21.80]; p=0.001) were significantly associated with aggression levels based on PANSS-EC. Age and occupational status were not significantly associated (p>0.05).

Logistic regression was carried out to determine the association between gender, marital status, and anemia, with PANSS-EC, as described in Table 3. Gender (95% CI [1.301–9.873]; p=0.014) and anemia (95% CI [3.298–32.634]; p<0.001) were risk factors of incidence of aggression based on PANSS-EC in patients with schizophrenia in Amino Gondohutomo Psychiatric Hospital.

Marital status, however, did not show a statistically significant association (95% CI

Table 1 Characteristics of Participants

Characteristics	Aggression*		No Aggression	
	(n=32)	%	(n=68)	%
Age				
<40 years old	26	81.3	48	70.6
>40 years old	6	18.8	20	29.4
Gender				
Men	15	46.9	46	67.6
Women	17	53.1	22	32.4
Marital Status				
Married	16	50.0	49	72.1
Unmarried	16	50.0	19	27.9
Occupational Status				
Employed	16	50.0	36	52.9
Unemployed	16	50.0	32	47.1
Anemia				
Anemic	15	46.9	7	10.3
Non-Anemic	17	53.1	61	89.7

Note: Aggression is defined as a PANSS-EC score≥20

[0.787–5.714]; p=0.137).

Discussion

Symptoms of aggression in patients with schizophrenia including poor control of impulses, tension, hostility, uncooperativeness, and aggressive behavior, can be measured using the validated subscale of PANSS score, namely PANSS-EC. Each item is scored from 1 to 7, and a total score of more than 20 is considered indicative of acute aggression.[12] Prevalence of aggression and factors associated with aggression were essential to effectively

Table 2 Association Between Characteristics of Participants and No Aggression Based on PANSS-EC

Variable	PANSS-EC		Total	p-value	PR (95% CI)
	(n=68)	%			
Age				0.257	1.80 (0.64–5.05)
<40 years old	48	70.6	74		
>40 years old	20	29.4	26		
Gender				0.047*	2.37 (1.00–5.60)
Men	46	67.6	39		
Women	22	32.4	61		
Marital Status				0.031*	2.57 (1.07–6.16)
Married	49	72.1	35		
Unmarried	19	27.9	56		
Occupational Status				0.748*	1.12 (0.48–2.60)
Employed	36	52.9	48		
Unemployed	32	47.1	52		
Anemia				0.001*	7.68 (2.70–21.8)
Anemic	7	10.3	22		
Non-Anemic	61	89.7	78		

Note: p-values are from Chi-square tests between groups; *statistically significant (p <0.05)

Table 3 Logistic Regression Analysis of Variables Associated with Aggression Based on PANSS-EC

Variables	p-value	PR	95% CI
Gender	0.014*	3.583	1.301–9.873
Marital Status	0.137	2.121	0.787–5.714
Anemia	<0.001*	10.375	3.298–32.634

Note: Statistically significant results (p<0.05)

control the risk of aggression in patients with schizophrenia. Previous study stated that aggression in patients with schizophrenia was associated with severe psychotic symptoms, substance abuse, previous history of violence, men, young age, unmarried status, and poverty.[13]

Out of 100 patients with schizophrenia involved in this study, 46 (67.6%) of 68 patients without aggression were men. Furthermore, 15 (46.9%) of 32 patients with aggression were men, compared to 17 women (53.1%). In this study, gender was associated with aggression in patients with schizophrenia (p <0.05), and men with schizophrenia was associated with a 2.37-fold greater risk (95% CI: 1.00–5.60) of aggression. Similar results were found in a previous study in England which stated that there was significant association between men with physical aggression (49.2%), assault attack (21.2%), and violence behavior against others (11.8%).[14] On the contrary, a study conducted by Krakowski stated that there were no significant gender differences in incidence of aggression. This result might be due to similar percentage of men and women in the study. Another previous study also reported that women experienced higher verbal violence and early disclosure of physical violence. Positive psychotic symptoms in women and men were associated with violence incidence. Physical violence was found to be more common in men, related to addiction of substance, criminal acts, and history of school truancy.[15]

Anemia can manifest in neuropsychiatry symptoms, including mood disorder, anxiety disorder, sleep disorder, and psychosis. Iron deficiency anemia, typical nutrient deficiency anemia, can present with fatigue, dizziness, or immune disorder. Iron is essential for every living organism to deliver oxygen, cellular respiration, immune system, neurotransmitter metabolism, and DNA synthesis.[13] A previous study reported that iron deficiency anemia was significantly associated with negative symptoms in patients with schizophrenia.[16]

Out of 100 patients with schizophrenia in this study, 61 (89.7%) of 68 patients without aggression had no anemia. Furthermore, 17 (53.1%) of 32 patients with aggression had no anemia, compared to 15 anemic patients (46.9%). Anemia was significantly associated with aggression in patients with schizophrenia (p<0.05). In addition, anemia in patients with schizophrenia had a 7.68-fold greater risk (95% CI: 2.70–21.8) of aggression. This study concludes that anemia influences the incidence of aggression in schizophrenia. So tailor-made management for schizophrenia patients is needed, especially for screening anemia.

Iron deficiency anemia is associated with schizophrenia related to dopamine receptor level and disrupt sensitivity function of brain region resulting in psychosis. Iron deficiency anemia also aggravates myelination in brain and monoamine metabolism disruption.[6] A previous study showed that iron deficiency anemia affects glutamate and GABA neurotransmitter homeostasis resulting in cognitive, memory, and behavioral disorder, as well as emotional and psychological disorder.[17] On the other hand, anemia is also a side effect of drugs that control psychosis and affect the production and longevity of red blood cells leading to anemia. Furthermore, lifestyles such as malnutrition and unhealthy eating habits can make inadequate intake of iron, vitamin B 12 and folate contribute to the development of anemia. This correlation between drug and lifestyle with aggression in schizophrenia patients can be conducted in future studies.

This study has several limitations. It was conducted at a single center and involved a relatively small sample size, which may limit the generalizability of the findings. Future multicenter studies with larger cohorts are necessary to further explore the relationship between anemia and aggression, and to evaluate other contributing factors, such as medication effects, nutritional deficiencies, and comorbid medical conditions. In conclusion, this study identified anemia and

male gender as significant risk factors for aggression in patients with schizophrenia at Amino Gondohutomo Psychiatric Hospital.

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Original Article

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Predictors of In-Hospital Mortality in Patients with Infective Endocarditis: A Single-Center Study

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Abstract

Background: Infective endocarditis remains a life-threatening condition with high in-hospital mortality, necessitating identification of predictive clinical factors.

Objective: To identify predictors of in-hospital mortality in infective endocarditis (IE) patients.

Methods: This single-center retrospective study included 88 patients with IE aged ≥ 18 years treated at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, between September 2019 and May 2023. During hospitalization, data regarding clinical characteristics, blood cultures, and clinical outcomes were assessed to identify the predictors of in-hospital mortality. Data were analyzed using chi-square and binary logistic regression.

Results: Among 88 patients with IE, the majority were male (56.8%) and aged < 60 years old (78%). More than two-thirds of patients had valvular heart disease. During treatment, 22 patients (25%) underwent cardiac surgery, and the total in-hospital mortality rate was 35.2%. Although not statistically significant, in-hospital mortality rate was lower in operated patients (22.7% vs 39.4%). In multivariate analysis, septic shock was the only significant predictor of in-hospital mortality (OR 40, 95% CI: 4.7–339, p<0.001)

Conclusion: Septic shock is a strong predictor of in-hospital mortality among patients with infective endocarditis. Invasive management by cardiac surgery does not significantly decrease the mortality risk.

Keywords: Infective endocarditis, in-hospital mortality, septic shock

Introduction

Infective endocarditis (IE) is a rare yet potentially life-threatening disease which involves the endocardial surface.[1] Recent data shows that the annual incidence of infective endocarditis (IE) worldwide is estimated to be 3-10 cases per 100,000 persons per year, with a continual increase observed each year.[2,3] In spite of the advancements in diagnostic capability, enhanced antimicrobial treatments, and improved techniques for surgical intervention in the modern era, infective endocarditis continues to be a dynamically developing condition with sustained high rates of mortality and morbidity.[4]Current evidence suggests an in-hospital mortality rate of around 20%, with a 6-month mortality rate of approximately 30%, rising to as high as 51% at 10 years, even with modern treatment.[5–7]

The epidemiological features of IE have shifted lately due to the changes in medical approaches and demographic changes.[1]

Previous studies have revealed significant differences in developing countries, characterized by higher rates of culture-negative infective endocarditis (IE), zoonotic infections, and increased mortality, with considerable regional variations. However, data on IE in developing countries, especially in South-East Asia, remain scarce.[2] There is a lack of information regarding the incidence of Infective Endocarditis (IE) in Indonesia, as well as information on mortality rates and factors influencing the mortality. Analyzing mortality rates and identifying predictors for fatal outcomes is crucial for recognizing modifiable factors and understanding treatment patterns to enhance overall outcomes. This approach aids in recognizing patients at the highest risk of death, guiding the necessity for escalated care interventions. Therefore, this study aimed to describe the clinical characteristics of patients with IE and to identify predictors of in-hospital mortality.

Methods

This was a retrospective and single-center study that included all consecutive IE patients aged ≥ 18 years old hospitalized in Dr. Hasan Sadikin General Hospital between September 2019 to May 2023. The total of 88 patients diagnosed with definite and possible IE in accordance with the modified Duke criteria were included in this study. Demographic data, clinical characteristics, microbiological findings, as well as surgical procedures and hospitalization outcomes were retrieved from the patient's medical records.

A multivariate analysis was performed on factors with a p-value of <0.05 in the univariate analysis to find the independent predictor of in-hospital mortality. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics software, version 27. This study was approved by the Health Research Ethics Committee of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia (Ethical approval number: LB.02.01/X.6.5/101/2020).

Results

Between September 2019 until May 2023, there were 88 cases of definite and possible IE that were hospitalized in RSUP Dr. Hasan Sadikin based on modified Duke Criteria. Among the participants, 56.8% of the participants (50 patients) were male, while the remaining 43.2% (38 patients) were female. with the mean age was 43.47 ± 16.92 years. Baseline characteristics of the patients are summarized in Table 1.

Most patients (95.5%) had native valve involvement. Of all patients, 28.4% of patients exhibited congenital heart disease. Additionally, over two-thirds of the patients (68.2%) had underlying valvular heart disease, with only 9.1% suffering from rheumatic heart disease. Diabetes mellitus affected 4.5% of patients, while 20.5% were diagnosed with hypertension. Moreover, 9.1% of patients on hemodialysis therapy, and 5.7% were identified as intravenous drug users.

In this study, the predominant complication observed among the subjects was heart failure, affecting 51.1% of the cases. Other complications included stroke in 17%, septic shock in 15.9%, glomerulonephritis in 10.2%, vasculitis in 4.5%, spondylodiscitis in 3.4%, and pulmonary embolism in 2.3% of the cases.

A total of 67% of the cases exhibited negative blood cultures. The most frequently isolated microorganisms were Streptococci (12.5%) and coagulase-negative staphylococci (8%).

The in-hospital mortality rate in this study was 35.2% (31 patients). Among the 22 patients who underwent cardiac surgery, 5 experienced in-hospital mortality, while 17 survived. For the 66 patients treated solely with medical treatment, 26 experienced in-hospital mortality, with 40 patients surviving. Although not statistically significant, in-hospital mortality rate was lower in operated patients (22.7% vs 39.4%) shown in Table 3. Univariate analysis showed that diabetes mellitus, septic shock, and spondylodiscitis were significantly associated with in-hospital mortality. However, multivariate analysis (Table 2) identified only septic shock as an independent predictor of in-hospital mortality (OR 40, 95% CI 4.7–339, p<0.001).

Discussion

In the current study, a notable finding indicates that septic shock emerged as the significant predictor in-hospital mortality. Among the 88 patients included, 14 (15.9%) experienced septic shock, with only one surviving. This finding aligns with Marques *et al*., where 20% of infective endocarditis (IE) cases were associated with septic shock, attributing one-third of the mortality.[8] Similarly, Ayad *et al*. demonstrated a statistically significant association between septic shock and mortality (p=0.01).[9]

Table 1 Characteristics of Patients with Infective Endocarditis and Their Association with In-Hospital Mortality (Univariate Analysis)

Characteristics	Total (n=88)	Univariate		
		Died (n=31)	Survived (n=57)	p-value
Age >60 years	19 (21.6%)	9 (29%)	10 (17.5%)	0.327
Sex				
Male	50 (56.8%)	18 (58.1%)	32 (56.1%)	1.000
Female	38 (43.2%)	13 (41.9%)	25 (43.9%)	
Predisposing conditions				
Prosthetic valve	4 (4.5%)	2 (6.5%)	2 (3.5%)	0.611
Congenital heart disease	25 (28.4%)	5 (16.1%)	20 (35.1%)	0.102
Valvular heart disease	60 (68.1%)	25 (80.6%)	35 (61.4%)	0.107
Rheumatic heart disease	8 (9%)	3 (9.7%)	5 (8.8%)	1.000
Diabetes mellitus	4 (4.5%)	4 (12.9%)	0 (0%)	0.013
Hypertension	18 (20.4%)	7 (22.6%)	11 (19.3%)	0.93
On Hemodialysis	8 (9%)	5 (16.1%)	3 (5.3%)	0.124
IV drug users*	5 (5.7%)	3 (9.7%)	2 (3.5%)	0.34
Complications				
Heart failure	45 (51.1%)	17 (54.8%)	28 (49.1%)	0.772
Septic shock	14 (15.9%)	13 (41.9%)	1 (1.8%)	<0.001
Glomerulonephritis	9 (10.2%)	5 (16.1%)	4 (7%)	0.269
Spondylodiscitis	3 (3.4%)	3 (9.7%)	0 (0%)	0.041
Vasculitis	4 (4.5%)	3 (9.7%)	1 (1.8%)	0.123
Pulmonary embolism	2 (2.27%)	1 (3.2%)	1 (1.8%)	1.000
Stroke	15 (17%)	7 (22.6%)	8 (14%)	0.471
Culture Findings				
Staphylococcus aureus	1 (1.1%)	0 (0%)	1 (1.8%)	1.000
CoNS*	7 (7.9%)	2 (6.5%)	5 (8.8%)	1.000
Streptococci	11 (12.5%)	4 (12.9%)	7 (12.3%)	1.000
Enterococci	2 (2.27%)	1 (3.2%)	1 (1.8%)	1.000
Gram negative bacteria	4 (4.5%)	3 (9.7%)	1 (1.8%)	0.123
Gram positive bacteria	1 (1.1%)	0 (0%)	1 (1.8%)	1.000
Negative culture	59 (67%)	20 (64.5%)	39 (68.4)	0.893
Treatment				
Cardiac surgery	22 (25%)	5 (16.1%)	17 (29.8%)	0.246

Notes: IV: intravenous; CoNS: *coagulase-negative staphylococci*

Table 2 Multivariable Logistic Regression Analysis of Predictors for In-Hospital Mortality in Patients with Infective Endocarditis

Variable	p-value	Odds Ratio (OR)	95% Confidence Interval (CI)
Septic shock	<0.001	40	4.7-339
Spondylodiscitis	0.999	1	
Diabetes mellitus	0.999	1	

Table 3 Management Type and In-Hospital Mortality in Patients with Infective Endocarditis

Treatment	In-hospital Death		Total
	Yes (%)	No (%)	
Cardiac surgery	5 (22.7)	17 (77.3)	22
Only medical treatment	26 (39.4)	40 (60.6)	66

Septic shock remains a concerning and potentially fatal condition, with mortality rate often exceeding 40%. While infective endocarditis (IE) primarily affects the inner surface of the heart, particularly the heart valves, it also manifests as a bloodstream infection, clinically characterized by the presence of sepsis-related signs and symptoms. With IE being the primary site of infection, the development of sepsis can lead into subsequent progression to septic shock. The mortality of septic shock depends on many factors, for instance the type of organism that causes severe sepsis.[10] A large meta-analysis of 510 studies reported that gram-negative bacteremia was associated with a higher mortality compared with gram-positive bacteremia. The most common bloodstream infections were due to coagulase-negative Staphylococcus and E. coli.[11]

The observed in-hospital mortality rate of 35.2% in this study is higher than the reported range in the literature (15–32%).[12–17] Despite the inherent surgical risks in IE patients, current evidence indicates that surgical intervention may confer a survival advantage of up to 20% in the first year. The recent guidelines recommend surgical intervention for patients with acute infective endocarditis, especially in those experiencing heart failure, uncontrolled infection, or presenting a high risk or established embolism.[18] Notably, this center deviates from the approach seen in other institutions, where cardiac surgery is employed in 40-69.7% of cases.[13,14,16] At this center, cardiac surgery is conducted in only 25% of cases. Some of the patients with guideline-recommended indications for surgery are not actually operated. Among the reasons given are poor prognosis irrespective of treatment, hemodynamic instability, death before surgery, and refusal for surgery.

In this study, although management by cardiac surgery was associated with a lower mortality rate (22.7% vs 39.4%), it was not statistically significant in univariate analysis, and management by cardiac surgery did not remain as a factor of better prognosis in the multivariate analysis (OR 0.452, 95% CI 0.149-1.377, p=0.246). This result aligns with the findings of Delahaye *et al*. in 2007, which stated that although surgery showed a lower mortality rate (14.4% vs 19.3%), this difference did not reach statistical significance in the univariate analysis. Furthermore, in their multivariate model, surgery did not remain a significant factor for a better prognosis (OR: 0.723, 95% CI 0.388-1.349).[19] However, this contrasts with findings by Marques *et al*. study in Italy, which indicated that cardiac surgery served as a main protective factor against mortality.[8] Moreover, Krajinovic *et al*. research in 2018 demonstrated that management by cardiac surgery had a favorable impact not only in in-hospital mortality but also on the one-year follow-up of IE patients with sepsis and septic shock. However, among patients without sepsis, there was no significant difference between those undergoing cardiac surgery and those receiving only medical treatment.[10]

The key to diagnosing infective endocarditis lies in identifying the responsible microorganisms, primarily through blood

cultures. This process is essential for promptly initiating targeted antimicrobial therapy specific to the identified organism. Unfortunately, this study revealed that microbial presence was not identified in two-thirds of the patients. Similar to the study done by Zhang *et al*., blood cultures were negative in 56.7% of cases.[20] A potential reason for the observed low detection rate in this study could be attributed to the administration of antibiotics before blood collection, fastidious slow-growing microorganisms or by truly non-cultivable intracellular bacteria, and errors during sample collection.[21–23]

This study holds strength as research in infective endocarditis is relatively scarce, particularly within Indonesia. This study also stands as one of the few focusing on the predictors of in-hospital mortality in patients with infective endocarditis in Indonesia. However, this research presents certain limitations that warrant consideration. Firstly, its execution within a tertiary care center introduces the possibility of referral bias, potentially skewing the findings toward more severe cases or specific demographics within that setting. Additionally, the sample size in this study was relatively limited, which could impact the generalizability of the results to broader populations. Another constraint arises from its retrospective design, relying solely on available data within medical records, which may lack comprehensive information or have inherent inconsistencies. Moreover, this study did not perform specific analyses related to sex or gender differences. As such, potential variations in clinical outcomes between male and female patients were not explored and remain an area for future investigation.

In conclusion, despite advances in antimicrobial and surgical therapies, IE remains a challenging condition with high in-hospital mortality. In this study, in-hospital mortality rate remained high (35.2%). Septic shock was a strong predictor of in-hospital mortality in this study, and independently increased the risk of in-hospital mortality of infective endocarditis patients. Nevertheless, invasive management by cardiac surgery did not significantly decrease the mortality risk.

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Case Report

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General Anesthesia Management of Super Refractory Status Epilepticus in Anti-N-Methyl-D-Aspartate-Receptor (NMDAR) Meningitis

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Abstract

Background: Super Refractory Status Epilepticus poses significant management challenges, requiring intensive therapeutic approaches including general anesthesia.

Objective: To discuss the management of Super Refractory Status Epilepticus (SRSE) with general anesthesia to control seizures.

Case Illustration: A 17-year-old female with tonic-clonic seizures, headache, unclear speech, and a change in behavior, who also appeared to be restless, was presented. She was admitted to the intensive care unit and administered anticonvulsant medication. A brain MRI with contrast showed the impression of meningitis, and cerebrospinal fluid examination showed a positive anti-NMDAR result. First-line therapy involved high-dose steroids and intravenous immunoglobulin for 5 days, followed by second-line therapy with rituximab. Patient received general anesthesia using sevoflurane volatile, dexmedetomidine, continuous rocuronium, propofol, ketamine, and fentanyl due to persistent seizures despite receiving anticonvulsant therapy. Monitoring was conducted for vital signs, seizure activity, and depth of anesthesia using the bispectral index (BIS). Tonic-clonic seizures in patients were successfully managed with general anesthesia. However, facial dyskinesia was still present despite the administration of general anesthesia. Facial dyskinesia worsened upon discontinuation of continuous rocuronium.

Conclusion: General anesthesia could be used in the management of SRSE with the aim of controlling seizures and preventing complications arising from continuous seizures.

Keywords: Anesthesia, Anti N-Methyl-D-Aspartate-Receptor, convulsion, super refractory status epilepticus

Introduction

Super Refractory Status Epilepticus (SRSE) is a severe and life-threatening medical condition characterized by seizures lasting 24 hours or more despite anesthesia treatment or when the anesthesia therapy dose is reduced. It affects 23–43% of patients and is linked to significant morbidity and mortality rates of 30–50%. SRSE can result from various central nervous system insults, including stroke, infection, or trauma.[1,2]

Encephalitis with anti-NMDAR antibodies can lead to the occurrence of SRSE. Therefore, in addition to immunotherapy, management for seizures is also required. Management of SRSE using general anesthesia may involve a combination of volatile and intravenous anesthesia.[2] Identifying the underlying cause of SRSE is also essential, along with the administration of general anesthesia to control seizures and to prevent potential

complications.[1,2] This case report presents a 17-year-old female patient with SRSE secondary to anti-NMDAR encephalitis, successfully managed with general anesthesia in the intensive care unit.. This study aims to explore the role of general anesthesia in managing SRSE due to anti NMDAR meningitis and the clinical challenges encountered.

Case

A 17-year-old female presented to the Emergency Department at Premier Bintaro Hospital in November 2023 with a one-week history of tonic-clonic seizures and headaches. The patient was also reported to be restless, speaking unclearly, and experiencing hallucinations. On physical examination, the patient was conscious and compos mentis, with blood pressure of 103/70 mmHg, pulse rate of 88 beats per minute, temperature of 36.9 degrees Celsius, and oxygen saturation of 100% on room air. Neurological examination did not reveal neck stiffness. Motor strength in both right and left extremities was 4/4, and no pathological reflexes were detected. Brain MRI without contrast was within normal limits. The patient was admitted to the intensive care unit and received intravenous phenytoin 200 mg in 50 mL of 0.9% NaCl, as well as oral valproic acid 3 times a day at 5 mL each.

On the seventh day of intensive care treatment, the patient experienced shortness of breath with desaturation and an increased work of breathing. The patient's consciousness became delirious, and vital signs revealed a blood pressure of 118/72 mmHg, a heart rate of 105 beats per minute, respiratory rate of 35-42 breaths per minute, and oxygen saturation of 81% with a non-rebreather mask (NRM) at 15 lpm. Arterial blood gas (ABG) analysis indicated venous impression with a pH of 7.41, pCO2 of 46.4 mmHg, pO2 of 39 mmHg, HCO3 of 30 mEq/L, BE of 5 mEq/L, and SaO2 of 73%. Subsequently, intubation and mechanical ventilation were initiated using PSIMV mode and sedation with midazolam at 2 mg/hour, along with analgesia using fentanyl at 300 mcg/day.

After the initiation of mechanical ventilation and sedation, there were no further tonic-clonic seizures, but there were still facial dyskinesia and myoclonic movements in both of the patient's hands. On the 12th day of treatment, spontaneous breathing efforts were observed in the patient, leading to a transition to spontaneous ventilation mode, and a decision was made to proceed with extubation. Following extubation, twitching movements were still observed. However, on the 13th day of treatment, the patient experienced focal seizures >7 times, leading to a diagnosis of status epilepticus. The patient was administered an additional anticonvulsant, intravenous phenobarbital at 700 mg over 30 minutes. Amidst the phenobarbital administration, there was another focal seizure lasting less than 1 minute, followed by oxygen desaturation. Consequently, endotracheal intubation was performed, and oxygen was administered via an endotracheal tube using the pressure support ventilation (PSV) mode, with a respiratory rate of 15 breaths per minute, PEEP of 6 cmH2O, FiO2 of 80%, tidal volume of 450 mL. Additionally, maintenance sedation was provided with fentanyl at 300 mcg/day and midazolam at 2 mg/hour.

While intubated, twitching persisted in the patient's eyelids and hands, prompting the decision to administer general anesthesia to manage the refractory seizures. On 14th day of treatment, the regiment of sedation changed into propofol 2mg/kg/hour and fentanyl 300 mcg/day. On the same day volatile anesthesia with sevoflurane at 9 mL/hour was initiated because the patient still has recurring seizures. On 17th day of treatment, dexmedetomidine 0.5 mcg/kg/hour was added to anesthesia regiment.

Despite general anesthesia, seizures continued, leading to the addition of continuous rocuronium at 30 mg/hour. Intravenous bolus doses of rocuronium at 10 mg were given if seizures persisted. Throughout general anesthesia, the depth of anesthesia was monitored using the Bispectral Index (BIS). The patient was diagnosed with super-refractory status epilepticus (SRSE) secondary to NMDAR meningitis. The patient was consulted to a hemato-oncology internal medicine specialist and planned to receive intravenous rituximab at 500 mg as a second-line therapy for NMDAR. During the administration of rituximab, the patient's condition remained stable, and there were no seizures. On the 20th day of treatment, continuous rocuronium was discontinued. When continuous rocuronium was stopped, the patient experienced twitching 16 times, prompting the administration of a 10 mg bolus of rocuronium, followed by the administration of ketamine at 2 mg/kg/hour. The administration of propofol and dexmedetomidine was stopped.

On the 23rd day of treatment, the patient

Table 1 Summary of Patient Progression

Day	Clinical Event
Day 0 (Admission)	17-year-old female presented with tonic-clonic seizures, headache, hallucinations; admitted to ICU; started on IV phenytoin and oral valproic acid.
Day 7	Developed shortness of breath and delirium; intubated and placed on mechanical ventilation; started sedation with midazolam and fentanyl.
Day 12	Spontaneous breathing observed; patient extubated; persistent twitching noted.
Day 13	Experienced >7 focal seizures; diagnosed with status epilepticus; reintubated; added IV phenobarbital.
Day 14	Seizures refractory to treatment; initiated general anesthesia with propofol, fentanyl, and sevoflurane.
Day 17	Dexmedetomidine added to anesthesia regimen; seizures persisted; continuous rocuronium infusion started.
Day 20	First dose of rituximab administered; seizures controlled; continuous rocuronium discontinued.
Day 23	Desaturation and apnea after rocuronium bolus; anesthesia adjusted; tracheostomy performed.
Day 29	Discontinuation of atracurium resulted in seizure recurrence; continuous atracurium restarted.
Day 31	Second dose of rituximab administered.
Day 33	Hypotension, fever, persistent twitching; vasopressor (norepinephrine) initiated; anesthesia regimen adjusted.
Day 34	Developed septic shock.
Day 36	Patient passed away.

experienced desaturation and apnea after receiving a bolus of rocuronium 10 mg. The patient's tidal volume on the ventilator was not achieved, leading to manual bagging, and the ketamine drip was stopped. A consultation with an Ear, Nose, and Throat (ENT) specialist was initiated for tracheostomy, and the anesthesia regimen shifted to volatile sevoflurane at 6.5 mL/hour titrated gradually, dexmedetomidine at 0.5 mcg/kg/hour, and continuous rocuronium at 30 mg/hour.

A tracheostomy was performed by an ENT specialist, and the ventilator was switched to an intelligent ventilator with iASV mode, MV 194%, PEEP 6 cmH2O, FiO2 41%, tidal volume of 499 mL, with desired target of EtCO2 35-40 mmHg, and oxygen saturation 96-100%. The anesthesia regimen was adjusted to volatile sevoflurane at 7.5 mL/hour titrated gradually, with a bolus of sevoflurane at 0.5 mL. Continuous atracurium was administered at 30 mg/hour, along with ketamine at 0.2 mg/kg/hour, and fentanyl at 400 mcg/day.

On the 29th day of treatment, continuous atracurium was discontinued, but seizures recurred >8 times. Consequently, continuous atracurium was resumed. On the 31st day of treatment, the patient received the second dose of rituximab. Subsequently, on the 33rd day of treatment, there was hypotension, fever, and persistent twitching in the patient. Vasopressor support with norepinephrine at 0.08 mcg/kg/minute was initiated. The anesthesia regimen was adjusted to include fentanyl at 400 mcg/day, ketamine at 1.5 mg/kg/hour, propofol at 2 mg/kg/hour, and continuous rocuronium at 30 mg/hour. In the event of seizures, a bolus of rocuronium at 10 mg was administered.

On day 34, the patient entered septic shock, with elevated creatine kinase (CK 540 U/L), lactate >20 mmol/L, and persistent clinical deterioration. Despite comprehensive treatment, the patient passed away on the 36th day of hospitalization.

Discussion

Status epilepticus that occurred despite the administration of first and second-line

anticonvulsants is referred to as refractory status epilepticus, requiring management with general anesthesia to control the ongoing seizures. However, if status epilepticus persists or recurs for ≥24 hours despite anesthesia treatment or when the anesthesia therapy dose is reduced, it is termed super-refractory status epilepticus (SRSE).[1]

In this case, a 17-year-old patient presented with tonic-clonic seizures lasting for 5 minutes before admission to the hospital, accompanied by a history of recurrent headaches for the past week. The patient was administered with anticonvulsant, and the seizures stopped. However, the patient experienced focal seizures >7 times, leading to the diagnosis of status epilepticus. Consequently, multiple anticonvulsants were administered to control the seizures. However, the seizure persisted despite the administration of the multiple anticonvulsants, and the patient was diagnosed with refractory status epilepticus. Then, this patient was given general anesthesia to manage the ongoing seizures. Nevertheless, despite receiving general anesthesia, the seizures still occurred, leading to the diagnosis of super-refractory status epilepticus (SRSE).

Encephalitis linked to anti-NMDAR antibodies is a rare autoimmune disorder characterized by antibodies that target the GluN1 subunit of the NMDAR. This condition can impair synaptic glutamatergic networks in the brain, which are essential for learning, memory, and neuroplasticity. Neurological symptoms associated with this disorder may include short-term memory issues, seizures, movement disorders, central hypoventilation, and reduced consciousness, often requiring intensive care.[2,3]

The causes of autoimmune encephalitis can include tumors, infections, or remain unknown (cryptogenic). This condition is often regarded as a classic paraneoplastic syndrome, prompting a thorough clinical evaluation for any hidden malignancy in suspected patients. Certain tumors can produce peptides resembling those in the nervous system, resulting in immune cross-reactivity and paraneoplastic neurological syndromes. The immune system responds to these tumors with cytotoxic and antibody-mediated actions that target not only the tumor but also the nervous system. Underlying malignancies are primarily found in individuals aged 12 to 45, with the majority being ovarian teratomas (94%), followed by extraovarian teratomas (2%) and other tumor types (4%).[4,5]

In this patient, a cerebrospinal fluid examination was conducted with positive results for anti-NMDAR antibodies. ANA profile, anti-Ds-DNA, and anticardiolipin antibody tests were also performed to rule out the possibility of other causes of autoimmune encephalitis. However, the results of these tests were negative. Treatments for this autoimmune disorder involve immunomodulation and tumor removal. In this patient, an abdominal ultrasound (USG) and CT scan were conducted, with normal results and no evidence of tumors found. First-line immunotherapy includes the administration of high-dose steroids through intravenous infusion, intravenous immunoglobulin, and/or plasmapheresis.[4] High-dose steroids can penetrate the blood-brain barrier, contributing to the control of persistent seizure activity. They also help reduce brain edema and intracranial pressure. The recommended high-dose steroid is intravenous methylprednisolone at 1 gram per day for 3-5 days, followed by intravenous methylprednisolone at 1 mg/kg per day for 7 days or longer.[2,6] For intravenous immunoglobulin (IVIG), a dose of 400 mg/kg/day for 5 days can be administered.[6] If the patient does not respond to first-line therapy, second-line treatment with rituximab is initiated at a dose of 375 mg/m^2 weekly for 4 weeks.[1,4]

Encephalitis with anti-NMDAR antibodies can lead to the occurrence of SRSE. Therefore, in addition to immunotherapy, management for seizures is also required. Seizures in this patient are managed with the administration of anticonvulsants such as valproic acid, phenytoin, levetiracetam, and phenobarbital. First-line anticonvulsants include benzodiazepines (lorazepam, diazepam), phenytoin, and intramuscular midazolam. Meanwhile, second-line options consist of valproic acid and levetiracetam.[6] Despite the administration of both lines of anticonvulsants, the patient continues to experience seizures indicates that they are facing refractory status epilepticus (RSE).

In this case, the patient experienced status epilepticus with altered consciousness and oxygen desaturation, leading to intubation and sedation. General anesthesia was induced to manage seizures. In this patient, seizures and twitching persisted even under the influence of general anesthesia or when the anesthesia drug doses were reduced. This supports the diagnosis of super-refractory status epilepticus (SRSE).

The goals of managing SRSE are: (1) control seizures to prevent early excitotoxicity. After

24 hours of continuous or recurrent seizures, the excitotoxic process that can cause brain damage may have already begun. (2) Neuroprotection, to inhibit the development of secondary processes triggered by early excitotoxicity. (3) Avoiding or Treating Systemic Complications: SRSE treatment often involves prolonged anesthesia.

Management of SRSE with general anesthesia is the foundation of therapy to achieve a burst suppression period, which aids in the remodulation of receptors, allowing antiepileptic therapy to become effective. Typically, anesthesia is continued for the first 24 hours, and then gradual attempts are made to reduce the administered anesthesia dosage once seizures are under control.[1] Midazolam, along with pentobarbital and propofol, is one of the three primary medications utilized when first- and second-line treatments are ineffective. It works by binding to the chloride ionophore complex of the gamma-aminobutyric acid (GABA) receptor in the central nervous system (CNS). This binding leads to membrane hyperpolarization and an increased frequency of chloride channel openings, enhancing GABA's inhibitory effects. Additionally, midazolam influences glycine receptors, acting as a muscle relaxant while exhibiting predictable anxiolytic, amnestic, hypnotic, anticonvulsant, and sedative properties. Its relatively short half-life, due to its water-soluble nature, makes it an effective choice for fast-acting pharmacokinetics with a lower risk of toxicity. However, midazolam's rapid onset can lead to tachyphylaxis and hypotension, and prolonged use often requires larger doses to sustain its therapeutic effects.[1]

Intravenous propofol is the third of the three most commonly used anesthetic agents for managing SRSE. It acts as a powerful depressant of the central nervous system (CNS), reducing the dissociation of GABA from its receptors, which extends the duration of chloride channel openings and enhances inhibitory effects on neurons. Propofol offers better control of anesthesia than midazolam and pentobarbital, thanks to its rapid onset of action and quick recovery, even with prolonged use. Additionally, propofol has minimal serious drug interactions and a lower incidence of hypotension and cardiorespiratory depression compared to midazolam and pentobarbital.[1,2,7]

Prolonged infusion of propofol carries a risk of propofol infusion syndrome (PRIS) especially in children and patients undergoing concurrent steroid or catecholamine therapy. PRIS can result in severe metabolic acidosis, hyperkalemia, hyperlipidemia, rhabdomyolysis, cardiac dysfunction, and renal failure. Therefore, during extended use of propofol, it is important to monitor laboratory values, including serum levels of creatinine kinase, lactate, and lipids.[2] In this patient, inhalation anesthesia with volatile sevoflurane was also administered when other therapies for SRSE were unsuccessful. Volatile inhalational agents offer deep sedation and act as strong anticonvulsants, typically reserved for patients experiencing seizures that do not respond to conventional intravenous medications like benzodiazepines, propofol, barbiturates, and standard antiepileptic drugs.

Sevoflurane is a versatile inhalational anesthetic known for its rapid induction, easy control of anesthetic depth, quick recovery, favorable hemodynamic responses, and minimal irritation to the airway. Sevoflurane also can alter neurotransmission by strongly enhancing GABAergic inhibition while reducing NMDA glutamatergic activity. Adverse effects of volatile anesthetics can include dose-dependent hypotension, increased intracranial pressure, and arrhythmias, along with rare but serious complications such as malignant hyperthermia..[8,9,10]

The patient was administered ketamine, a potent NMDA receptor antagonist with equal affinity for various NMDA receptor types. As an anesthetic agent, ketamine is effective in the advanced stages of SRSE. Ketamine also acts as neuroprotective agent by inhibiting glutamate excitotoxicity induced by NMDA receptors and a good alternative to propofol. Ketamine has a low risk of cardiac depression and hypotension, making it the preferred agent in emergencies involving cardiocirculatory instability.[1,2]

In a study involving seven critically ill with SRSE, the use of ketamine achieved electroencephalographic control of seizures in 50% of cases without causing hemodynamic instability. Additionally, a retrospective study found that ketamine treatment in refractory status epilepticus resolved seizures in 57% of cases, terminated them in 32% of cases, and provided seizure control in approximately 13% of cases when administered intravenously.[1]

Additionally, ketamine should be avoided in patients with cerebral damage because it can raise intracranial pressure (ICP). Beyond increasing ICP, ketamine also elevates cerebral oxygen consumption and cerebral blood flow. In patients with SRSE, earlier initiation and longer infusion of ketamine may enhance its effectiveness and improve clinical

outcomes..[1,2,11] Neuromuscular blocking agent (NMBA) used to optimize the use of mechanical ventilation during endotracheal intubation. NMBAs induce skeletal muscle relaxation by inhibiting impulse transmission at the neuromuscular junction. Rocuronium is an intermediate-acting NMBA and the only nondepolarizing agent currently used for rapid sequence induction and intubation. It does not trigger histamine release and has minimal effects on hemodynamics. Continuous infusions of NMBAs, as opposed to intermittent boluses, have been reported to reduce the risk of prolonged paralysis. Most significantly, neuromuscular blockade can lead to prolonged immobility, which may result in acquired weakness, myopathy, pressure ulcers, nerve injuries, and an increased risk of deep venous thrombosis (DVT).[12]

Electroencephalography (EEG) is essential for adjusting medication doses and confirming the cessation of electrographic seizures. Maximal therapy should be continued for 12 to 24 hours after the last clinical or electrographic seizure, after which the dosage can be tapered. If seizures reoccur, therapy can be resumed or modified as needed..[4,13] However, limitations in the hospital's facilities prevent continuous EEG monitoring from being performed in the intensive care unit.

Seizure activity in this patient is monitored using the bispectral index (BIS), a quantitative EEG device that assesses the effects of anesthetics and sedative medications. BIS values between 40 and 60 indicate an appropriate level of general anesthesia. It is particularly sensitive for patients undergoing invasive procedures in the ICU, such as intubation, tracheostomy, chest tube placement, and bronchoscopy. BIS can also aid in monitoring seizures in patients receiving neuromuscular blockade, where clinical detection of seizures may be challenging. A BIS value of 30 can detect burst suppression with a sensitivity of 99% and specificity of 98%. However, it may not identify regional epileptic activity.[14]

This patient is also monitored for esophageal pressure, levels of lactate and creatinine kinase are also examined. Esophageal pressure monitoring is a straightforward bedside technique for estimating changes in pleural pressure, which can enhance the cardiovascular performance of critically ill patients receiving assisted ventilation. It provides the most accurate estimate of pleural pressure. [15]

During the ICU stay, there is a significant increase in the levels of lactate and creatinine kinase in this patient. This could be caused by seizures leading to metabolic stress. Whole-body muscle contractions and catecholamine release elevate oxygen demands in the brain, muscles, and heart, while impaired breathing hinders the body's ability to compensate for this increased demand. Stressed tissues release metabolites like lactate, ammonia, and urea, while damaged skeletal muscles leak creatine kinase (CK) and myoglobin. Serum lactate levels are elevated in 90% case of seizures. A conducted retrospective study and meta-analysis showed a significant elevation in CK after 48 hours in epileptic seizures.[16]

In this patient, seizures recurred when the anesthesia dosage was reduced. The occurrence of seizures during the dosage reduction phase necessitated the reintroduction of anesthesia. This can prolong the stay in the ICU and may lead to complications and could complicate the management of the primary condition.[1,2,5] In conclusion, the management of SRSE associated with anti-NMDAR meningitis requires a multimodal therapeutic approach, where general anesthesia serves as a cornerstone in controlling refractory seizures. This case highlights the complexity and high mortality associated with SRSE and emphasizes that early aggressive seizure control, combined with targeted immunotherapy, is critical to improving outcomes.

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Case Report

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Eribulin in Heavily Pre-Treated Metastatic Breast Cancer: A Case Series

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Abstract

Background: Treatment options are limited for heavily pre-treated metastatic breast cancer patients, with Eribulin showing promise in improving survival outcomes.

Objective: To evaluate Eribulin outcomes in patients with MBC. Metastatic or incurable diseases are observed in 4% to 10% of women despite advances in breast cancer treatment. To address this problem, EMBRACE, an important randomized phase III clinical trial was carried out by comparing eribulin to the treatment selected by physicians for individuals with previously treated locally recurrent or metastatic breast cancer (MBC). The results showed a significant and prolonged increase in median overall survival among patients treated with eribulin, compared to those who received the physician's selected treatment.

Case Series: This study presents three patients who showed favorable outcomes after treatment with eribulin, despite multiple lines of previous therapy. Patient 1 was diagnosed with triple-negative breast cancer and initially achieved remission before experiencing a recurrence involving a chest lesion and enlarged lymph nodes. After two cycles of eribulin, the patient showed significant improvement. Patient 2 developed brain and liver metastases following the completion of hormonal therapy, prompting the initiation of eribulin as the next line of treatment. Patient 3 had disease progression despite undergoing multiple lines of hormonal and chemotherapy. Eribulin was administered and patient remained stable.

Conclusion: Patients with MBC tend to have substantially favorable outcomes with eribulin chemotherapy even after extensive previous treatment.

Keywords: Breast cancer, eribulin, heavily pre-treated, metastases

Introduction

According to GLOBOCAN 2020 data, breast cancer is the most commonly diagnosed cancer worldwide and ranks as the fifth leading cause of cancer-related death, with an estimated 2.3 million cases.[1] Despite advances in treatment, metastatic or incurable diseases are observed in 4% to 10% of women. The three subtypes for treatment stratification are hormone receptor positive/human epidermal growth factor receptor 2 (HER2) negative (treated with endocrine targeted therapy and/or targeted therapy), HER2 positive (treated with HER2-directed therapy), and triple negative. Briefly, for patients presenting with hormone receptor–positive/HER2-negative MBC, early therapy relies on endocrine therapy either alone or in combination with agents targeting phosphoinositide 3-kinase, mechanistic target of rapamycin, or cyclin-dependent kinase [CDK] 4/6 inhibitors.

Chemotherapy is reserved for patients with hormone receptor–positive/HER2-negative MBC either refractory to endocrine therapy or for patients with extensive symptomatic visceral involvement. In this context, eribulin, a synthetic analog of halichondrin B, falls within the halichondrin class and serves as an inhibitor of microtubule dynamics. The drug has a distinctive binding site, setting it apart from other agents that target microtubules.[2-4] In the European Union, eribulin is approved for treating patients with locally advanced or metastatic breast cancer (MBC) whose disease has progressed following at least one previous chemotherapeutic regimen for advanced stages.

In the United States, eribulin is indicated for MBC following the failure of at least two prior chemotherapy regimens. In Japan, it is approved for inoperable or recurrent breast cancer. EMBRACE, an important randomized phase III clinical trial comparing eribulin to the treatment selected by physicians was carried out for individuals with previously treated locally recurrent or MBC. The results showed a significant and prolonged increase in median overall survival among patients treated with eribulin, compared to those who received the physician's selected treatment (13.1 months vs. 10.6 months, respectively; hazard ratio [HR], 0.81; 95% CI, 0.66-0.99; p=.041).[5] Until recently, eribulin use was limited in certain regions due to accessibility constraints. In 2023, eribulin was included under national universal health coverage in Indonesia, allowing broader clinical application in patients with MBC. Physicians can now observe and evaluate disease progression and assess potential side effects associated with eribulin chemotherapy, especially in Indonesia. This case series describes three patients with heavily pre-treated MBC who achieved favorable clinical outcomes with eribulin therapy. Treatment timelines are presented in Fig. 1.

Cases

Patient 1

A 48-year-old Chinese woman was admitted with a left breast lump and underwent modified radical mastectomy in 2015, without additional chemotherapy. Histopathology and immunochemistry was done and confirmed stage IIA triple-negative invasive breast cancer (ER-negative, PR-negative, HER2-negative). Medical and psychosocial history were remarkable, and there was no family history of breast cancer. Four years later, cancer recurrence occurred in the chest wall and was treated with four cycles of doxorubicin and cyclophosphamide, leading to complete remission.

One year later, a second recurrence in the chest wall was treated with paclitaxel and carboplatin, resulting in partial remission sustained for one year. Lung metastasis occurred one year after remission, and docetaxel chemotherapy was implemented, leading to partial remission. Another chest wall recurrence occurred after two years and radiotherapy was executed with a partial response. Four months after the end of radiotherapy, the patient developed progressive disease with left arm edema, chest wall lesions, and lymph nodes in the supraclavicular and axillary regions with PD-L1 expression >10%. Laboratory findings were

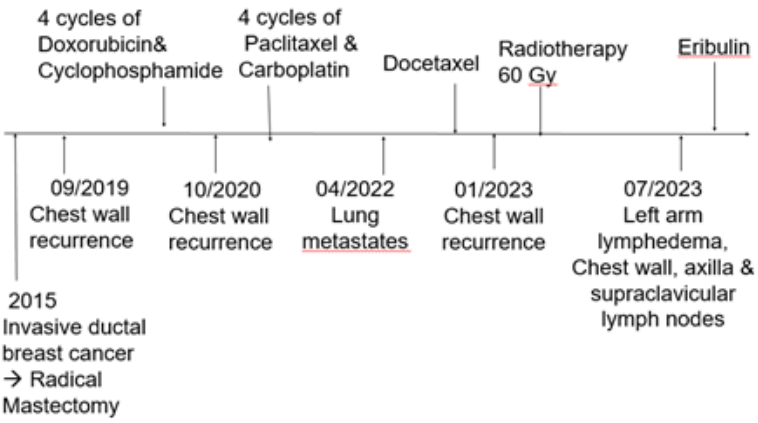

Fig. 1A. Timeline Case Report for Patient 1

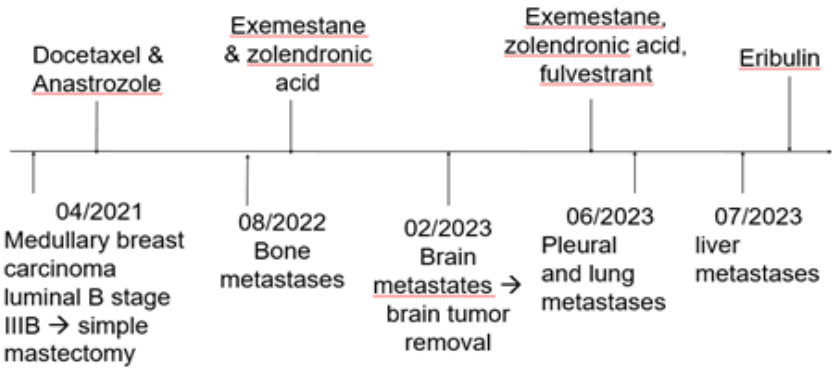

Fig. 1B. Timeline Case Report for Patient 2

within normal limit. On breast ultrasound showed solid lesion with cystic component 18x9x4.18cm on right parasternal extended to left parasternal. Treatment was carried out with eribulin chemotherapy (1.4 mg/m^2 day 1 and 8 every 21 days, administered as IV bolus 2–5 minutes) and granulocyte-colony stimulating factor (GCSF) support. After two cycles of eribulin treatment, the chest lesions improved and the axillary lymph nodes showed a decrease in size by> 50% as depicted in Fig. 2-3. The patient experienced grade I chills, constipation, and anemia as adverse events. The patient remained under follow-up for eight years (2015–2023) from initial diagnosis through eribulin therapy.

Patient 2

A 54-year-old Chinese woman was present with right breast lump. Past medical and psychosocial history were remarkable, and there was no family history of breast cancer. The patient diagnosed with luminal B stage IIIB medullary breast carcinoma in April 2021 and was subjected to simple mastectomy in October 2021. Treatment was carried out using docetaxel followed by anastrozole, and then 16 months later, bone metastasis occurred. Exemestane and zoledronic acid were administered for four months, after which fulvestrant was added. Two months later, the patient experienced a severe headache, and brain imaging showed metastases in left frontoparietalis sized 3.64 x 4.40 x 2.29cm. Brain tumor removal was performed three months after the diagnosis and one month later, pleural and lung metastases were detected on radiographic examinations.

The disease continued to progress, and a 1-month abdominal ultrasound examination showed liver metastasis on right right hepatic lobe, 1.42x1.27x1.32cm. She also had slight anemia [Hemoglobin 11.6g/dL [(normal value 12.3-15.3 g/dL)]. One month after

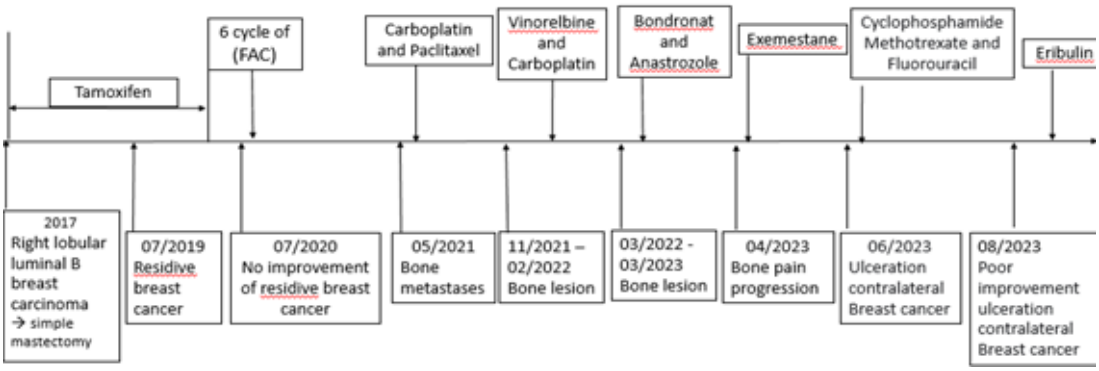

Fig. 1C. Timeline Case Report for Patient 3

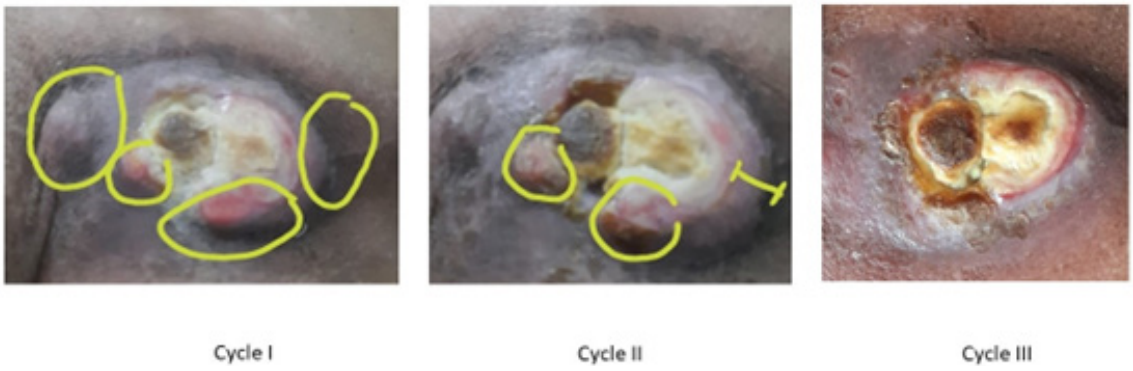

Fig. 2. Chest Wall Lesion of Patient 1

the development of the liver metastases, eribulin (1.4 mg/m^2 day 1 and 8 every 21 days, administered as IV bolus 2-5 minutes) was initiated and a partial response was observed after three cycles of treatment. No adverse events were observed. The patient was followed for two years (2021–2023) from initial diagnosis through eribulin therapy.

Patient 3

A 45-year-old Batak woman presented wwith a right breast mass and a history of type II diabetes mellitus managed with insulin. Histopathology and immunohistochemistry confirmed right invasive lobular breast carcinoma luminal B-stage IIB in 2017 and was subjected to simple mastectomy. Tamoxifen was administered as hormonal therapy and two years later, the patient experienced recurrent left breast cancer. Although tamoxifen was continued, the drug did not improve the condition, leading to six cycles of fluorouracil, adriamycin, and cyclophosphamide chemotherapy initiated in July 2020. Nine months later, the patient developed bone metastases and received carboplatin, paclitaxel, along with zoledronic acid.

After six months, the regimen was changed to vinorelbine and carboplatin for three months due to bone lesion progression followed by hormonal therapy with anastrozole for one year. Anastrozole was replaced with exemestane for two months due to the progression of bone pain. In June 2023, the patient received cyclophosphamide, methotrexate, and fluorouracil due to disease progression in the left breast with an ulcer in the tumor mass but no improvement in the lesion. She had anemia [Hemoglobin 10.3g/dL (normal value 12.3-15.3 g/dL)]. Chest CT showed bone litic lesion on vertebrae C6, C7 and T1 and sclerotic lesion on manubrium and corpus strernum (bone metastases). Eribulin (1.4 mg/m^2 on days 1 and 8 every 21 days, administered as IV bolus for 2–5 minutes) was initiated. Disease stabilization was achieved with no adverse events reported. The patient was followed for six years (2017–2023).

Fig. 3. Lymph Node Enlargement of Patient 1

Table 1 Summary of Reported Cases of Metastatic Breast Cancer Treated with Eribulin

Author, Year of Diagnosis	Age/ sex	Histo-logy	Stage	Subtype	Eribulin ChT	Time from Diagnosis to Eribulin	Outcome	AE
Garrido, 1994[8]	90/F	IDC	IV	ER+/ PR+/ HER2-	5th line	19 years	Alive (partial response)	Grade III febrile neutropenia
Karasuno, 2006[9]	79/F	None	IV	TNBC	3rd line	28 months	Alive	Alopecia, anemia Hb 10
Garrido, 2007[8]	70/F	MIC	IV	ER+/ PR+/ HER2-	3rd line	7 years	Alive (Stable disease)	Febrile neutropenia
Wee, 2009[10]	56/F	IDC	IV	TNBC	3rd line	7 years	Alive	No AE
Garrido, 2010[8]	80/F	IDC	IV	ER+/ PR+/ HER2-	4th line	5 years	Alive (Stable disease)	Polyneuropa-thy
Fumet, 2010[11]	37/F	None	IV	ER+/ PR+/ HER2-	5th line	5 years	Death	No AE
Medici, 2012[12]	55/F	IDC	IV	ER+/ PR+/ HER-2	5th line	3 years	Partial response	No AE
Feng Xie, 2012[13]	55/F	None	IV	TNBC	8th line	4 years	Death	No AE
Tran, 2013[14]	61/F	None	IV	TNBC	4th line	3 years	Alive	Severe skin rash
Sancho, 2014[15]	68/F	IDC	IV	TNBC	3rd line	1 year	Death	No AE
Patient 1, 2015	48/F	ILC	IV	TNBC	4th line	8 years	Alive	Chill, constipation, Anemia
Borgonovo, 2015[16]	59/F	IDC	IV	ER+/ PR+/ HER2-	4th line	2 years	Partial response	Alopecia
Manthri, 2015[17]	48/F	IDC	IV	TNBC	3rd line	32 months	Alive (partial response)	No AE
Yoshinori, 2018[18]	42/F	SCC	IIIC	TNBC	3rd line	20 months	Complete Response	No AE
Sheik, 2019[19]	49/F	None	IV	ER+/ PR+/ HER2-	2nd line	1 year	Alive	Confusion
Kitada, 2020[20]	75/M	IDC	IV	ER-/ PR-/ HER2+	2nd line	6 months	Alive (partial response)	No AE

Abbreviations: AE = adverse event; ChT = chemotherapy; Dx = diagnosis; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; Histol = histology; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; MIC = mixed invasive carcinoma; PR = progesterone receptor; SCC = squamous cell carcinoma; TNBC = triple-negative breast cancer

Discussion

Patient 1 had triple-negative breast cancer (TNBC) with PD-L1 positivity and disease progression after anthracycline, taxane, and radiotherapy. Due to financial limitations, anti–PD-L1 therapy was not administered. Eribulin was used as fourth-line chemotherapy. Meanwhile, patients 2 and 3 had hormone receptor-positive, HER-2 negative breast cancer, with imminent organ failure and progressive disease after several lines of ET (estrogen therapy). However, none of the patients was treated with a CDK 4/6 or an mTOR inhibitor due to the unavailability of national health insurance coverage. Eribulin was given as second-line therapy in patient 2 and as fifth-line in patient 3. The time from diagnosis to eribulin treatment was eight, three, and six years in patients 1, 2, and 3, respectively.

To the best of current knowledge, this is the first case report of MBC patients in Indonesia from various ethnic backgrounds who underwent Eribulin chemotherapy since its inclusion in the government health insurance program. These three cases showed substantial benefit from Eribulin. According to previous reports, patients with MBC often show resistance to anthracyclines and taxanes, which are typically used as the initial treatment options. Treatment failure frequently occurs in most patients even when these medications are used. However, cytotoxic chemotherapy remains the predominant approach for managing MBC, particularly in women with hormone receptor-positive breast cancer who do not respond to endocrine therapy, those experiencing visceral crisis, and TNBC.[6]

The ESMO guideline (2021) states that eribulin is recommended as third-line therapy in mTNBC and beyond the second line in hormone-positive, HER-2-negative MBC. In this context, single-agent chemotherapy agents include anthracyclines, taxanes, capecitabine, eribulin, vinorelbine, and other drugs for patients with imminent organ failure or progressive disease after several lines of endocrine (ET) + targeted therapy. For patients diagnosed with metastatic triple-negative breast cancer (mTNBC), chemotherapy, with or without immune checkpoint inhibitor (ICI) therapy based on PD-L1 status should be considered.[7]

Patient 1 initially developed chest wall recurrence and lymph node enlargement, but experienced improved lesion and size reduction after eribulin chemotherapy. Patient 2 developed brain and liver metastases before treatment with eribulin as second-line chemotherapy. According to previous studies, eribulin showed a significantly higher overall response rate (ORR) in patients with liver and brain metastases (BM). Based on the results, seven instances of complete responses were observed in various metastatic sites such as lung, liver, bone, and others. A partial response was also recorded specifically in cases of brain metastases.[6] A post hoc analysis by Shaughnessy stated that patients with liver metastases randomly assigned to receive eribulin showed a nominally significant difference in overall survival (OS) compared to those randomized to receive TPC or capecitabine (median:13.4 versus 11.3 months; HR, 0.84 [95% CI: 0.72, 0.97]).[4]

A retrospective study used data from Cancer Treatment Centers of America to estimate overall survival (OS) in clinical practice for patients with advanced breast cancer and visceral metastasis (liver or lung) treated in third-line setting with eribulin, gemcitabine, or capecitabine. The results showed that patients treated with eribulin had a numerically higher median OS compared to those who received other regimens. Specifically, the median OS was 9.8 months (95% CI 8.3, 12.8) for eribulin, 7.2 months (95% CI 5.8, 10.3) for gemcitabine, and 9.1 months (95% CI 6.3, 15.4) for capecitabine.[22] Renaud *et al*., in another study, found that 75% of patients experienced progressive brain metastases after eribulin administration. This led to the conclusion that eribulin had a limited impact on brain metastases evolution.[23] Additionally, patients 1 and 3 developed bone metastasis with a nominally significant difference in OS (median: 14.6 versus 12.5 months).[4] All three patients are still alive at present, surviving for four, three, and three months post-erilubin treatment respectively.

The most common side effects of eribulin in the EMBRACE trial were asthenia or fatigue (54%), and neutropenia (52%). Discontinuation of treatment was primarily attributed to peripheral neuropathy, the most frequent adverse event, observed in 5% of patients.[5] In patient 1, the adverse events (AEs) including grade I chills, grade I constipation, and grade II anemia did not lead to eribulin discontinuation. Based on the available literature, chills as AEs have not been previously reported.[5] Despite the associated toxicity, eribulin showed favorable outcomes for most patients. According to Fujii, the drug has a potential antitumor mechanism that may

prevent the development of new metastases as well as a positive impact on the immunological status of patients with breast cancer.[24,2]

Previous reports of patients with breast cancer who received eribulin as both early and late chemotherapy regimens are presented in Table 1.

In phase 3 open-label randomized study, eribulin monotherapy was compared with treatment of physician's choice (TPC) in patients with MBC (EMBRACE). The results showed that eribulin monotherapy caused a clinically significant enhancement in overall survival compared to TPC in women with MBC despite extensive previous treatments.[5] The antitumor activity of eribulin is characterized by a unique interaction with microtubules, specifically inhibiting the growth phase without affecting the shortening phase. In addition to the mitotic effects, in vitro and preclinical studies suggest that eribulin may engage in non-mitotic mechanisms, including vascular remodeling, reversing epithelial-to-mesenchymal transition (EMT), as well as inhibiting cancer cell migration and invasion. Some of these effects have also been observed clinically, for example, in the United States, eribulin is approved for treating patients with MBC after receiving at least two previous chemotherapeutic regimens for metastatic disease, including anthracycline and taxane in either the adjuvant or metastatic setting. Furthermore, the approval of eribulin for MBC has been extended to second-line metastatic settings in other regions, including the European Union.[3,21]

In conclusion, eribulin chemotherapy was associated with favorable clinical outcomes in heavily pre-treated patients with metastatic breast cancer, including those with liver, lung, bone, and brain metastases. This case series provides real-world evidence supporting the use of eribulin in similar clinical settings. Eribulin may be considered for MBC patients who have progressed after two to three prior taxane- or anthracycline-based regimens. Further studies exploring combinations of eribulin with other chemotherapy agents, targeted therapies, or immunotherapy are warranted.

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