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Original Article

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Frequency of EGFR Mutations and Associated Clinical Factors in Thai Patients with Non-small Cell Lung Cancer (NSCLC)

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ABSTRACT

OBJECTIVE Understanding clinical factors related to epidermal growth factor receptor (EGFR) mutation in lung cancer patients is imperative for effective treatment planning. It is also crucial to recognize ethnic differences. Hence, studying the prevalence and types of EGFR mutations in Thai patients with non-small cell lung cancer (NSCLC) is essential. Investigating clinical factors influencing EGFR mutation detection remains critical.

METHODS Etiognostic research with a retrospective observational cohort design collected clinical data from NSCLC patients undergoing EGFR molecular testing using real-time PCR from November 1, 2017 to September 30, 2022. The relationship between smoking as well as other clinical factors of interest and the detection of EGFR mutation through regression were analyzed.

RESULTS The EGFR mutation rate was 46.55%, with 108 cases detected out of 232 patients. EGFR mutation was detected in 63.41% of the never smoking group. Exon 19 deletion (51.85%) and exon 21 L858R mutation (36.11%) were the predominant types. Univariable regression analysis identified factors correlated with EGFR mutation detection, including female gender, non-smoker status, adenocarcinoma lung cancer type, and bone metastasis. A statistically significant reduction in EGFR mutation detection was observed in patients with squamous cell carcinoma lung cancer. Multivariable regression analysis confirmed non-smoker and adenocarcinoma lung cancer type as significant independent predictors of EGFR mutation detection (adjusted OR 2.84, 95%CI 1.20-6.74, $p = 0.018$) (adjusted OR 14.39, 95%CI 1.77-116.84, $p = 0.013$), respectively. The survival analysis results showed significant survival differences between stage 4 NSCLC patients with EGFR mutations and EGFR wild-type (median overall survival: 22.98 months vs 8.72 months, median survival time difference: 12.60 months, $p < 0.001$).

CONCLUSIONS Adenocarcinoma and non-smoker status represent significant factors associated with EGFR mutation. Nonetheless, performing an EGFR test before initiating treatment remains crucial as it enhances treatment precision and specificity.

KEYWORDS epidermal growth factor receptor, EGFR, non-small cell lung cancer, NSCLC, Thai, clinical factors

INTRODUCTION

Genetic alterations in the epidermal growth factor receptor (EGFR) gene are widely acknowledged to have a significant role in non-small cell lung cancer (NSCLC) pathogenesis (1, 2). EGFR plays a critical role in a multitude of cellular processes, encompassing cell proliferation, differentiation, motility, and survival. Binding of epidermal growth factor (EGF) to EGFR induces receptor dimerization, autophosphorylation, and subsequent activation, initiating a myriad of molecular pathways that culminate in cell activation. Normally, EGFR activation ceases upon exhaustion of its ligands, including EGF, transforming growth factor alpha (TGF-α) and various other growth factors. EGFR gene mutations can overactivate EGFR signaling pathways, leading to uncontrolled cellular proliferation and tumor development (3). International studies have reported varying frequencies of EGFR mutations among Asian and Western populations. Western populations have a 10% prevalence rate of EGFR mutation, while in Asian populations, the prevalence ranges between 50-60% (4, 5). Understanding the mechanisms of EGFR gene alterations in NSCLC is crucial for developing precise therapeutic interventions and improving patient outcomes. In NSCLC with overexpressed EGFR, inhibition of receptor signaling, particularly with TKIs like gefitinib, erlotinib and osimertinib, is considered optimal for those with EGFR-activating mutations (6, 7).

Epidemiological data and clinical behaviors related to EGFR and lung cancer vary among ethnic groups (8, 9). In Thailand, a study was conducted on the frequency of detection of EGFR mutations in patients with NSCLC from formalin-fixed paraffin-embedded tissue using polymerase chain reaction–single strand conformational polymorphism (PCR–SSCP). It was found that EGFR mutations occurred in about 58% of the cases (10, 11). However, the data from that study has limitations due to the small sample size and because it does not include the clinical relationship dimension of the patients, especially clinical factors related to smoking, because the data was derived from pathological examination. This gap in information on the patient clinical profiles may have affected the interpretation of the EGFR mutation frequency. Moreover, factors related to lung cancer treatment, such as treatment efficacy and patient outcomes, also need to be considered. These factors may vary depending on the presence or absence of EGFR mutations in practical clinical settings, highlighting further limitations in the study's findings.

The present study aims to investigate the prevalence of EGFR mutations in Thai patients with NSCLC, as well as the types of mutations detected and clinical factors that affect EGFR mutation detection.

METHODS

This is an etiognostic research study with a retrospective observational cohort design. It collected clinical factors data from patients with NSCLC stage 4 who received treatment at the Oncology Unit, Buddhasothorn Hospital and who underwent EGFR molecular testing using real-time PCR between November 1, 2017 and September 30, 2022.

Determination of whether the data conformed to a normal distribution was determined by conducting a Shapiro–Wilk test for independent categorical variables. Data from the test are displayed as counts and percentages. The data were analyzed and compared using either the Chi-square test or Fisher's exact test. The relationship between smoking and other clinical factors of interest and the detection of EGFR mutations was investigated using regression analysis. The survival analysis was conducted using the Kaplan–Meier curve, and the mean differences in survival between the EGFR mutation group and the wild-type group were tested using Laplace regression.

The objective of the research is to study both the frequency of EGFR mutation in patients with NSCLC and the types of mutations in Thai patients. Additionally, the research aims to investigate the relationship between smoking and types of NSCLC with the detection of EGFR mutations, as well as to explore the correlation between detection of EGFR mutations and clinical factors.

The study protocol was approved by the Institutional Review Board of Buddhasothorn Hospital (number BSH-IRB 010/2566).

RESULTS

Data are for 392 patients with NSCLC stage 4 treated at Buddhasothorn Hospital between November 1, 2017 and September 30, 2022. A total

of 160 cases were excluded due to insufficient data because the EGFR molecular test had not been performed, and 232 cases were analyzed in the study. The flowchart for data selection is shown in Figure 1. Among the patients, 121 (52.16%) were male and 111 (47.84%) were female. The average age of patients of both genders combined was 63.51 years, with a standard deviation of ± 0.70. Concerning NSCLC cell types, the majority of cases were adenocarcinoma, accounting for 90.52%. Squamous cell carcinoma followed with 8.19%, and other cell types with 1.29%. The distribution of initial metastatic sites demonstrated variability. Specifically, there were 26 cases (11.21%) of brain metastasis, 187 cases (80.60%) of lung-to-lung metastasis, 118 cases (50.86%) of pleural metastasis, 38 cases (16.38%) of liver metastasis, and 76 cases (32.76%) of bone metastasis (Table 1).

Analysis of EGFR mutation frequencies determined that there were 124 cases (53.45%) of the EGFR wild type and 108 cases (46.55%) of mutations. EGFR mutations detected were primary mutations before the start of treatment. The types of EGFR mutations identified included Exon 19, accounting for 51.85%, and Exon 21 L858R, which constituted 36.11%. Additionally, we observed an uncommon EGFR mutation comprising Exon 18 G719X and Exon 21L861Q to be present in 4.63% of cases. Furthermore, a dual EGFR mutation involving both Exon 19 deletion and Exon 21L858R was identified in 2.78% of cases. Other mutations, such as EGFR Exon 20 insertions, were present in 1.85% of cases. Additionally, a common EGFR mutation plus the primary T790M mutation was observed in 1.85% of cases, and a primary EGFR T790M mutation was found in 0.93% of cases (Table 2).

After categorizing the mutations into the EGFR wild type and EGFR groups, we investigated the correlation with clinical factors. Analysis

Table 1. Baseline characteristics of non-small cell lung cancer (NSCLC)

	Mean age (±SD) / 95%CI
Overall patients	63.51 (±0.70) / 62.14-64.89
Male	64.44 (±0.97) / 62.51-66.37
Female	62.50 (±0.99) / 60.53-64.47
	Number (%)
Smoking	
Former/current smokers	109 (46.98)
Never-smokers	123 (53.02)
Type of NSCLC	
Adenocarcinoma	210 (90.52)
Squamous cell carcinoma	19 (8.19)
Other type	3 (1.29)
Initial metastatic site	
Brain metastasis	26 (11.21)
Lung to lung metastasis	187 (80.60)
Pleural metastasis	118 (50.86)
Liver metastasis	38 (16.38)
Bone metastasis	76 (32.76)

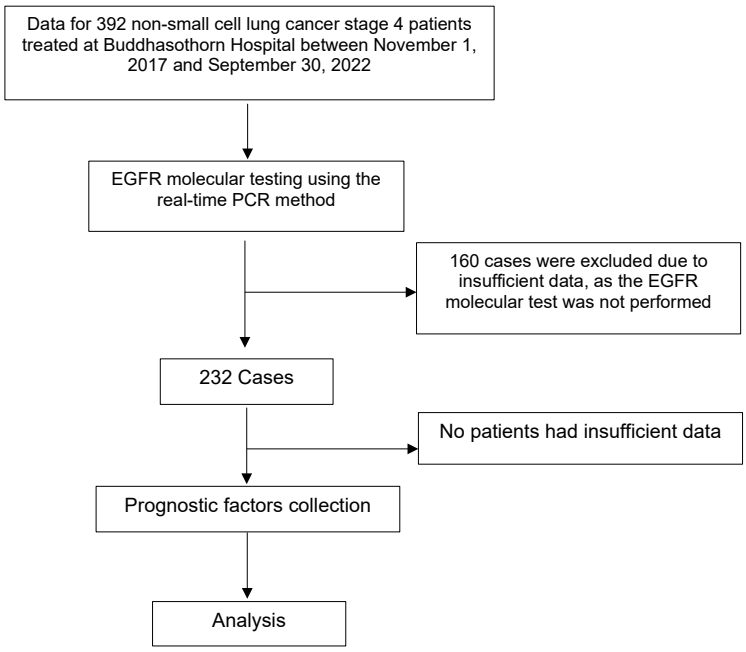

Figure 1. Study flow diagram

Table 2. Frequency of EGFR mutations in non-small cell lung cancer (NSCLC)

EGFR	Number (%) N = 232
EGFR wild type	124 (53.45)
EGFR mutation	108 (46.55)
Type of EGFR mutation	**Number (%) N = 108**
Exon 19 deletion	56 (51.85)
Exon 21 L858R mutation	39 (36.11)
Uncommon EGFR mutation	5 (4.63)
Dual common EGFR mutation	3 (2.78)
EGFR exon 20 insertions	2 (1.85)
Common EGFR mutation plus primary T790M mutation	2 (1.85)
Primary EGFR T790M mutation	1 (0.93)

showed that the EGFR wild type was present in 124 cases, comprising 53.45% of the total. Among those cases, 81 were male (65.32%) and 43 were female (34.68%). Notably, 63.71% of the EGFR wild type cases were smokers, while 36.29% were non-smokers. Regarding NSCLC subtype distribution, adenocarcinoma predominated at 83.26%, followed by squamous cell carcinoma at 14.52%, with other cell types comprising 2.42%. Conversely, EGFR mutation was found in 108 cases, making up 46.55% of the total. Within the EGFR mutation group, 40 were male (37.04%) and 68 were female (62.96%). Moreover, 27.78% of EGFR mutation cases were smokers, while 72.22% were non-smokers. Remarkably, NSCLC consisted primarily of adenocarcinoma, observed in 99.07% of cases, with squamous cell carcinoma identified in only 0.93%. No other cell types were detected (Table 3).

Gender, smoking history, and lung cancer subtype are considered clinical factors associated with EGFR mutation in NSCLC. This study included 124 cases in the EGFR wild type group and 108 cases in the EGFR mutation group. Among female participants, 68 cases (62.96%) had EGFR mutation, which was higher than the 43 cases (34.68%) in the EGFR wild type group. Among male participants, 40 cases (37.04%) had EGFR mutation, which was lower than the 81 cases (65.32%) in the EGFR wild type group. Among non-smokers, 78 cases (72.22%) had EGFR mutation, higher than the 45 cases (36.29%) in the EGFR wild type group. Among smokers, 30 cases (27.78%) had EGFR mutation. Additionally, there were 107 cases (99.07%) with the EGFR mutation adenocarcinoma subtype, which is higher than the 103 cases (83.06%) in the EGFR wild type group. Only 1 case (0.93%) of squamous cell carcinoma had EGFR mutation, while there were 18 cases (14.52%) in the EGFR wild type group. No other subtypes showed EGFR mutation; however, only 3 cases (2.42%) were found in the EGFR wild type group (Table 3).

In univariable regression analysis, factors associated with detecting EGFR mutation were identified. Female gender, a history of not smoking, adenocarcinoma subtype lung cancer, and bone metastasis were among the factors identified. Additionally, there was a statistically significant decrease in the detection of EGFR mutation, particularly in cases of squamous cell carcinoma. Subsequently, multivariable regression analysis confirmed that non-smokers and the adenocarcinoma subtype of lung cancer remained significant independent factors in EGFR mutation detection (Table 4).

Survival analysis indicated that patients with stage 4 NSCLC had a median overall survival of 13.57 months (95%CI 10.56-15.15). Comparing the

Table 3. The relationship between detecting EGFR mutation and clinical factors

	EGFR wild type N=124 (%)	EGFR mutation N=108 (%)	*p*-value
Gender			
Male	81 (65.32)	40 (37.04)	<0.001
Female	43 (34.68)	68 (62.96)	<0.001
Smoking			
Former/current smoker	79 (63.71)	30 (27.78)	<0.001
Never-smoker	45 (36.29)	78 (72.22)	<0.001
Type of NSCLC			
Adenocarcinoma	103 (83.06)	107 (99.07)	<0.001
Squamous cell carcinoma	18 (14.52)	1 (0.93)	<0.001
Other types	3 (2.42)	0 (0.00)	0.250

Table 4. Results of univariable and multivariable regression analyses of potential clinical variables as independent predictors of EGFR mutation in NSCLC

	Univariable analyses			Multivariable analyses		
	uOR	95% CI	*p*-value	aOR	95% CI	*p*-value
Female	3.20	1.87-5.48	<0.001	1.32	0.56-3.11	0.517
Non-smoker	4.56	2.61-7.97	<0.001	2.84	1.20-6.74	0.018
Age ≥ 60 years	0.77	0.45-1.32	0.342	0.78	0.42-1.45	0.439
Adenocarcinoma	21.82	2.88-165.15	0.003	14.39	1.77-116.84	0.013
Squamous cell carcinoma	0.06	0.01-0.42	0.005	1 (omitted)		
Other types	1 (omitted)			1 (omitted)		
Brain metastasis	0.58	0.30-1.13	0.112	0.57	0.27-1.22	0.145
Lung to lung metastasis	1.76	0.89-3.44	0.102	1.50	0.67-3.35	0.329
Pleural metastasis	1.64	0.97-2.75	0.063	1.50	0.81-2.78	0.201
Liver metastasis	1.52	0.76-3.06	0.241	1.10	0.49-2.47	0.818
Bone metastasis	1.98	1.13-3.45	0.016	1.63	0.86-3.10	0.134

uOR, unadjusted odds ratio; aOR, adjusted odds ratio; CI, confidence interval

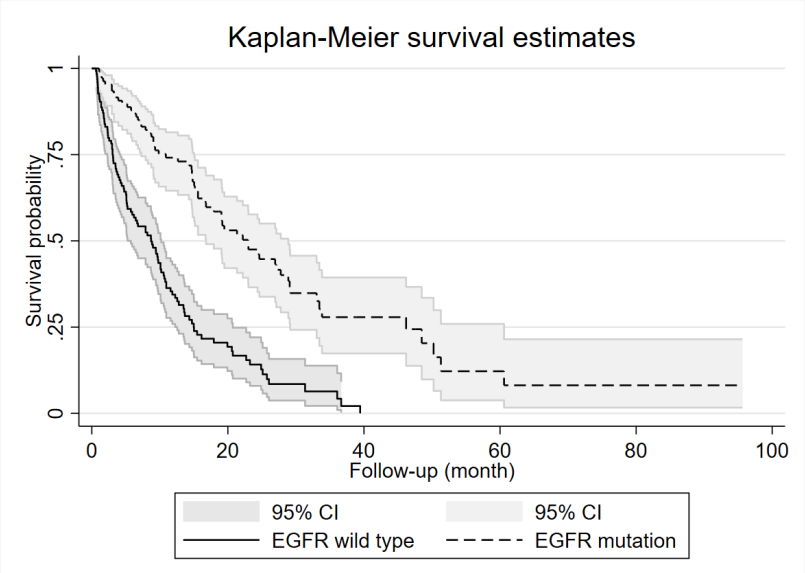

Figure 2. Kaplan-Meier survival analysis according to EGFR status

EGFR wild type and mutation groups, the mutation group had a median overall survival of 22.98 months (95%CI 16.79-28.89), compared to 8.72 months (95%CI 5.74-10.20) for the wild type group. The results showed significant survival differences between patients with EGFR mutations and EGFR wild-type (median survival time difference 12.60 months, 95% CI: 7.78-17.42, $p < 0.001$). Figure 2 shows the Kaplan-Meier curve for EGFR status.

DISCUSSION

EGFR mutation was identified in approximately 47% of cases. Within the non-smoker group, EGFR mutation prevalence was notably higher at 63%, compared to around 28% in the smoking group. The frequencies of EGFR mutation types were predominantly around 90%, consisting of common mutations such as exon 19 deletion and exon 21 L858R. This indicates a significant association between smoking status and EGFR mutation rates, with distinct patterns observed in different subgroups.

We examined the relationship between EGFR mutation and various clinical factors in NSCLC patients. Our analysis, conducted using logistic regression, revealed significant associations of adenocarcinoma and non-smoking status with EGFR mutation in both univariable and multivariable analyses. Demographic characteristics, tumor features, and clinical metastatic site were thoroughly assessed using statistical analysis techniques to determine their association with EGFR mutation. Adenocarcinoma presented the highest risk (ad-

justed odds ratio [aOR] 14.39, 95%CI 1.77-116.84, p = 0.013), followed by non-smoking status (aOR 2.84, 95%CI 1.20-6.74, p = 0.018). Understanding the influence of adenocarcinoma and non-smoking status is imperative for predicting EGFR mutation, providing valuable insights for personalized treatment strategies.

Lung cancer in never-smoker Asian females represents a distinct clinical entity, with the majority of these cancers arising from oncogenic mutations. Specifically, in female Asian nonsmokers with adenocarcinoma lung cancer, there is a 70-80% association with identifying oncogenic mutations. Among these mutations, EGFR mutations are frequently associated with older age and a predominantly acinar pattern, while ALK rearrangements are principally associated with younger age and a predominantly solid pattern (12).

The data suggest that three main factors—female gender, non-smoking, and adenocarcinoma subtype—are associated with EGFR mutation detection (13-15). The influence of gender on EGFR mutation detection may stem from hormonal receptors. A meta-analysis found a correlation between high nuclear expression of ER-beta and EGFR mutation in non-small cell lung cancer, supporting the role of hormone receptors in mutation development (16, 17). Scientific evidence from epidemiological studies and molecular analyses has been reported regarding the differences in molecular pathways between smokers and non-smokers (18-20). Smoking has been shown to lead to significant differences in genetic alterations compared to non-smokers, such as the upregulation of genes like the AKR1B10 gene from the aldo-keto reductase superfamily (AKR), which is consistently found in smokers (21-23). Additionally, observational studies have reported the presence of EGFR mutations in smokers. Therefore, smoking is likely an important environmental factor influencing EGFR mutations, as indicated by numerous studies in the field (24, 25).

According to the available data, adenocarcinoma lung cancer is observed predominantly in females who do not smoke. This may suggest a correlation with the detection of EGFR mutations.

One limitation of this study is that the observed frequency of EGFR mutations may not accurately represent the true prevalence. This discrepancy arises from the exclusion of approximately 40% of the cohort due to the absence of EGFR molecular testing, a procedure reimbursable in Thailand since 2021. Despite its limitations, this study contributes significant insights. This research provides preliminary evidence suggesting a higher prevalence of EGFR mutations among Thai populations, including both smokers and nonsmokers, compared to Western countries.

CONCLUSIONS

Adenocarcinoma and non-smoking status represent significant factors associated with EGFR mutation. Additionally, targeted therapy designed for EGFR mutation is accessible for lung cancer treatment. In Thailand, reimbursement for first-line therapy is available, enabling access to targeted therapy customized for EGFR mutation in lung cancer treatment. Therefore, in the case of individuals diagnosed with adenocarcinoma and no history of smoking it may be appropriate to consider EGFR mutation during the exploration of personalized treatment options. However, research data suggests that patients with squamous cell carcinoma and/or a history of smoking may also harbor EGFR mutations. Thus, testing for EGFR mutations before initiating treatment is crucial to ensure precise therapeutic approaches.

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CONFLICT OF INTEREST

All authors have no conflict of interest to declare.

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Original Article

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Visual Outcomes Following Surgical Treatment of Pituitary Adenomas: Functional Versus Non-functional

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ABSTRACT

OBJECTIVE This study aims to compare visual outcomes following surgical resection of functional and non-functional pituitary adenoma.

METHODS A retrospective observational study included 103 patients with pituitary adenoma who underwent tumor resection at Chiang Mai university hospital between January 2010 and December 2019. Basic characteristics, tumor specific data, hormonal status and neuro-ophthalmic data were collected and statistically analyzed to identify differences in visual outcomes between functional and non-functional tumors.

RESULTS Between the 51 (49.50%) functional pituitary adenoma and 52 (50.50%) non-functional pituitary adenoma patients in this study, there were no differences in mean age at initial visit, sex, duration of onset, type of surgery, or adjunct radiotherapy. Initial visual acuity in logMAR in both the better and the worse eye, as well as the initial visual impairment score (VIS) which represents a combination of visual acuity and visual field, showed no statistically significant differences. The final visual acuity of the better eye was significantly better in the functional group (0.08±0.15) than in the non-functional group (0.22±0.47), with a *p*-value of 0.04. Similarly, the VIS score was significantly better in the functional group (18.37±19.85) than in the non-functional group (28.87±26.83), with a *p*-value of 0.028.

CONCLUSIONS Patients with functional pituitary adenomas have potentially better visual outcomes than those with non-functional pituitary adenomas after surgical resection.

KEYWORDS functioning pituitary adenoma, non-functioning pituitary adenoma, visual outcome, visual impairment score

INTRODUCTION

Pituitary adenomas are common intracranial tumors that arise from the pituitary gland, accounting for approximately 10-15.5% of all intracranial neoplasms (1, 2) and 25% of surgically resected intracranial tumors (1). The incidence rate of these tumors is about 1/1,000 population (3-7), although systematic autopsy studies have reported a 25% prevalence of pituitary adenomas in the normal population (1).

These tumors can be classified into functional and non-functional types based on their hormonal activity. Functional pituitary adenomas (FPA) secrete excess hormones, which can lead to various endocrine disorders, e.g., Cushing's disease from excess adrenocorticotropic hormone (ACTH),

acromegaly and gigantism from excess growth hormone, and amenorrhea, galactorrhea, sexual dysfunction, and infertility from excess prolactin. In contrast, non-functional pituitary adenomas (NFPA) do not secrete hormones and are often detected incidentally or due to mass effects that may lead to later diagnosis (6, 8).

Visual impairment is often caused by a pituitary tumor pressing on the optic chiasm. Evidence suggests that factors predicting visual outcomes after surgery include retinal nerve fiber layer thickness, severity of the preoperative visual deficit, duration of the visual symptoms, tumor size, extent of the tumor resection, and the patient's age (9, 10). Early diagnosis and good visual acuity before surgery are strong predictors of positive visual outcomes post-treatment (11-13). In contrast, severe visual impairment before surgery is associated with poorer visual outcomes after the procedure (14).

There has been only limited comparative research on postoperative visual outcomes between functional and non-functional pituitary adenomas. The present study provides clinical and neuroophthalmic comparisons between these two groups and evaluates visual outcomes following surgical resection. These outcomes could be used to predict visual outcomes and to provide a better understanding of appropriate patient care.

METHODS

This retrospective study involved patients with pituitary adenomas who visited or were referred to the ophthalmology department at Chiang Mai University Hospital between 2010 and 2019 and underwent tumor resection.

The study received approval from the Ethics Review Board of the Faculty of Medicine, Chiang Mai University (code number: OPT-2567-0262). Informed consent from the patients was waived due to the retrospective nature of the study.

Inclusion criteria

Patients in the study presenting to the Ophthalmology Department of Chiang Mai University Hospital with pituitary adenoma and underwent either tumor resection craniotomy or endoscopic transsphenoidal surgery.

Exclusion criteria

Patients with comorbidities that could potentially affect neuro-ophthalmic presentation, e.g., glaucoma, retinal disease, stroke, and those with incomplete ophthalmic examinations or medical records, were excluded.

Data collection

Collected demographic patient data included age at initial visit, sex, and underlying diseases. Neuro-ophthalmic manifestations assessed were initial presentation, best corrected visual acuity (BCVA), visual field (VF), extraocular movement (EOM), and optic disc findings. This study used neuroimaging to measure the tumor size, defined as the maximal diameter in any dimension, and recorded the presence of apoplexy.

The FPA group was classified based on clinical and/or laboratory evidence of excess hormone production, while the NFPA group was classified based on the absence of both clinical and laboratory evidence of abnormal hormone production.

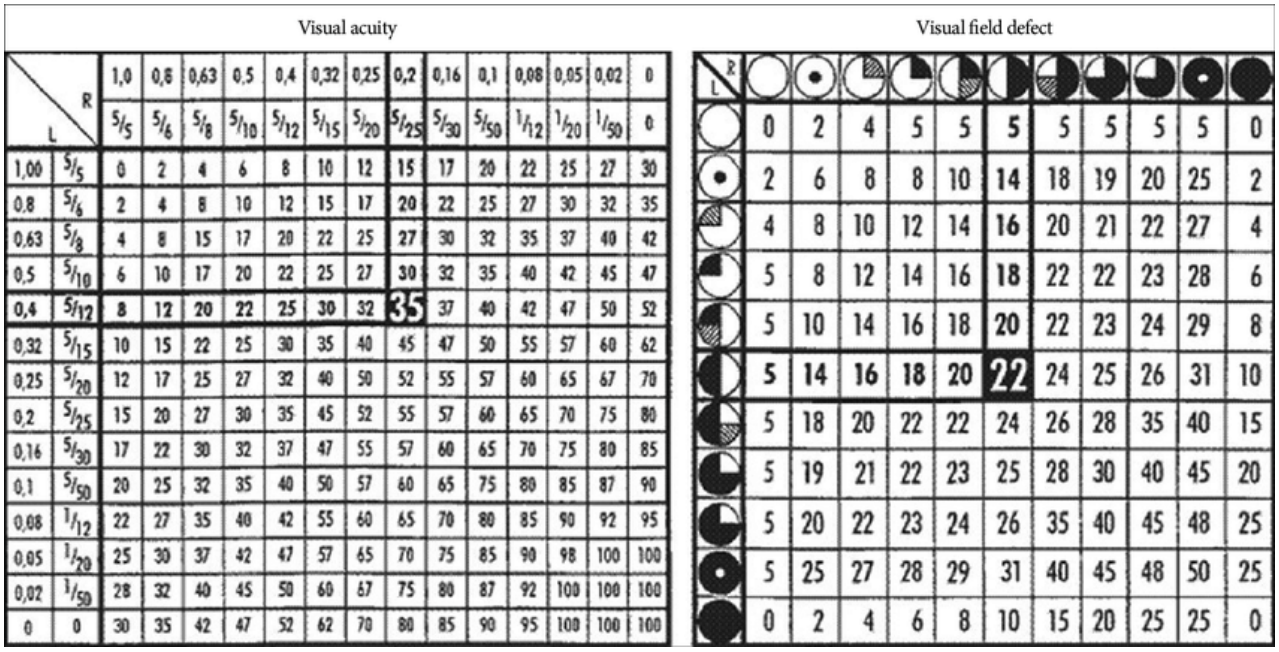
Results of pre-treatment and post-treatment ophthalmological examinations were reviewed to compare visual outcomes after tumor resection and to identify potential predictive factors. Blood tests for hormonal levels were conducted in most cases, so data on abnormal hormone levels and initial endocrine disorder manifestations were also collected. Postoperative data were gathered for at least six months following surgery.

Snellen visual acuity was converted to logMAR for statistical analysis and to decimal visual acuity (VA) for visual impairment score (VIS) calculation. In this study, Goldmann kinetic perimetry was used to determine the VF defect with I-4e stimulus (size: ¼ mm^2, brightness: 0 dB) and II-4e stimulus (size: 1 mm^2, brightness: 0 dB) (13). VF defects were categorized as:

- Bilateral: bitemporal hemianopia, bitemporal quadrantanopia, homonymous hemianopia, central defect, generalized depression, constricted VF
- Unilateral: temporal hemianopia, temporal quadrantanopia, central defect, generalized depression, nasal quadrantanopia, constricted VF

The VIS, developed by the German Ophthalmological Society, was calculated by combining BCVA and VF defect scores for both eyes, as shown in Figure 1 (15). The score range was 0 to 100 and was divided into four visual impairment grades:

Grade 1 (score 0-25): no or minimal visual impairment; Grade 2 (score 26-50): moderate visual impairment; Grade 3 (score 51-75): severe visual impairment; Grade 4 (score 76-100): subtotal or complete visual impairment.



L \ R	1,0	0,8	0,63	0,5	0,4	0,32	0,25	0,2	0,16	0,1	0,08	0,05	0,02	0
	5/5	5/6	5/8	5/10	5/12	5/15	5/20	5/25	5/30	5/50	1/12	1/20	1/50	0
1,00 5/5	0	2	4	6	8	10	12	15	17	20	22	25	27	30
0,8 5/6	2	4	8	10	12	15	17	20	22	25	27	30	32	35
0,63 5/8	4	8	15	17	20	22	25	27	30	32	35	37	40	42
0,5 5/10	6	10	17	20	22	25	27	30	32	35	40	42	45	47
0,4 5/12	8	12	20	22	25	30	32	35	37	40	42	47	50	52
0,32 5/15	10	15	22	25	30	35	40	45	47	50	55	57	60	62
0,25 5/20	12	17	25	27	32	40	50	52	55	57	60	65	67	70
0,2 5/25	15	20	27	30	35	45	52	55	57	60	65	70	75	80
0,16 5/30	17	22	30	32	37	47	55	57	60	65	70	75	80	85
0,1 5/50	20	25	32	35	40	50	57	60	65	75	80	85	87	90
0,08 1/12	22	27	35	40	42	55	60	65	70	80	85	90	92	95
0,05 1/20	25	30	37	42	47	57	65	70	75	85	90	98	100	100
0,02 1/50	28	32	40	45	50	60	67	75	80	87	92	100	100	100
0 0	30	35	42	47	52	62	70	80	85	90	95	100	100	100

R \ L											
	0	2	4	5	5	5	5	5	5	5	0
	2	6	8	8	10	14	18	19	20	25	2
	4	8	10	12	14	16	20	21	22	27	4
	5	8	12	14	16	18	22	22	23	28	6
	5	10	14	16	18	20	22	23	24	29	8
	5	14	16	18	20	22	24	25	26	31	10
	5	18	20	22	22	24	26	28	35	40	15
	5	19	21	22	23	25	28	30	40	45	20
	5	20	22	23	24	26	35	40	45	48	25
	5	25	27	28	29	31	40	45	48	50	25
	0	2	4	6	8	10	15	20	25	25	0

Figure 1. The chart is used to calculate the VIS based on visual acuity and visual field defects. This example shows a patient with a visual acuity of 0.4 (4/10) in the left eye and 0.2 (2/10) in the right eye, along with a bitemporal visual field defect. Adding the corresponding scores, 35 and 22, gives a total of 57. This value represents the VIS, which has a maximum possible score of 100.

Statistical analysis

Data were collected using Microsoft Excel and SPSS version 25. Categorical data are shown as percentages and frequencies, while continuous data are shown as mean±SD. T-tests and Mann-Whitney U tests were used for inferential analysis. The critical level of statistical significance was set at a *p*-value less than 0.05.

RESULTS

A total of 103 patients (206 eyes) were included in the final analysis. The demographic data and clinical manifestations are summarized in Table 1. The mean age at initial visit was 46.45±13.21 years. Fifty-two patients (50.49%) were male. An equal number of patients of both sexes (52, 50.49%) had NFPA. In the functioning group, the most common abnormal presentation was giantism and acromegaly, observed in 14 patients (27.45%). There were 11 cases (10.68%) of pituitary apoplexy. The maximum tumor diameter was 3.08±1.08 centimeters. Most of the patients had ophthalmic symptoms, with 79 patients (76.70%) having a decrease in visual acuity and 72 patients (79.12%) with an abnormality in the VF. However, seventeen patients (16.50%) had a normal initial visual impairment score (VIS = 0). Approximately one-third of the patients (34.95%) complained of headaches, and only five patients (4.85%) had limitation of ocular movement.

A comparison of age at initial visit, sex, duration of onset, tumor size, and presentation of pituitary

Table 1. Patients' demographic data and clinical manifestations

Characteristic (N = 103 patients)	Value
Age at initial visit (mean±SD, years)	46.45±13.21
Sex	
Male (N, %)	52 (50.49)
Female (N, %)	51 (49.51)
Duration of onset (mean±SD, years)	0.52±0.62
Headache (N, %)	36 (34.95)
Ocular movement limitation (N, %)	5 (4.85)
Visual acuity	
Normal (N, %)	24 (23.30)
Unilateral vision loss (N, %)	26 (25.24)
Bilateral vision loss (N, %)	53 (51.46)
Visual field (N=91)**	
Normal (N, %)	19 (20.88)
Unilateral visual field defect (N, %)	13 (14.28)
Bilateral visual field defect (N, %)	59 (64.84)
Type of adenoma	
Functioning (N, %)	51 (49.51)
Non-functioning (N, %)	52 (50.49)
Maximum tumor diameter (mean±SD, cm)	3.08±1.08
Pituitary apoplexy (N, %)	11 (10.68)

cm, centimeter; N, number; SD, standard deviation
**An initial visual field test was performed on 91 patients

apoplexy showed no statistically significant difference between FPA and NFPA. Additionally, there was no difference in the type of surgical intervention (both craniotomy and endoscopic transsphenoidal surgery) or in the receipt of radiotherapy. Visual acuity in both the better and worse eye, as well as the VIS at the first presentation, indicated no significant difference between the two groups, as shown in Table 2.

After surgical intervention, the study found improvement in visual acuity in 75 patients (72.41%) and improvement in the VF in 43 patients (47.22%) with a follow-up period of more than 6 months, with the longest follow-up time being 10 years. Table 3 shows better final visual acuity in the better eye in the functional adenoma group, with a statistically significant *P* value of 0.04. In the worse eye, there was no statistically significant difference in final visual acuity, but better visual acuity was correlated with the better eye. The final VIS of the functional group was also statistically significantly better, with a *P* value of 0.03. A total of 54 (52.40%) patients had more than a 10% VIS improvement, of whom 24 (44.40%) had functional and 30 (55.60%) had non-functional edemas.

DISCUSSION

In this study, we specifically investigated the differences between functional and non-functional pituitary adenoma patients. We found no statistically significant differences in age at initial visit, sex, or duration of onset between the groups. In contrast, a study by Jiayin Qin et al. reported a similar sex distribution but found significant differences in age and duration of onset (2). That study found older age and larger tumor size were associated with non-functional adenomas, with a longer duration of onset in the functional group. In the present study, the ratio of patients with functional to non-functional adenomas was approximately 1:1 (51:52), whereas in the Qin study the ratio was 0.7:1 (30:43).

Most patients in our study experienced visual impairments, with 76.70% showing decreased visual acuity and 79.12% having VF abnormalities,

Table 2. Comparison of baseline and ophthalmic characteristics between patients with FPA and those with NFPA

Characteristic	FPA (N = 51)	NFPA (N = 52)	*p*-value
Age at initial visit (mean±SD, years)	45.84±13.82	47.04±12.70	0.65
Sex (male : female)	22 : 30	29 : 23	0.16
Duration of onset (years)	0.52±0.62	0.51±0.52	0.96
Maximum tumor diameter (cm) (mean±SD)	3.13±1.40	3.24±1.11	0.68
Presenting with pituitary apoplexy (N,%)	5 (9.80)	6 (11.54)	0.70
Intervention (N, %)			
Craniotomy	16 (31.37)	14 (26.92)	0.67
ETSS	35 (68.63)	38 (73.08)	0.67
Adjuvant radiotherapy	13 (25.49)	16 (30.77)	0.43
Initial VA (mean±SD, logMAR)			
Better eye	0.19±0.26	0.23±0.35	0.48
Worse eye	0.66±0.68	0.96±0.91	0.07
Initial VIS, mean ± SD	32.17±31.96	39.56±26.54	0.22

ETSS, endoscopic transsphenoidal surgery; FPA, functional pituitary adenoma; logMAR, logarithm of the minimum angle of resolution; NFPA, non-functional pituitary adenoma; SD, standard deviation; VA, visual acuity; VIS, visual impairment score

Table 3. Comparison of visual outcomes between patients with FPA and NFPA

Variable	FPA (N = 51)	NFPA (N = 52)	*p*-value
Final VA (mean±SD, logMAR)			
Better eye	0.08±0.15	0.22±0.47	0.04*
Worse eye	0.53±0.84	0.82±1.09	0.13
Final VIS, mean±SD	18.37±19.85	28.87±26.83	0.03*

FPA, functional pituitary adenoma; logMAR, logarithm of the minimum angle of resolution; NFPA, non-functional pituitary adenoma; SD, standard deviation; VA, visual acuity; VIS, visual impairment score

which is consistent with previous studies (16-19). Visual acuity and VF defects are caused by the mass effect of the pituitary tumor at the optic nerve and the optic chiasmal region. In this study, the VIS to measure visual function was developed by combining bilateral visual acuity and VF defect patterns as a suitable representation of visual outcome. Additionally, the correlation between visual acuity and VF defect was determined (20). The worse final visual acuity and final VF defect (presented as final VA and final VIS in our study) in the non-functional group could be due to compression from macroadenomas, which have previously been reported to be more frequent in NFPA (2, 21). Additionally, the absence of hormonal symptoms in NFPAs often delayed diagnosis, leading to a longer duration of compression (6, 7, 20, 22). Differences in growth patterns (23) and vascular dysfunction (24, 25) also contributed to the more severe visual impairment observed in NFPA. In our study, initial visual acuity and VIS showed no statistical significance between the functional and non-functional groups. Post-surgical removal, visual outcomes considering in the better eye (VA and VIS) were significantly better in patients with FPA. Although the lack of statistical significance in the final visual acuity of the worse eye might be due to a floor effect of improvement, the lack of recovery was likely due to more extensive damage to the optic nerve. Some studies have indicated that maintaining good visual function prior to treatment is a positive indicator for better visual outcomes following treatment (12, 13, 15). Previous studies have indicated that the severity of the preoperative visual deficit, the duration of symptoms before diagnosis, tumor size, and patient age are all predictors of visual outcomes post-treatment (9, 11-13). In our study, these variables were not statistically significantly different between the groups, suggesting that the type of pituitary adenoma (functional or non-functional) could have a greater effect on the final visual outcome. One study reported that, in tumors of the same size, the functional group had better visual outcomes than the non-functional group (2), suggesting underlying mechanisms beyond mass effect on visual dysfunction in pituitary tumors as has been previously discussed regarding growth patterns (23) and vascular dysfunction (24, 25). Recent studies of the molecular features of pituitary adenomas, including immunohistochemical types, pituitary-specific transcription factors, hormone genes, and proliferative markers, have indicated an enhanced aggressiveness of these tumors (23, 26). This research area may help uncover underlying reasons why functional adenomas have a better visual prognosis.

Limitations of this study

This study had several limitations. The retrospective nature of the study and some instances of incomplete data may have undermined the strength of our findings. There might also have been selection bias due to the surgeon's preference in the choice of surgery. Additionally, we did not include molecular studies, which restricted our understanding of the underlying mechanisms. Despite these limitations, this is the first paper to compare FPA and NFPA using the VIS score with no statistical baseline or ophthalmic characteristic differences, thus providing new insights into their different hormonal impacts on visual outcomes.

CONCLUSIONS

Our study showed that although the duration of symptoms before diagnosis, tumor size, patient's age at initial visit, sex, presence of pituitary apoplexy, type of surgery, and adjuvant radiation, as well as initial VA and VIS, did not significantly differ between FPA and NFPA. Patients with FPA had better visual outcomes after surgery. This suggests that the type of adenoma could be an important factor in visual recovery. This study was the first to compare FPA and NFPA using the VIS score, offering new insights into the visual prognosis of these patients.

Future research should explore the molecular and genetic features of pituitary adenomas prospectively to better understand the differences in visual outcomes.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

ADDITIONAL INFORMATION

Author contributions

P.K.: conceptualization, investigation, methodology, formal analysis, validation, writing – original draft; L.H.: Conceptualization, investigation, methodology, supervision, writing – review and editing; C.P.: Data curation, investigation; P.T.: data curation; T.V.: supervision, investigation; K.U.: supervision, investigation.

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Original Article

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Prevalence of and Risk Factors for Caregiver Burden in Palliative Care in Thailand

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ABSTRACT

OBJECTIVE Caregivers are highly important in both conventional and palliative care. Their responsibilities, which include biological, psychological, and social aspects, can lead to stress and other complications. The objectives of this study were to determine (i) the prevalence of caregiver burden in palliative care and its severity, and (ii) risk factors associated with caregiver burden in palliative care settings.

METHODS This cross-sectional study was conducted with palliative care patients and main caregivers in palliative care in both in- and out-patient departments of a hospital in Thailand. Baseline characteristics of caregivers and patients, including patients' quality of life, caregivers' self-efficacy, and caregiver burden were collected using Zarit Burden Interview (ZBI) scores. Linear regression was used to determine the association between caregiver burden and potential risk factors.

RESULTS One hundred and two caregivers and their patients were included in the analysis. Caregivers' mean age was 48.2±13.1 years. Most were female (77.5%) and married (65.7%). The mean age of the 102 patients of those caregivers was 64.9±13.8 years. The majority were female (57.8%) and most lived together with their caregiver (72.6%). The mean ZBI score of the caregivers was 13.4±13.9 of whom one-fourth had experienced caregiver's burden (23.53%), with most having mild severity (17.7%). Factors negatively associated with ZBI scores were the patient's quality of life (coefficient -0.46, 95% CI -0.89 to -0.04, p = 0.027) and the caregiver's self-efficacy (coefficient -0.17, 95% CI -0.31 to -0.02, p = 0.033).

CONCLUSIONS The prevalence of caregiver burden in Thai palliative caregivers is relatively small. Greater caregiver self-efficacy and improved patient quality of life may help reduce caregiver burden. Assessment of caregiver burden level should be included as an integral aspect of the patient-care process.

KEYWORDS caregiver, burden, burnout, palliative care, hospice care

INTRODUCTION

According to the World Health Organization (WHO), palliative care is "the prevention and relief of suffering of patients and their families facing problems associated with life-threatening illness. These problems include the physical, psychological, social, and spiritual suffering of patients, and psychological, social, and spiritual suffering of family members (1)." Palliative care can be integrated with conventional care, including clinical

assessment and management, to help relieve suffering through communication between the patient, the patient's family, and the health care team. Palliative care can provide a better quality of life, including increased patient and caregiver satisfaction and can help in the development of a plan of management. It can also lead to improved medical resources distribution (2, 3). Thailand has been classified by the World Health Organization as an aging society, with the proportion of older adults increasing annually (4), resulting in an increase in age-related disability which may consequently lead to increased demand for palliative care (5).

Caregivers are irreplaceable and arguably one of the most important factors in both conventional and palliative care. Their responsibilities almost always include biological, psychological, and social factors related to the patient. Commonly the role of the caregiver includes decision making, assistance with daily activity, caring for other family members, and economic management. The presence of a caregiver can also result in emotional dependency of the patient on the caregiver (6, 7). Research in older populations has found that approximately one-fourth of caregivers for older adults had poor mental health scores. Significant factors related to caregivers' poor mental health include the functional dependence of the patient on the caregiver, the duration of care, and the caregiver's financial status (8, 9). In Thailand, placing older patients in a nursing home is sometimes considered as "abandonment" (10). All these factors sometimes pressure children to take care of the older adults themselves in addition to being responsible for other roles, which can lead to caregiver burden.

Caregiver burden is defined as a feeling of burden "including the caregiver's health, psychological well-being, finances, and social life as well as the relationship between the caregiver and the impaired person" (11). The level of caregiver burden is a subjective appraisal of objective experience from the caregiver's point of view. The caregiver burden affects both the caregiver and the care receiver (12). For caregivers, caregiver burden is significantly associated with caregiver burnout and strain, terms which are sometimes used interchangeably (13-15). Caregiving strain is significantly associated with a higher estimated stroke risk and mortality rate. Highly strained caregivers were almost two times more likely to die than caregivers reporting some strain over an average period of 5.29 years (16, 17). The caregiver burden is also associated with negative psychological health such as depression and anxiety (18-20). In terms of the social aspect, caregiver burden has negative consequences on physical activity and work productivity (21). Overall, caregiver burden is associated with lower quality of life (22). It is important to note that care-receivers also experience the impact of caregiver burden, including mistreatment and abusive behavior (23-25). Exploring potential risk factors for caregiver burden could potentially be beneficial for planning strategies for the reduction and prevention of caregiver burden.

Caregiver burden affects multiple dimensions of the individual, including physical, psychological, social, and spiritual aspects. Sleep disturbance is the most prominent physical effect. Other symptoms include fatigue, weakness, weight loss, and back pain among others. Depression is also common in the psychological domain. Socially, the caregiver spends time on caregiving, which leads to limited opportunities for interaction with others. Reduced work hours and high financial demands may result in financial problems. Caregiver burden can also have an impact on the spiritual well-being of the caregiver. These effects are often present in both palliative and non-palliative caregivers (26).

Although the caregiver burden in palliative care has recently been studied in many countries, the latest study in Thailand was done almost ten years ago. That study included informal caregivers of older adults with advanced cancer (27). The prevalence of caregiver burden in the present study was 37% of whom 31% had a mild burden. Internationally the prevalence of caregiver burden in palliative care has been higher (47.4% to 96.2%) (28-31). Risk factors found in previous studies include, e.g., age, gender, education, caregiver income, relation with the patient, hours of care per day, and the caregiver's self-efficacy and satisfaction as well as the patient's functional status and their quality of life (27, 28, 32-41). Changes in resources, management, and policies, including cultural changes, may result in different outcomes. The objective of this study is to conduct an exploratory investigation to determine (i) the

prevalence and severity of caregiver burden in palliative care and (ii) risk factors associated with caregiver burden in the case of palliative care patients.

METHODS

Study design and setting

This cross-sectional study was conducted at Maharaj Nakorn Chiang Mai Hospital, a tertiary care hospital which has one of the largest palliative care units in northern Thailand providing both in-patient and out-patient care. The palliative care unit accepts both cancer and non-cancer patients through consultations with other medical specialties.

Study population

Participants included dyads of caregivers and their care receivers. For the caregivers, the inclusion criteria were (i) age ≥ 18 years old, (ii) being a main caregiver and (iii) being able to communicate in Thai. The exclusion criteria were (i) diagnosed with schizophrenia, bipolar disorder, psychosis, or dementia, (ii) appearing to be in emotional distress or situation, e.g., immediately after receipt of bad news, after an acute life-threatening event, or the end-of-life process, and (iii) not currently working as a caregiver. For the patients, the inclusion criteria were (i) age ≥ 18 years and (ii) undergoing palliative care during the information-gathering period.

Sampling method

Non-probability, convenience, and consecutive sampling methods were used. The caregivers were approached individually by research assistants during the patient's admission to the hospital or outpatient clinic. The details of the study were explained to the eligible participants. If they agreed to participate, consent regarding the study protocol was obtained via the digital (RedCap program) or as a written consent form.

Study tools

Data were obtained on caregivers' characteristics (e.g.,age, gender, income status), care-receivers' characteristics (e.g., age, gender, insurance status), palliative performance scale (PPS), patient's functional status and quality of life (EQ-5D-5L, Thai version (EuroQol Group)), caregivers' perceived self-efficacy and Zarit Burden Interview (ZBI) results. The PPS tool requires professional evaluation which was provided by health care providers. Other tools and questionnaires were administered by the study researchers.

Palliative Performance Scale (PPS)

The PPS is an assessment form for measuring health decline in palliative patients and their prognosis. It consists of five dimensions: ambulation, activity level and evidence of disease, self-care, intake, and level of consciousness. The scale ranges from 0 percent (deceased) to 100 percent (maximum health and function) with 10 percent increments. This study used the Thai version of PPS (Chiang Mai University, Thailand) (42). The Cohen's kappa reliability test score from a study of Thai nurses and physicians was 0.55, indicating moderate agreement (43). This tool is available for public use.

The 5-level EQ-5D version (EQ-5D-5L)

The EQ-5D-5L questionnaire, developed by the EuroQol Group in 2009, includes five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels ranging from no problems to extreme problems (score 1 to 5). The visual analog part uses a qualitative scoring system ranging from 0 to 100. Respondents are asked to 'mark an X on the scale to indicate how your health is TODAY'. From a study of Thai patients, the intraclass correlation coefficient of the EQ-5D-5L was 0.89 and the weighted kappa coefficients ranged from 0.44 to 0.60 in the five dimensions of the EQ-5D-5L (44). The present study used the visual analog part of this questionnaire (45). Written permission was obtained from the EQ-5D-5L group.

The Perceived Self-Efficacy Score (PSE)

The PSE assessment consists of ten items, for example, 'I can always resolve difficult problems' and 'I can face problems calmly'. Using a 4-point scale from 1 (very true) to 4 (false), the maximum total score is 40. Higher scores indicate perceived better self-efficacy. The Thai version of the tool was developed by Sukmak et al., and its Cronbach alpha coefficient is 0.84 (46).

Zarit Burden Interview (ZBI), Thai version

The ZBI consists of 22 items, using a 5-point scale ranging from 0 (never) to 4 (always). ZBI scores (range 0 to 88) are classified as no burden (0-20), mild burden (21-40), moderate burden (41-60), and severe burden (61-88). These can be categorized dichotomously as no burden (0-20) and burden (21-88). The Thai version of the 22-Zarit burden scale was developed by Toonsiri et al. and has been used in a study of a in chronic disease population, showing a Cronbach's alpha of 0.92 (47).

Data collection and procedures

Caregivers and patients (if conscious) were approached by a research assistant to obtain their consent to participate in the study. Caregivers were then interviewed separately from their patient to minimize response bias. Data collection was conducted from August 2022 through September 2023. Data was collected by the researcher and research assistants (nurses). Research assistants asked participants for consent and also assisted in data collection. Prior to the data collection process, a meeting with the assistants was held to clarify the objectives of the study, to familiarize them with the study tools, and to review the questionnaire. The first few interviews were supervised by the researcher after which the research assistants conducted interviews alone to minimize variability.

Questionnaire administration

Participants were interviewed by the researcher or an assistant and were advised to ask if they had any questions and to stop if they began feeling uncomfortable. Participants took approximately 15 minutes to complete the questionnaire with help from a research assistant, e.g., to clarify the meaning of words.

Sample size calculation

Sample size was calculated using Statulator (https://statulator.com/SampleSize/ss1P.html). The infinite population proportion with 95% confidence interval and 10% precision was used. Based on the 2012 study Burden among Caregivers of Older Adults with Advanced Cancer and Risk Factors by Chindaprasirt et al. (27) which was conducted with older adults with advanced cancer in Srinagarind Medical School Hospital, the expected incidence of caregiver burden was 37%, suggesting a sample size of 90 participants. Available data was collected from 100 caregivers-patient pairs.

Statistical analysis

Data analysis was done using Stata 16 (StataCorp, College Station, TX, USA). Categorical variables, e.g., gender, highest educational level, and marital status, are presented as numbers and percentages, and continuous variables are presented as means and standard deviations (SD). Inferential statistics utilizing the Chi-square and t-test were used to evaluate correlation. Linear regression was used to analyze the association between caregiver burden score (ZBI) and other variables using an exploratory approach. *P* values < 0.05 were considered statistically significant. Correlation coefficients and 95% confidence intervals (CI) are reported to indicate the strength of association between variables.

RESULTS

One hundred and two patient-caregiver pairs were included in this study.

Caregivers' characteristics

Categorizing caregivers into those with caregiver burden and those without, the caregivers' mean age was 49.3±2.6 and 47.8±1.5 years, respectively. More than one-third were female in both groups (79.2% in the group with caregiver burden and 76.9% in the group without). The mean value of perceived self-efficacy was 29.9±1.7 in the group with caregiver burden and 33.4±0.7 in the group without caregiver burden ($p = 0.024$). Caregivers' career change after caring, confidence in their caregiving ability, and perceived self-efficacy were statistically significantly different between the groups, while there was no difference in other variables, e.g., age, gender, education level, marital status, income, etc. Details of caregivers' characteristics are presented in Table 1.

Patient characteristics

The mean age of patients of caregivers with caregiver burden and those without was 67.7±2.3 and 64.1±1.6 years, respectively. More than half the patients were female (75.0% in the burdened

Table 1. Caregiver characteristics by caregiver burden status

Demographic characteristics	Frequency n (%)		*p*-value
	Burden (n=24)	No burden (n=78)	
Age (years) (Mean±SD)	49.3±2.6	47.8±1.5	0.648
Gender			0.818
Male	5 (20.8)	18 (23.1)	
Female	19 (79.2)	60 (76.9)	
Highest education level			0.261
None	0 (0.0)	1 (1.3)	
Primary school	2 (8.3)	15 (19.2)	
Middle school	4 (16.7)	4 (5.1)	
High school	2 (8.3)	6 (7.7)	
(High) Vocational Certificate	5 (20.8)	7 (9.0)	
Bachelor's degree	9 (37.5)	33 (42.3)	
Higher than Bachelor's degree	2 (8.3)	12 (15.38)	
Marital status			0.606
Married	18 (75.0)	49 (62.8)	
Unmarried	5 (20.8)	23 (29.5)	
Divorced	1 (4.2)	3 (3.9)	
Widowed	0 (0.0)	3 (3.9)	
Household income (THB per month)			0.576
< 5000	4 (16.7)	8 (10.3)	
5,000-10,000	3 (12.5)	7 (9.0)	
> 10,000	17 (70.8)	63 (80.8)	
Career change after caring			0.030
Yes	9 (37.5)	13 (16.7)	
No	15 (62.5)	65 (83.3)	
Underlying diseases			0.640
Yes	10 (41.7)	28 (36.4)	
No	14 (58.3)	49 (63.6)	
Other caregivers			0.885
Yes	20 (83.3)	64 (82.1)	
No	4 (16.7)	14 (18.0)	
Living with the patient			0.758
Yes	18 (75.0)	56 (71.8)	
No	6 (25.0)	22 (28.2)	
Relationship with patient			0.609
Spouse	6 (25.0)	16 (20.5)	
Parent	0 (0.0)	5 (6.4)	
Child	14 (58.3)	37 (47.4)	
Grandchild	1 (4.2)	9 (11.5)	
Sibling	2 (8.3)	5 (6.4)	
Others	1 (4.17)	6 (7.69)	
(e.g., In-laws, Neighbor)			0.249
Duration of care per day	7 (29.2)	33 (42.3)	
<14 hours	17 (70.8)	45 (57.7)	
≥14 hours			
Health care service satisfaction level			0.654
Lowest	0 (0.0)	0 (0.0)	
Low	0 (0.0)	0 (0.0)	
Middle	0 (0.0)	1 (1.3)	
High	6 (25.0)	14 (18.0)	
Highest	18 (75.0)	63 (80.8)	
Confidence in caring			0.006
Lowest	2 (8.3)	1 (1.3)	
Low	0 (0.0)	1 (1.3)	
Middle	7 (29.2)	5 (6.4)	
High	10 (41.7)	35 (44.9)	
Highest	5 (20.8)	36 (46.2)	
Perceived self-efficacy (Mean±SD)	29.9±1.7	33.4±0.7	0.024

group and 52.6% in the non-burdened group). There was a statistically significant difference in quality of life on the visual analog scale between groups: 33.2±3.5 in the burdened caregiver group and 52.2±2.4 in the non-burdened caregiver group (p = <0.001). Other characteristics, gender, insurance, and PPS, revealed no statistically significant difference. Table 2 shows patient characteristics.

Caregiver burden among palliative caregivers

The ZBI scores were categorized into non-burdened (0-20) and burdened caregivers (21-88), with three levels of severity: mild (21-40), moderate (41-60), and severe (61-88). About three-fourths showed no burden (76.47%). Caregivers (23.53%) were further categorized as having mild burden, moderate burden, and severe burden which were 17.7%, 4.9%, and 1.0%, respectively. The mean ZBI score was 13.4±13.9. There was a statistically significant inverse association between ZBI score and the caregivers' perceived self-efficacy (coefficient -0.46, 95%, CI -0.89 to -0.04) as well as patients' quality of life by analog scale (coefficient -0.17, 95% CI -0.31 to -0.02) (p < 0.05). Both variables appeared to be protective factors against caregiver burden. Other caregivers' sociodemographic and patients' characteristics did not show a statistically significant association with ZBI scores. The data are shown in Table 3.

DISCUSSION

Palliative caregivers were mainly middle-aged females with an education level above bachelor's degree, most were married and lived together with the patient. Half the caregivers were patients' children age under xx and approximately one-fourth were the spouse of the caregiver patients. Care-receivers were mostly elderly females who were eligible for Thailand's Universal Health-care Coverage and who had a PPS score of 30-40. Approximately one-fourth of the caregivers had caregiver burden. Caregiver burden was statistically significantly inversely associated with the caregivers' perceived self-efficacy and the patients' quality of life.

The caregivers' characteristics are similar to previous studies in Asian countries (27). Unsurprisingly, most of the caregivers were female, a common prevalence among caregivers in many countries (48-50). Culturally, females often have a gender ideal of a "nurturing" role that puts them at a disadvantage in caregiving arrangements, while males have a more "masculine" image and are more flexible in such arrangements (51).

Table 2. Caregiver characteristics by caregiver burden status

Demographic characteristics	Frequency n (%)		p-value
	Burden (n=24)	No burden (n=78)	
Age (years) (Mean±SD)	67.7±2.3	64.1±1.6	0.261
Gender			0.052
Male	6 (25.0)	37 (47.4)	
Female	18 (75.0)	41 (52.6)	
Insurance			0.553
Government officer	12 (50.0)	32 (41.0)	
Social service	3 (12.5)	7 (9.0)	
Universal coverage	9 (37.5)	39 (50.0)	
Palliative Performance Scale			0.290
10	2 (8.3)	2 (2.6)	
20	4 (16.7)	6 (7.7)	
30	8 (33.3)	19 (24.4)	
40	6 (25.0)	19 (24.4)	
50	0 (0.0)	8 (10.3)	
60	2 (8.3)	13 (16.7)	
70	2 (8.3)	6 (7.7)	
80	0 (0.0)	5 (6.4)	
Quality of life (EQ-5D-5L) – Visual analog scale (Mean ± SD)	33.2±3.5	52.2±2.4	<0.001

Table 3. Association between caregiver burden and caregiver and patient characteristics

Caregiver burden	Coefficient	*p*-value	95% confidence	Interval
Caregiver characteristics				
Age	-0.07	0.592	-0.31	0.17
Male	-2.61	0.425	-9.10	3.87
Education level	0.31	0.756	-1.67	2.29
Marital status	-3.33	0.097	-7.27	0.62
Household income	-3.83	0.177	-9.43	1.77
Career change	5.04	0.162	-2.06	12.15
Underlying disease	3.47	0.270	-2.74	9.78
Other caregivers	-0.42	0.909	-7.74	6.90
Living with the patient	-0.30	0.926	-6.77	6.17
Relation	-0.45	0.628	2.27	1.37
Duration of care	3.68	0.288	-3.16	10.51
Healthcare service satisfaction level	-4.08	0.206	-10.44	2.28
Confidence in caring	-0.80	0.640	-4.17	2.58
Perceived self-efficacy	-0.46	0.033	-0.89	-0.04
Patient characteristics				
Age	-0.02	0.856	-0.23	0.19
Gender	-1.39	0.631	-7.12	4.34
Insurance	0.46	0.770	-2.64	3.55
Palliative Performance Scale	-1.04	0.289	-2.98	0.90
Quality of life-VA	-0.17	0.027	-0.31	-0.02

Whether male or female, caregivers were almost always a member of the family of the patient.

Approximately one-fourth of the caregivers in this study were classified as having caregiver burden, and in more than half the cases, the burden was of mild severity. This result is consistent with another study in Thailand conducted by Chindaprasirt et al., in which the prevalence of caregiver burden among informal caregivers of elderly patients with advanced cancer was also around one-third (37%), with more than half having a mild burden (31%) (27). Studies in Thailand of caregiver burden in cases of patients with more severe conditions, however, showed a higher prevalence of caregiver burden, e.g., around half the caregivers of stroke patients and eighty percent of the caregivers of elderly individuals with physical disabilities had caregiver burden (33, 52-53). Studies in Malaysia, Spain, Brazil and Saudi Arabia have reported a higher prevalence of palliative caregiver burden at 47.4%, 63.7%, 88% and 96.2%, respectively (28-31).

The ZBI score's mean value in this study was 13.4±13.9. This is on the low side compared to ZBI scores in many other studies, but is consistent with a previous study in Thailand where the mean ZBI score was 19.15 + 12.85 among palliative caregivers, with one-third having experienced caregiver burden (27). Both the ZBI scores and the incidence of caregiver burden are also consistent with many studies of palliative caregivers, e.g., a study in Malaysia showed a mean ZBI score of 23.33±13.7 with half of the caregivers found to have caregiver burden (28). A study from Turkey, however, had a mean ZBI score of 52.12±16.1 (54).

Variables included in the present study were selected based on risk factors included in previous studies conducted in both palliative and non-palliative care settings. For example, a study in Malaysia conducted in palliative care units showed that being highly educated and spending more than 14 hours per day on caregiving was related to a higher risk of caregiver burden (28). On the other hand, in another study less educated caregivers were found to be associated with a lower incidence of caregiver burden (34). The age and gender of both the caregiver and care-receiver have been identified as risk factors, as has a spousal relationship with the care-receiver and the financial status of the caregiver (34-36). The caregiver's self-efficacy, confidence and satisfaction level as well as the patient's quality of life were also found to be inversely associated with caregiver burden (32, 37-39, 55). In Thailand, the caregiver's age, gender, marital status, educational level, and the care-receiver's functional status have been re-

ported to be associated with caregiver burden (27, 33, 40, 41). However, none of these factors were found to be associated with caregiver burden in the present study.

In this study, factors found to be protective against caregiver burden include caregiver's perceived self-efficacy and patient's quality of life. Contrarywise, a study in Turkey of caregivers of cancer patients reported that self-efficacy was found to have a negative association with the caregiver burden score (56). Studies using a different tool (FACIT-Pal) have reported that higher patient quality of life is associated with a higher caregiver burden (57). However, in this study, the correlation was minimal, suggesting that this relationship should be carefully considered before taking action.

A study of caregivers for cancer patients showed that an individualized caregiver training intervention focused on infection prevention, pain control, nutrition, and specific care issues significantly increased caregiver self-efficacy (58). A 4-session online psychoeducation program, "Learning Skills Together," showed an improvement in mean caregiver self-efficacy in caregivers of dementia patients (59). Establishing the existence of a causal relationship between caregiver self-efficacy, the patient's quality of life, and caregiver burden might not be possible due to the cross-sectional nature of the present study. Greater caregiver self-efficacy, defined as "a person's perception of their ability to perform tasks related to caregiving competently, capably, and with control" (60), and better patient quality of life might mitigate caregiver burden. Further prospective studies to follow up patients might be beneficial.

This study has some limitations. First, being a cross-sectional study limits interpretation of the causality of relationships. Second, the relatively small sample size might lead to an increased error rate and less precise data interpretation. Third, due to time limitations for interviews and the emotional state of some of the caregivers, the selection of participants focused primarily on the more stable patient-caregiver pairs among the Thai participants' results may be different in other palliative situations, e.g., end-of-life care. Finally, using data from a single hospital setting may reduce the study's generalizability. A qualitative study exploring caregivers' perspectives might be beneficial in increasing understanding of underlying problems related to caregiver burden.

CONCLUSIONS

Although the prevalence of caregiver burden in this study could be considered relatively small, identification of factors associated with caregiver burden should be considered a crucial part of holistic care and palliative care. Increased caregiver self-efficacy and patient quality of life could potentially reduce caregiver burden. Caregiver burden assessment and management should be included in the patient care process. Appropriate and timely intervention may result in better care and better health for both patients and caregivers.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

ADDITIONAL INFORMATION

Author contribution

C.R.: conceptualization, methodology, data collection, analysis, writing–review and editing; N.B.: methodology, analysis, writing–review and editing; K.P.: conceptualization, analysis, writing–review and editing; N.D.: data collection, analysis, writing–review and editing; L.C.: supervision, writing–review and editing; T.R.: supervision, writing – review and editing; A.C.: conceptualization, methodology, analysis, writing – review and editing.

Data availability statement

"The data that support the findings of this study are available from the corresponding author upon reasonable request."

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Original Article

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Incidence of Cardiotoxicity Associated with the Use of Pegylated Liposomal Doxorubicin in Gynecologic Malignancies

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ABSTRACT

OBJECTIVE This study aims to evaluate the incidence of cardiotoxicity in patients with gynecologic cancer undergoing pegylated liposomal doxorubicin (PLD) treatment and to identify risk factors for developing changes in the left ventricular ejection fraction (LVEF).

METHODS A retrospective analysis was conducted on patients with gynecologic malignancies who had received PLD treatment at Phramongkutklao Hospital from January 2013 through December 2022. Cardiotoxicity was defined as a confirmed diagnosis of congestive heart failure or a decline in LVEF of 10% or more. Spearman's correlation and mixed modeling were used to analyze the relationship between patient factors and MUGA variations.

RESULTS A total of 34 patients were included in the study. The median number of PLD cycles was six, with a median cumulative dose of 240 mg. No patient experienced doxorubicin-induced cardiotoxicity. Among the 19 patients with available pre- and post-treatment LVEF measurements, no significant decline in LVEF was observed following PLD (MD 6.6%, p = 0.124). However, Spearman's correlation analysis revealed a negative correlation between high cumulative PLD doses (exceeding 1,500 mg) and LVEF change (coefficient = -0.53, $p < 0.001$). Mixed model analysis suggested a potential association between higher body mass index (BMI) and decreased LVEF post-treatment ($\beta = -1.21$, $p = 0.036$), while diabetes may be associated with improved LVEF outcomes ($\beta = 12.18$, $p = 0.033$).

CONCLUSIONS There were no cases of cardiotoxicity after PLD treatment. A potential association between higher BMI and decreased LVEF was found. A high cumulative PLD dose is correlated negatively with LVEF change. Cardiac monitoring is recommended for selected patients, particularly those who are obese or have received cumulative PLD doses exceeding 1,500 mg.

KEYWORDS pegylated liposomal doxorubicin, anthracycline, gynecologic cancer, cardiotoxicity

INTRODUCTION

Pegylated liposomal doxorubicin (PLD) is one of the mainstay chemotherapy treatments for advanced or recurrent gynecologic cancer because of its efficacy and tolerable toxicity (1, 2). PLD has been previously shown to have a safer cardiac toxicity profile compared with doxorubicin (3, 4). However, due to the lack of consistent standards

and recommendations, anthracycline-induced heart failure remains a source of concern and confusion in some aspects of cardiotoxicity monitoring. Cardiac function evaluation before PLD treatment can include multiple-gated acquisition (MUGA) or echocardiography (5). Subsequently, repeat testing may be performed at the physician's discretion. Several studies have demonstrated that gynecological cancer patients who received PLD did not develop heart failure or a decrease in left ventricular ejection fraction (LVEF) (6, 7). However, patients who received a high PLD dose and individuals with preexisting cardiovascular disease experienced doxorubicin-induced cardiotoxicity (8). Therefore, the necessity for and cost-effectiveness of LVEF monitoring in this patient population remains unclear.

The present study was conducted to investigate the incidence of anthracycline-induced cardiotoxicity among PLD-treated gynecologic cancer patients with the aim of establishing associations between LVEF changes and the cumulative dose of PLD, as well as correlations between LVEF changes and presumed risk factors.

METHODS

A retrospective study was conducted at Phramongkutklao Hospital in Bangkok, Thailand, between January 1, 2013 and December 31, 2022. The study protocol was approved by the hospital Institutional Review Board. The study cohort consists of gynecologic cancer patients who had undergone chemotherapy with PLD. Patients who received conventional doxorubicin treatment and those with incomplete medical records were excluded. A previous study reported a cardiotoxicity rate of 3 out of 235 cases in patients who were administered PLD (9). Based on that information, a sample size of 17 was determined, with a margin of error of 0.05. Clinical data were obtained from medical records and included demographic information such as age, height, and weight, as well as co-morbidities such as hypertension, diabetes mellitus, and dyslipidemia. Additionally, information on pre-existing cardiovascular diseases such as cerebrovascular accidents, venous thromboembolism, chronic kidney disease, and myocardial and pericardial disorders was collected.

Information was acquired on the types, grades, and International Federation of Gynecology and Obstetrics staging of the gynecologic cancers. For PLD, we focused on the number of cycles, the mean dosage per cycle, and the cumulative dose. We obtained LVEF data from a MUGA scan or echocardiography as a percentage before therapy as well as a subsequent value after PLD use. Doxorubicin-induced cardiotoxicity can manifest in two situations: 1) in patients diagnosed with congestive heart failure during PLD treatment, and 2) in asymptomatic patients whose LVEF decreased by over 10% from baseline (5).

Statistical analyses were conducted using STATA version 17. Descriptive statistics are reported as frequency (percentage), mean ± standard deviation, and median (interquartile range). Spearman's correlation was used to measure the correlation between patient factors and MUGA variations. The mixed model was used to conduct univariate and multivariate analyses due to the small sample size and the non-normal data distribution. A p-value < 0.05 was considered statistically significant.

RESULTS

The study identified 38 gynecologic cancer patients treated with PLD between 2013 and 2022. From that number, three patients who had received conventional doxorubicin and one patient with missing LVEF data were excluded, giving a study population of 34 patients. The baseline characteristics of the included patients are described in Table 1. Fourteen patients had primary disease, while 20 had recurrent disease. A total of 24 ovarian cancer cases, 6 endometrial cancer cases, 3 peritoneal cancer cases, and 1 fallopian tube cancer case had previously been identified. The average age of the patients was 58 years and the average body mass index (BMI) was 23.75 kg/m^2. Pre-existing medical conditions included cardiovascular disease (5 cases), hypertension (12 cases), dyslipidemia (11 cases), and diabetes (5 cases). The majority (82%) had received a PLD dose of 40 mg/m^2. The median cumulative PLD dose was 240 mg (IQR: 140–360 mg). The median number of cycles per patient was six (IQR: 3–9 cycles). Pre-treatment LVEF averaged 61.78%. The first and second post-treatment measurements showed an average LVEF of 66% and 65%, respectively (Table 2).

Table 1. Patients' baseline characteristics data (N = 34)

Characteristics	N (%)
Age (years)	58.15±10.76
Height (cm)	155.88±5.85
Weight (kg)	57.5±12.31
BMI (kg/m^2)	23.75±5.34
Type of cancer	
Endometrium	6 (17.7)
Fallopian tube	1 (2.9)
Ovary	24 (70.6)
Peritoneum	3 (8.8)
Treatment type	
Primary disease	14 (41.2)
Recurrent disease	20 (58.8)
Underlying disease	
Hypertension	12 (35.3)
Dyslipidemia	11 (32.4)
Diabetes mellitus	5 (14.7)
Cardiovascular disease	5 (14.7)

Table 2. Treatment data of patients receiving pegylated liposomal doxorubicin (PLD) (N = 34)

Treatment data	N (%)
PLD dose	
40 mg/m^2	28 (82.4)
30 mg/m^2	6 (17.6)
Number of previous CMT regimens (cycles), median [IQR]	9 [6, 12]
Numbers of PLD given (cycles), median [IQR]	6 [3, 9]
Accumulated PLD dose (mg), median [IQR]	240 [140, 360]
Clinical CHF	0 (0.0)
%LVEF decreases > 10%	0 (0.0)
%LVEF from MUGA	
Pre-treatment LVEF (n=34)	61.78±12.55
1st follow-up LVEF (n=19)	66.11±8.97
2nd follow-up LVEF (n=12)	65.67±7.87

CHF, congestive heart failure; CMT, chemotherapy; MUGA, multiple-gated acquisition; LVEF, left ventricular ejection fraction

No patient developed congestive heart failure during PLD therapy. Nineteen patients underwent pre-treatment and the first follow-up LVEF assessment. Although a mean improvement of 6.6% in LVEF was observed following PLD treatment (pre-treatment: 59.5%, follow-up: 66.1%), this change was not statistically significant (p = 0.124).

Among the investigated factors associated with LVEF changes (Table 3 and Figure 1), PLD appears to have had no impact on LVEF when the total dosage used was below 660 mg. However, we observed a significant decrease in LVEF for patients who received a higher cumulative dose of between 1,560 mg and 1,680 mg (correlation coefficient = -0.53, $p < 0.001$). Both BMI and the number of PLD cycles were statistically significantly associated with a negative impact on LVEF, with correlation coefficients of -0.47 and -0.48, respectively. Hypertension and dyslipidemia also demonstrated negative correlations with LVEF, but those associations were not statistically significant. In contrast, patient age was positively associated with LVEF changes with a correlation coefficient of 0.35. Diabetes was also found to have a positive association with LVEF; however, the effect correlation was not statistically significant.

Table 3. Spearman's rank correlation of various risk factors and LVEF changes

Variables	LVEF change	
	r	p-value
Weight	-0.464	0.005
BMI	-0.470	0.004
Age	0.355	0.036
PLD dose	-0.270	0.117
Accumulated PLD dose	-0.530	0.001
Cycles of PLD given	-0.483	0.003
Hypertension	-0.037	0.832
Dyslipidemia	-0.149	0.393
Diabetes mellitus	0.310	0.070
Cardiovascular disease	0.165	0.342

BMI, body mass index; LVEF, left ventricular ejection fraction; PLD, pegylated liposomal doxorubicin

In univariate regression analysis, five variables were found to be statistically linked with LVEF changes: BMI, age, accumulated dose of PLD, cycles of PLD administration, and diabetes. The multivariate regression analysis showed that BMI is a significant predictor of negative changes in LVEF, with a β coefficient of -1.21 and a p-value of 0.036, while diabetes is statistically associated with increases in LVEF (β = 12.18, p = 0.033). The patient's age is also statistically associated with slightly positive changes in LVEF (β = 0.61, p = 0.035). Multivariate analysis showed that the cumulative dose and number of PLD cycles had no statistically significant effect on LVEF change (Table 4).

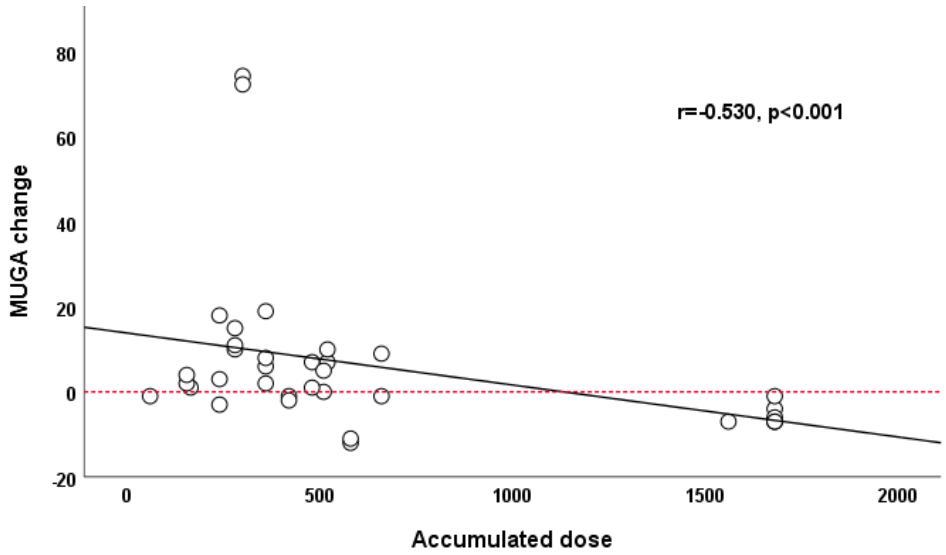

Figure 1. Correlation between accumulated PLD dose and LVEF changes

Table 4. Univariate and multivariate regression analysis by mixed model

Variables	Univariate				Multivariate			
	Beta coefficients	95%CI		*p*-value	Beta coefficients	95%CI		*p*-value
Weight	-0.70	-1.13	-0.26	0.002*				
BMI	-1.28	-2.33	-0.22	0.018*	-1.21	-2.35	-0.08	0.036*
Age	1.00	0.29	1.71	0.006*	0.61	0.04	1.17	0.035*
PLD dose	-0.02	-1.30	1.27	0.978				
Accumulated dose	-0.01	-0.02	0.00	0.022*	0.01	-0.05	0.06	0.775
Cycles of PLD given	-0.82	-1.59	-0.04	0.039*	-0.24	-3.94	3.47	0.900
Hypertension	5.26	-6.78	17.30	0.392				
Dyslipidemia	2.92	-9.20	15.05	0.637				
Diabetes mellitus	20.70	8.10	33.29	0.001*	12.18	0.97	23.38	0.033*
Cardiovascular disease	-0.57	-16.54	15.41	0.944				

PLD, pegylated liposomal doxorubicin

DISCUSSION

We observed around 50% of the cohort using MUGA scans for cardiac monitoring. There were no incidences of anthracycline-induced cardiotoxicity in the PLD-treated gynecologic patients. There were no significant differences between LVEF prior to and following PLD therapy (mean difference 6.6%, p = 0.124). None of the patients in the cohort presented with high-risk factors for cardiotoxicity, e.g., a history of chest wall/mediastinal radiotherapy or a previous diagnosis of congestive heart failure (10) which could explain the low incidence of anthracycline-induced cardiotoxicity in our group.

Cumulative PLD dosages below 660 mg showed no effect on LVEF variations. In contrast, a high cumulative PLD dose was correlated negatively with LVEF change. Previous studies have reported that LVEFs demonstrate a clinical reduction when exposed to cumulative doses exceeding 1,000 mg/m^2 (9, 11). Several previous studies have reported no significant association between high cumulative PLD doses (exceeding 1,000 mg/m^2) and cardiotoxicity (7). One study reported minimal LVEF changes in only 14% of patients within the high-dose group (3). In the present study, two of the thirty-four patients with PLD levels of 1,560 and 1,680 mg, respectively, did not develop clinical heart failure. While Spearman's analysis indicated a negative correlation between high PLD dose and LVEF change, this relationship did not show statistical significance in multivariate analysis. This discrepancy may be due to the small sample size, with only two cases exceeding 1,000 mg PLD doses.

Mixed model analysis indicates that obesity significantly reduces LVEF. A retrospective study investigating breast cancer patients treated with anthracyclines reported an association between obesity and cardiotoxicity (odds ratio [OR] 3.02; 95%CI 1.10–8.25; $p = 0.03$) (12). Surprisingly, diabetes seems to have a statistically significant beneficial effect on LVEF changes, although other cardiovascular risk factors, e.g., underlying cardiovascular disease, hypertension, and dyslipidemia, do not show a significant effect on the change in LVEF. However, as the present study had a limited sample size, further research with a larger number of participants is needed to confirm these findings.

A strength of the study is that a greater proportion of the patients had undergone cardiac monitoring which aided the effort to establish a correlation between LVEF changes and several potential risk factors. Limitations include a relatively small sample size. Lack of sufficient Data on the median follow-up duration was also a challenge in our study.

Our findings suggest that routine cardiac monitoring may not be necessary for most gynecologic cancer patients undergoing PLD. However, continuous cardiac monitoring should be considered for high-risk patients (8), such as those who are obese or have received cumulative PLD doses exceeding 1,500 mg.

CONCLUSIONS

There were no cases of cardiotoxicity after PLD treatment. A potential association between higher BMI and decreased LVEF was found. A high cumulative PLD dose is correlated negatively with LVEF change. Cardiac monitoring should be considered in selected patients.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

ADDITIONAL INFORMATION

Author contributions

T.A.: Data curation, writing- original draft preparation; S.P.: conceptualization, methodology, writing – review & editing; K.R.: review & editing; S.I.: supervision, review & editing.

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Original Article

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Association Between use of a Single-Piston CPR Device in the Resuscitation Process and the Short-Term Survival of OHCA Patients

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ABSTRACT

OBJECTIVE There is still a lack of evidence regarding the efficacy of using a single point piston without suction cup mechanical cardiopulmonary resuscitation (CPR) device in the resuscitation of out of hospital cardiac arrest (OHCA) cases in a moving ambulance setting. The aim of this study is to evaluate and compare short term survival rate return of spontaneous circulation (ROSC) of emergency medical service (EMS) delivered to OHCA patients receiving single point piston without a suction cup mechanical CPR device and manual CPR.

METHODS This case control study was conducted using data on OHCA patients between 1 January 2017 and 31 March 2020 using part of the Pan-Asian Resuscitation Outcomes Study (PAROS) data. Cases were classified as ROSC or no ROSC. Logistic regression analysis was used for the multivariable analysis of the primary objective.

RESULTS A total of 206 cases were included in this study, 68 ROSC cases and 138 no ROSC cases. The multivariable analysis found no significant difference in the ROSC rate of EMS delivered OHCA patients who received only manual CPR and patients who received the mechanical CPR either in the EMS (OR: 0.49, 95% confidence interval [CI]: 0.13-1.78) or the emergency department (ED) (AOR: 16.05, 95% confidence interval [CI]: 0.18-1435.78).

CONCLUSIONS The use of the single point piston without suction cup CPR device in OHCA cases was not found to be inferior in terms of ROSC rate compared with manual CPR. Also, potential benefits in a prehospital setting could be provided by the device use, e.g., fewer staff required in the EMS. Use of the device should be considered in appropriate situations.

KEYWORDS cardiopulmonary resuscitation; heart arrest; mechanical chest compressions

INTRODUCTION

High-quality cardiopulmonary resuscitation (CPR), according to current international guidelines, is emphasized as being an important factor associated with desirable outcomes in patients with cardiac arrest and classified by certain criteria (1). Despite being highlighted, a body of evidence has shown that there are potential problems that may prevent the provision of high-quality CPR through the conventional method (manual compression) (2, 3). To overcome the limitations of conventional manual CPR, mechanical chest compression devices were introduced as an alternative. Although several studies have found that

mechanical CPR might be able to provide more high-quality chest compression than manual CPR, (4, 5) current evidence still does not support the existence of any difference in out-of-hospital cardiac arrest (OHCA) patient survival between the two protocols (6, 7). CPR with mechanical chest compression currently provides no clear advantage over CPR with conventional manual chest compression in general situations, and current international guidelines still suggest the use of manual chest compression in most situations when CPR is indicated (1).

A few circumstances may cause performance of CPR to be more challenging. These include operating in a moving ground ambulance where performing CPR poses a great risk to the rescuers (8). The mechanical chest compression device, which has been proven to be capable of delivering high-quality CPR, is recommended by international guidelines as a reasonable alternative to the manual CPR (1).

There is a gap of knowledge, as suggested by the Cochrane review, regarding mechanical CPR efficacy in some special circumstances where sustained high-quality CPR is needed and in situations where manual CPR is considered to be difficult to provide or not safe for the rescuers such performing CPR in a moving emergency medical system (EMS) vehicle (7). Most current studies have evaluated only the Autopulse (Zoll Medical, Chelmsford, MA, USA) load distributing band device and the LUCAS (Physio Control Inc./Jolife AV, Lund, Sweden) piston device with suction cup, and other similar kinds of devices including single point piston devices without suction cup, e.g., Lifeline ARM (Defibtech, Guilford, CT, USA); however, additional information regarding their efficiency in providing favorable outcomes and improving survival is needed. The aim of this study is to compare the short-term survival rate (ROSC) of EMS delivered to OHCA patients who received single point piston mechanical CPR device and those who received manual CPR.

METHODS

Setting and study design

This case-control study used the Maharaj Nakorn Chiang Mai Hospital's emergency department (ED) database which is part of the Pan-Asian Resuscitation Outcomes Study (PAROS) (9). The present study followed the Utstein-style template and adhered to all relevant guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement. Data about EMS and ED care of OHCA patients who arrived during the study period (January 1, 2017 through March 31, 2020) was collected. During the study period, the use of the Lifeline ARM (Defibtech, Guilford, CT, USA), a single point piston mechanical CPR device without suction cup, was documented. EMS providers had been trained to use the device by a product specialist. The decision to use the device was based entirely on the judgement of the physician in charge of each case. Recorded cases were categorized into ROSC (case) and no ROSC (control) groups. Inclusion criteria were non-traumatic cardiac arrest cases age at least 18 years who were brought to the hospital's ED by EMS. Cases were excluded if the patient's age was unknown, if data about ROSC use was not recorded, and if the patient did not receive any CPR.

The study protocol was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University (Permit No. EXEMPTION-8008/64/0) and the Thai Clinical Trials Registry Committee, Medical Research Foundation of Thailand (Permit No. TCTR20210401002).

Variables

Short-term outcome data, including use of ROSC at the scene, in the EMS and at the ED was collected and used for assigning patients to either the case or the control group. Potential confounders, e.g., data on prognostic factors that may have influenced the resuscitation outcome, including age of the patient, medical history, response time, duration of OHCA events, witnesses to the OHCA events, use of AED by bystanders, the use of CPR by bystanders, location where the arrest occurred, initial arrest rhythm, if defibrillation was applied, if endotracheal intubation was done, and duration of CPR was collected. For the exposure to a mechanical CPR device, data on the use of a mechanical CPR device both in the EMS and the ED was also obtained.

Definitions

In this study, ROSC, in concordance with the Utstein-style criteria, is defined as a persistent

palpable pulse for at least 20 seconds (10). The duration of CPR is presumed to be the interval between CPR initiation and the first ROSC, or the decision to cease the resuscitation attempt. For cases where the time of CPR initiation was unknown or where the initial CPR resuscitation was done by a bystander, the time was assumed to be either the time the collapse was witnessed or the time of the emergency call. For cases that did not receive bystander CPR, the time of EMS arrival at scene was considered to be the time of CPR initiation.

Sample size

The sample size was calculated using the Stata version 16 (Stata Corp LLC, College Station, TX, USA) asymptotic z test (sample size estimation with odds ratio) based on data from a comparable study (11). As a case control study, patients were sorted into 2 groups, ROSC achieved (case) and no ROSC achieved (control). Parameters for the study size calculation were set as follows: power at 80%, alpha error at 0.05 (two-sided), ratio between case and control 1:1, probability of exposure among control patients 0.44, odds ratio of exposure in cases relative to controls 2.66. The number of cases calculated using that formula was 69 per group. A 20% dropout rate was added to the calculated total N of 138, resulting in the planned total sample size of 173.

Statistical analysis

Descriptive statistics were used for the outcome report. Frequencies and percentages were used to describe categorical data, while mean and standard deviation (SD.) or median and interquartile range (IQR) were used to describe continuous data. The independent Student's t-test, the two-sample Wilcoxon rank-sum test and the chi-square test were used as appropriate for the comparison of each of the baseline characteristics between the case and control groups. As this is a retrospective study, it was not feasible to allocate or randomize the exposure equally between the study groups. Also, each decision regarding use of the mechanical CPR was based entirely on the on-site judgement of the attending resuscitation team. The issues mentioned above could have resulted in the occurrence of selection bias. For that reason, statistical methods to lessen the effect of such possible bias, e.g., logistic regression analysis were used. Univariable and multivariable analysis was done using logistic regression analysis.

RESULTS

Baseline characteristics of studied cases

Based on the data collected as part of the PAROS between January 1, 2017 and March 31, 2020 in which 329 cases were recorded, 109 of those cases were excluded as the exclusion criteria were met. After exclusion there were 74 ROSC cases and 146 no ROSC cases. Of those, a further 14 cases (6 ROSC cases and 8 no ROSC cases) were excluded due to insufficient data regarding the use of a mechanical CPR device. Finally, 206 patients were included in the analysis, consisting of 68 ROSC cases and 138 no ROSC cases (Figure 1). The mean age of the ROSC group was 49.2±24.7 years while in the no ROSC group the mean age was comparatively older at 56.3±20.4 years (p = 0.033). A greater proportion of the ROSC patients were covered by the Thai Government Universal Health Care Coverage scheme than those who did not have ROSC (66.2% vs. 42.8%; p = 0.002). There were more cases witnessed by bystanders and more cases with bystander CPR in the ROSC group than in the no ROSC group (73.5% vs. 45.6%, p = 0.001 and 45.6% vs. 20.3%, p < 0.001), respectively). The total number of instances of using mechanical CPR was 27 out of 206 (13.1%). A higher incidence of mechanical CPR deployment was found in the no ROSC group compared to the ROSC group in all three health care settings: unspecified (17.4% vs. 4.4%; p = 0.031), in the EMS (8.7% vs. 4.4%; p = 0.275), and at the ED (14.5% vs. 2.9%; p = 0.023). In addition, a higher incidence of shockable initial arrest rhythm was found in the ROSC patients than in the no ROSC patients (17.7% vs. 12.3%; p = 0.005). More patients who did not have ROSC received defibrillation than no ROSC patients (50.7% vs. 35.3%; p = 0.038). The median CPR duration was lower in the ROSC group compared to the no ROSC group (22 (IQR: 9, 40) vs. 30 (IQR=21,45) minutes; p 0.024). Additional details are shown in Table 1.

Univariable and multivariable analysis

Results of the univariable and multivariable logistic regression analysis of factors potentially

Table 1. Comparison of baseline characteristics of ROSC and no ROSC cardiac arrest patients both in and outside the hospital

Variable	ROSC n=68 (%)	No ROSC n=138 (%)	*p*-value
Age (year)			
Mean±SD	49.2±24.7	56.3±20.4	0.033
Gender			
Female	20 (29.4)	44 (31.9)	0.718
Male	48 (70.6)	94 (68.1)	
Race			
Thai	59 (86.8)	119 (86.2)	0.916
Other	9 (13.2)	19 (13.8)	
Past medical history			
Cardiac disease	5 (7.4)	17 (12.3)	0.711
Cancer	2 (2.9)	6 (4.3)	0.547
Hypertension	22 (32.4)	28 (20.3)	0.080
Diabetes	12 (17.6)	20 (14.5)	0.327
Dyslipidemia	7 (10.3)	8 (5.8)	0.305
Renal disease	8 (11.8)	12 (8.7)	0.348
Respiratory disease	3 (4.4)	13 (9.4)	0.718
Stroke	4 (5.9)	8 (5.8)	0.477
HIV infection	0 (0.0)	3 (2.2)	0.587
Other	18 (26.5)	23 (16.7)	0.130
None	2 (2.9)	4 (2.9)	0.986
Unknown	34 (50.0)	62 (44.9)	0.531
Arrest witnessed			
Yes	50 (73.5)	67 (45.6)	0.001
No	18 (26.5)	71 (51.5)	
CPR by bystander			
Yes	31 (45.6)	28 (20.3)	<0.001
No	37 (54.4)	110 (79.7)	
AED applied by bystander			
Yes	4 (5.9)	8 (5.8)	0.513
No	63 (92.6)	131 (94.9)	
Arrest location			
Home	23 (33.8)	79 (57.3)	0.002
Public place	45 (66.2)	59 (42.8)	
Response time (minutes)			
Median (IQR)	4 (2,7)	5 (2,9)	0.140
CPR duration (minutes)			
Median (IQR)	22 (9,40)	30 (21,45)	0.024
Arrest time			
Day	34 (50.8)	67 (49.3)	0.843
Night	33 (49.2)	69 (50.7)	
ETI			
Yes	66 (97.1)	136 (98.6)	0.475
No	2 (2.9)	2 (1.4)	
First arrest rhythm			
Unshockable rhythm	23 (33.8)	77 (55.8)	0.005
Shockable rhythm	12 (17.7)	17 (12.3)	
Defibrillation done			
Yes	24 (35.3)	70 (50.7)	0.038
No	44 (64.7)	68 (49.3)	

Table 1. Comparison of baseline characteristics of ROSC and no ROSC cardiac arrest patients both in and outside the hospital (continued)

Variable	ROSC n=68 (%)	No ROSC n=138 (%)	*p*-value
Mechanical CPR done prehospitally/ at the ED			
Yes	3 (4.4)	24 (17.4)	0.031
No	65 (95.6)	114 (82.6)	
Mechanical CPR done in the EMS vehicle			
Yes	3 (4.4)	12 (8.7)	0.275
No	65 (95.6)	126 (91.3)	
Mechanical CPR done at the ED			
Yes	2 (2.9)	20 (14.5)	0.023
No	66 (97.1)	118 (85.5)	

Data are presented as mean ± standard deviation (SD), median (IQR) or number (%).
CPR, Cardiopulmonary resuscitation; ETI, endotracheal intubation; AED, automated external defibrillator; CPR duration, defined as the time from initiation of CPR by emergency medical technicians to either return of spontaneous circulation or death; Night, 7.00 p.m. to 6.59 a.m.; Day, 7.00 a.m. to 6.59 p.m.; ED, emergency department; EMS, emergency medical service

Table 2. Univariable and multivariable analysis of factors potentially related to ROSC in cardiac arrest patients both in and outside of the hospital

Valiable	Univariable		Multivariable	
	OR (95%CI)	*p*-value	AOR (95%CI)	*p*-value
Age	0.98 (0.97-0.99)	0.031	0.95 (0.90-0.99)	0.027
Male sex	1.12 (0.60-2.12)	0.718	-	-
Past history (cardiac disease)	1.05 (0.78-1.44)	0.711	-	-
Arrest witnessed	2.94 (1.56-5.55)	0.001	0.88 (0.14-5.72)	0.895
Bystander CPR applied	3.29 (1.75-6.20)	< 0.001	11.01 (1.09-110.70)	0.045
Bystander AED applied	1.49 (0.45-4.86)	0.513	-	-
Location of OHCAs (public)	2.62 (1.43-4.80)	0.002	5.95 (0.95-37.13)	0.056
CPR duration	0.96 (0.93-0.99)	0.027	0.95 (0.88-0.99)	0.047
Any defibrillation done	0.53 (0.29-0.96)	0.038	0.51 (0.06-4.12)	0.526
Shockable first arrest rhythm	1.58 (1.15-2.18)	0.005	3.49 (0.88-13.82)	0.076
Mechanical CPR (EMS)	0.49 (0.13-1.78)	0.275	-	-
Mechanical CPR (ED)	0.18 (0.04-0.79)	0.023	16.05 (0.18-1435.78)	0.226

CI, confidence interval; CPR, cardiopulmonary resuscitation; AED, automated external defibrillator; OHCAs, out of hospital cardiac arrest; EMS, emergency medical service; ED, emergency department; OR, crude odds ratio; AOR, adjusted odds ratio (adjusted for age, sex, past history (cardiac disease), witnessed arrest, bystander CPR, bystander AED applied, location of OHCAs (public), CPR duration, any defibrillation done, shockable first arrest rhythm, mechanical CPR (EMS) and mechanical CPR (ED).

related to successful ROSC in OHCA patients are shown in Table 2. Of the 12 variables (age, male sex, past history (cardiac disease), arrest witnessed, bystander CPR, bystander AED applied, location of OHCAs (public), CPR duration, use of defibrillation, shockable first arrest rhythm and mechanical CPR (EMS) and mechanical CPR (ED), three variables, age (AOR = 0.95, 95% confidence interval [CI]: 0.90-0.99), bystander CPR (AOR: 11.01, 95% confidence interval [CI]: 1.75-6.20), and CPR duration (AOR: 0.95, 95% confidence interval [CI]: 0.88-0.99) were found to be significantly associated with ROSC in OHCA patients. The use of mechanical CPR, either at the ED or in the EMS, was not found to be significantly associated with ROSC in OHCA patients.

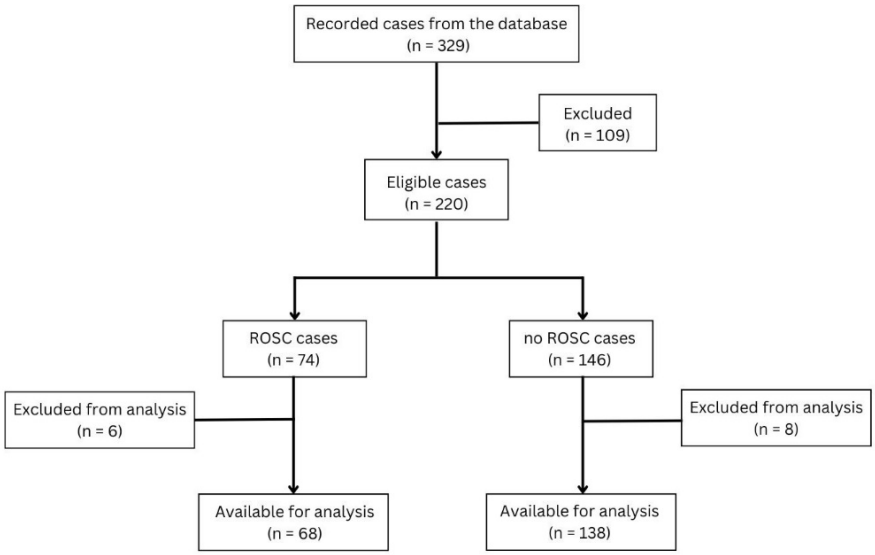

Figure 1. Flow chart of the study

DISCUSSION

Despite a body of evidence showing that performing CPR in a prehospital setting, e.g., in a moving ambulance, can be more challenging for achieving high-quality CPR using manual chest compression compared to mechanical chest compression, (5, 8, 12) the present study did not find any significant difference. Our findings do not support the hypothesis of an improved ROSC rate in patients receiving mechanical CPR. This discordance might be explainable by several factors, including unrecorded device application time, unrecorded pauses in chest compression for device deployment, prolonged duration of chest compression, varying distance from the site to the ED, difference in the urgency for each patient delivery and other surrounding factors, e.g., the patients' family, site characteristics and differences in attending staff decisions. Additionally, there is currently a lack of evidence regarding the survival outcome of single point piston CPR devices without suction cup use in the EMS.

In both patients who achieved ROSC and patients who did not achieve ROSC, having bystander CPR done, younger age of the patient and shorter CPR duration were found to be significantly associated with ROSC, a finding consistent with some previous studies (13, 14).

Although the present study's results are consistent with the recently updated Cochrane review comparing mechanical CPR and manual CPR efficacy, (7) the mechanism of this study's referenced device was different from those in the review (compression only vs. compression-decompression and load distribution band). That difference could potentially have affected the comparability of the two studies' results.

Some other studies' findings were contrary to the results of this study. Anatharaman et al. reported that early use of a mechanical CPR device (LUCAS-2) is associated with a higher incidence of achieving ROSC (15). Similarly, a study by Seewald et al. suggested there is an improved ROSC rate in OHCA patients receiving mechanical CPR (LUCAS and Autopulse) (16). The incongruity of these results and those of the present study may be due to differences in the mechanical CPR device used, the number of witnessed cases, the duration of device application and the number of the mechanical CPR devices used.

Despite the lack of supportive results regarding the improved survivability of OHCA patients who received mechanical CPR, it might still have a role in the resuscitation of OHCA patients. Some non-clinical studies have reported that more consistent high-quality CPR was achieved with mechanical CPR compared to manual CPR in the setting of a moving ambulance (4, 8). That may help reduce the number of staff required for the resuscitation of OHCA patients in an ambulance. It is may also provide increased safety for EMS staff who would otherwise sometimes have to do manual CPR in potentially harmful situations, including in a moving ambulance. As this study's results suggest, mechanical CPR has no significant disadvantages compared to conventional manual

CPR, so it may be an appropriate substitute for manual CPR in situations where continuity of CPR is required and where performing manual CPR either poses a threat to the CPR provider's safety or where it may be less likely to yield high quality CPR according to the current standard guidelines and in situations where it is preferable to use fewer staff for resuscitation and transportation of emergency patients, e.g., during the present COVID-19 pandemic.

Further investigative comparison of mechanical and manual CPR in terms of safety and duration of use of the mechanical chest compression device is needed. Future studies should address the potential benefits of mechanical CPR in terms of safety either via the use of questionnaires or other methods and should include the precise time during which the mechanical CPR was done. Additionally, the present study was conducted using cases in urban and nearby areas of Chiang Mai, Thailand so the majority of this study's population were Thai. For these reasons, interpretation of the results of the present study should be done with caution.

Limitations

This study has some limitations. First, this was a retrospective single centered study, so the study could only reach as far as the pre-existing data provided, and there was a portion of the population whose first arrest rhythm was not recorded. Additionally, data on the time during which the mechanical chest compression device was applied either at the scene or in the EMS was not available. A few additional factors, e.g., the limited number of available mechanical CPR devices at the study hospital's ED, could have led to unequal distribution of the use of the device among cases and thus could have resulted in selection bias. The MCPR devices in this study were not significantly different from models which have been thoroughly evaluated in many previous studies. There was also limited data regarding EMS actions which may have affected the outcomes. Also, the small number of cases receiving mechanical CPR in this study could have resulted in an overestimated adjusted odds ratio in the multivariable analysis of the association with ROSC. Lastly, in this study, the number of mechanical CPR devices used was rather small which may have affected the power of the statistical analysis.

CONCLUSIONS

Despite the lack of significant evidence of benefits of mechanical CPR over traditional manual CPR, this does not argue against the use of the device in OHCA patients. The mechanical CPR devices have some potential benefits which may help facilitate the resuscitation process of OHCA patients, especially in the prehospital setting. Benefits include a reduced number of staff required for the EMS, increased EMS staff safety and more consistent CPR efficacy in a moving EMS. Use of the single piston mechanical CPR device should be considered in circumstances where their benefits would be an asset to patients and/or hospital staff.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

ADDITIONAL INFORMATION

Author contributions statement

P.R.: review, editing, conceptualization (lead), writing – original draft (lead); B.W.: formal analysis (lead), methodology (lead), software, writing – review and editing (equal); T.T.: conceptualization (supporting), writing – original draft (supporting), writing – review and editing (equal).

Informed consent

Due to the retrospective nature of the study, the need of informed consent was waived by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University.

Consent for publication

Not applicable

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Original Article

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Effect of Adding Dexmedetomidine to 0.5% Bupivacaine on Scalp Block on Intraoperative Hemodynamics During the First Hour of Surgery and Anesthetic Requirement in Intracranial Surgery

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ABSTRACT

OBJECTIVE Dexmedetomidine has been used as a perineural local anesthetic (LA) adjunct to improve the quality of block and decrease opioid consumption. This study aims to determine the efficacy of adding dexmedetomidine to 0.5% bupivacaine on scalp block on hemodynamic responses during the first hour of surgery, intraoperative propofol and fentanyl doses, and analgesic requirements in the first 24 hours post-craniotomy.

METHODS A prospective randomized controlled trial was conducted in forty-seven elective craniotomy patients receiving a scalp block with either 1 mcg/kg of dexmedetomidine (group D) or normal saline (group C) added to 0.5% bupivacaine (20 mL in total). Intraoperative blood pressure and heart rate at baseline and at 22 other time points during the first hour following the skin incision as well as the amount of intraoperative propofol and fentanyl and postoperative tramadol doses during the first 24 hours were collected and analyzed. The student t-test was used to compare means between groups, while repeated measure ANOVA with Bonferroni correction was used for comparing repeated means within each group. *P*-value less than 0.05 was considered statistically significant.

RESULTS During skull pin fixation (T4), the mean arterial pressure (MAP) and heart rate (HR) of both groups increased from baseline, but there were no statistically significant differences between groups. During the first hour of the operation (T7–T22), both groups had lower MAPs than their baselines, and group D had lower MAPs than group C at all time points. Intraoperative doses of fentanyl (mcg/kg) and propofol (mg/kg) in group D were significantly lower than those in group C, $p = 0.027$ and $p = 0.030$, respectively.

CONCLUSIONS The addition of 1 mcg/kg dexmedetomidine tends to enhance the efficacy of scalp block with 0.5% bupivacaine in attenuating intraoperative hemodynamic responses during the first hour of surgery and reducing intraoperative fentanyl and propofol requirements during intracranial surgery.

KEYWORDS scalp block, dexmedetomidine, bupivacaine, hemodynamic response

INTRODUCTION

Stabilizing hemodynamics in patients undergoing intracranial surgery is vital, particularly in patients at risk due to impaired cerebral autoregulation caused by brain pathology. Not only does this improve surgical outcomes, but it also helps prevent complications such as intracerebral hemorrhage, brain ischemia, and ruptured aneurysms caused by acute hemodynamic changes. Slightly higher blood pressure (BP) during neurosurgical procedures such as skull pin insertion, skin incision, or dural opening can result in increased cerebral blood flow and cerebral blood volume, followed by an increase in intracranial pressure (1, 2). For craniotomy, blocking the nerves that supply the relevant region of the scalp can attenuate the nociceptive response and thus control high BP and tachycardia. Additionally, it has shown evidence of effectively controlling post-operative pain in patients undergoing craniotomy for supratentorial brain lesions (3-5).

In neurosurgical anesthesia, an intravenous bolus or infusion of dexmedetomidine as an anesthetic adjuvant can reduce sympathetic response and hemodynamic variability associated with skull pin application and during an operation (6, 7) and can reduce intraoperative opioid usage (8). Nowadays, dexmedetomidine has been extensively added to local anesthetics as a perineural adjunct to prolong the duration of analgesia, sensory block, and motor block (9). However, the efficacy of dexmedetomidine in combination with local anesthetics in scalp blocks has a had only a limited number of clinical research studies. The primary purpose of this study was to determine whether there was any difference in hemodynamic response between scalp block with bupivacaine and scalp block with bupivacaine and dexmedetomidine, especially during intense pain stimuli such as skull pin insertion, skin incision, and dural opening during intracranial surgery. The secondary objective of the study was to determine if the addition of dexmedetomidine to bupivacaine had any effects on intraoperative opioid consumption, propofol use, and postoperative analgesic requirements.

METHODS

This single-center, prospective randomized controlled trial was conducted at Maharaj Nakorn Chiang Mai Hospital from April 1, 2020 to August 31, 2022. The trial enrolled 48 patients who underwent an elective craniotomy to remove intracranial tumors. The study was approved by the Institutional Review Board of the Faculty of Medicine, Chiang Mai University (ANE-2562-06956), and registered on Thaiclinicaltrials.org (ID: TCTR20200106002). Written informed consent was obtained from patients who met the inclusion criteria one day before the scheduled surgery who were then assigned in a 1:1 ratio either to a study group receiving scalp block with dexmedetomidine and bupivacaine or to a group receiving bupivacaine only (Figure 1). The inclusion criteria were age 18 to 65 years, ASA physical status I-III, Glasgow Coma Scale scores 14-15, and scheduled for elective craniotomy. Exclusion criteria included known allergic reactions to bupivacaine and/or dexmedetomidine, coagulopathy, hypertension, clinically increased intracranial pressure, history of bradyarrhythmia, history of myocardial ischemia or history of traumatic brain injury.

Procedures

The random allocation for both arm groups was generated using a computer-generated randomization sequence. Each random number was then concealed in an opaque, sealed envelope prepared by personnel not connected with the study. A nurse anesthetist not participating in the anesthetic care of the patients opened each envelope and prepared the drugs immediately before the scalp block was performed. The patients, anesthetists, neurosurgeons, data collectors, and outcome assessors were all blinded to the randomization assignments.

Before induction of anesthesia, BP, pulse oxygen saturation, heart rate (HR), and ECG rhythm were monitored. After performing a radial arterial catheterization for direct BP measurement, the patient's baseline (T0) hemodynamic paameters were recorded. All patients received pre-oxygenation with 100% oxygen for three to five minutes, fentanyl 2 mcg/kg IV, and propofol IV starting at an effect-site concentration (Ce) of 3.0 mcg/mL by a target-controlled infusion (TCI) using a Schneider model syringe pump. Propofol was titrated to maintain bispectral index (BIS) values in the range of 40-60, followed by rocuronium at 0.8 mg/kg IV to enable endotracheal intubation. Scalp block was performed in both arm

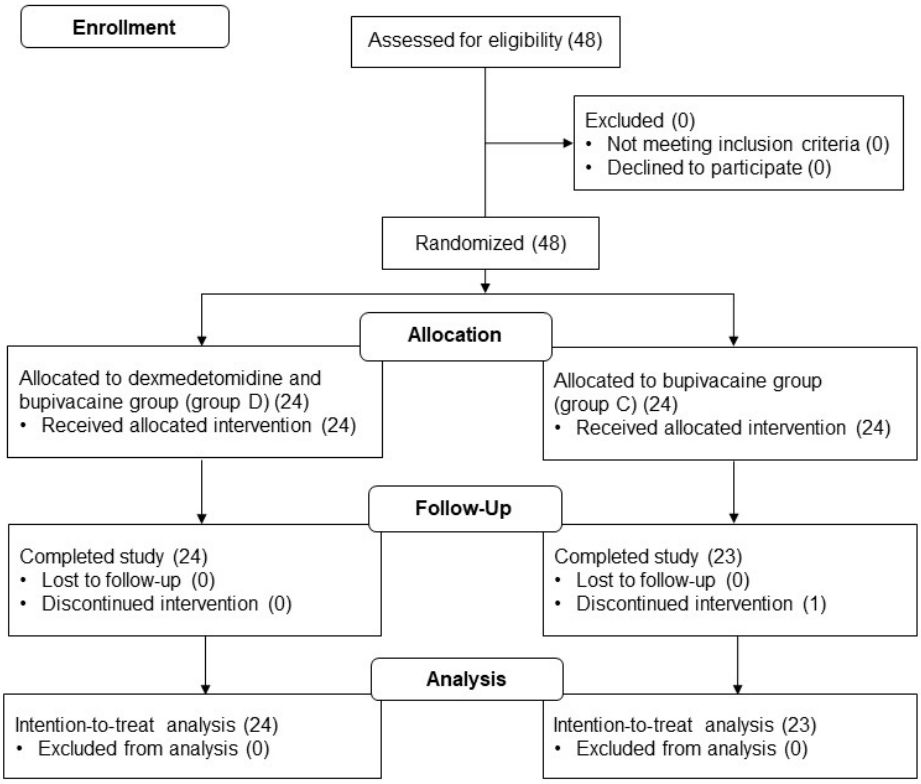

Figure 1. Consort flow diagram

groups who received a 20 mL solution containing either dexmedetomidine 1 mcg/kg (0.01 mL/kg) and 0.5% bupivacaine (group D) or 0.9% NaCl 0.01 mL/kg and 0.5% bupivacaine (group C). Six nerves supplying the scalp (supratrochlear, supraorbital, zygomaticotemporal, auriculotemporal, greater occipital, and lesser occipital nerves) were blocked bilaterally using the technique described by Pinosky et al. (10). Then 2% lidocaine 2 mL was injected at each skull pin site marked before skull pin application by a neurosurgeon and applied after five minutes of scalp block. Anesthesia was maintained with propofol TIVA-TCI, rocuronium, and fentanyl to achieve balanced anesthesia. If the BP and HR increased by more than 20% from baseline (T0), intraoperative fentanyl 0.5-1 mcg/kg was intravenously administered, with supplemental nicardipine or esmolol IV if the BP and HR still increased by more than 20% from baseline after being given fentanyl 1 mcg/kg. Bradycardia was treated by the administration of IV atro-pine 0.6 mg. Hypotension was treated by the administration of IV ephedrine in 3 mg boluses or IV norepinephrine in 10 mcg boluses. After the operation was finished, neuromuscular blockade was reversed with 0.05 mg/kg neostigmine and 0.02 mg/kg atropine. Removal of the endotracheal tube was done if the patient fulfilled the criteria for extubation before transfer to the neurosurgical intensive care unit. Intravenous tramadol was used postoperatively as rescue analgesia.

Systolic BP (Ps), diastolic BP (Pd), mean arterial pressure (MAP), and HR were recorded and analyzed at 23 timepoints: 1) T0 at baseline, 2) T1 before scalp block, 3) T2 one minute after scalp block, 4) T3 before a skull pin fixation, 5) T4 during a skull pin fixation, 6) T5 one minute after a skull pin fixation, 7) T6 five minutes after a skull pin fixation, 8) T7 during skin incision, 9) T8 one minute after skin incision, 10) T9 to T20 every five minutes for one hour after skin incision, 11) T21 during skull opening, and 12) T22 during the dural opening. Perioperative data, including total propofol infusion dose, total fentanyl dose given, adverse hemodynamic events, e.g., hypotension (MAP < 65 mmHg or decrease > 20% of baseline and treatment with a vasopressor drug), hypertension (treated with an anti-hypertensive drug), and bradycardia (HR < 60 /min), and postoperative analgesic requirements with tramadol IV in 24 hours were all collected.

Sample size calculation and statistical analysis

Based on a previous study by Kumar et al. (11), two repeated mean changes of baseline pre-block MAP and during skull-pin fixation MAP in two independent groups were used: 86.37±10.55 to 110.37±17.39 mmHg in the control group, and 83.22±11.13 mmHg to 89.46±16.56 mmHg in the dexmedetomidine with bupivacaine group, respectively. For a desired power of 0.80 and a type I error of 0.05, the total number of participants in both study arms was 48, including 20% in case some participants dropped out of the study.

Discrete categorical data are presented as frequency (percent) and are compared between groups using chi-square or Fisher's exact test as appropriate. Continuous data such as arterial pressure and HR are presented as mean ± SD and compared between groups using the independent t-test for normal distribution data or the Mann-Whitney U test for non-normal distribution data, while repeated measure ANOVA with Bonferroni correction was used for comparing repeated means within the group. A P-value less than 0.05 was considered statistically significant. All statistical analyses were performed using Stata statistical software version 16.1 (StataCorp LLC, College Station, TX, USA).

RESULTS

Forty-eight patients were enrolled in the study by randomization into group D (24 patients) and group C (24 patients). However, 1 patient from group C was excluded from the study due to a technical error in data collection. No significant differences were found between groups in demographic characteristics (Table 1). The surgical sites were not different between the two groups and were mostly performed in the frontal and frontotemporal regions. The time from scalp block to skull pin insertion was 13.00±6.26 minutes in group D and 13.17±5.73 minutes in group C, p = 0.921. The operating-room extubation rate was

Table 1. Demographics data

Variable	Group D n=24 (%)	Group C n=23 (%)	*p*-value
Gender (male/female) (%)	6/18 (25.0/75.0)	9/14 (39.1/60.9)	0.359
Age (years)	48.29±10.74	47.00±13.32	0.716
BMI (kg/m^2)	23.10±2.43	23.88±4.45	0.457
GCS score	15	15	
ASA PS (1/2/3) (%)	6/16/2 (25.0/66.7/8.3)	5/17/1 (21.7/74.0/4.3)	0.963
Surgical diagnosis (%)			0.008
Meningioma	12 (50.0)	3 (13.0)	
Glioma	4 (16.7)	2 (8.7)	
Astrocytic tumor	3 (12.5)	6 (26.1)	
Pituitary	2 (8.3)	0 (0.0)	
Brain metastasis	1 (4.2)	3 (13.0)	
Others	2 (8.3)	9 (39.2)	
Surgical site (%)			0.250
Frontal	6 (25.0)	6 (26.2)	
Parietal	0 (0.0)	2 (8.7)	
Temporal	2 (8.3)	3 (13.1)	
Occipital	0 (0.0)	1 (4.3)	
Fronto-temporal	12 (50.0)	8 (34.8)	
Fronto-parietal	3 (12.5)	0 (0.0)	
Temporo-occipital	0 (0.0)	1 (4.3)	
Fronto-temporo-parietal	0 (0.0)	1 (4.3)	
Parieto-occipital	0 (0.0)	1 (4.3)	
Temporo-parietal	1 (4.2)	0 (0.0)	
Duration of surgery (min)	226.33±71.15	296.70±122.51	0.020
Duration of anesthesia (min)	298.58±69.75	384.61±132.03	0.007
Time from scalp block to skull pin insertion (min)	13.00±6.26	13.17±5.73	0.921
Time from scalp block to skin incision (min)	45.04±2.04	48.70±2.11	0.220
Operating room extubation (%)	16 (61.5)	10 (38.5)	0.147

BMI, body mass index; GCS, Glasgow coma score; ASA PS, American Society of Anesthesiologists physical status

greater in group D (61.5% vs. 38.5%, $p = 0.147$).

The hemodynamic profiles (Ps, Pd, MAP, and HR) at 23 different timepoints are shown in Figures. 2-5. The baseline (T0) Ps, Pd, and MAP were comparable between group D and group C. HR in group D was greater than group C ($p = 0.038$), but it was comparable prior to scalp block (T1). In group D, the Ps and MAP increased immediately one minute after scalp block (T2) and persisted higher than baseline for about 13 minutes (T3). In contrast, the HR of group D dropped at the first minute after scalp block (T2), which was 73.38± 13.29, compared to 79.48±14.68 minutes of group C, $p = 0.142$, and group D remained lower consistently for one hour after skin incision. During skull pin fixation (T4), the BP values of each group were not different from their baselines and were comparable between groups, but the MAP of group C increased significantly from T1 (before scalp block), with a mean difference of 13.35 ± 3.18 mmHg, 95%CI [0.5, 26.2], $p = 0.031$, while the MAP of group D did not increase significantly. At one minute after skin incision (T7), hemodynamic responses (Ps, Pd, and MAP) were attenuated and decreased from baseline values in both groups. In group D, the mean difference of MAP between T7 and T1 was -23.67 mmHg, 95%CI [-34.9, -12.5], $p < 0.001$, while it was -21.52 mmHg, 95%CI [-33.0, -10.1], $p < 0.001$ in group C. Additionally, patients in group D had lower Ps, Pd, MAP, and HR than those in group C persistently for one hour after skin incision (T7-T21) and during the dural opening

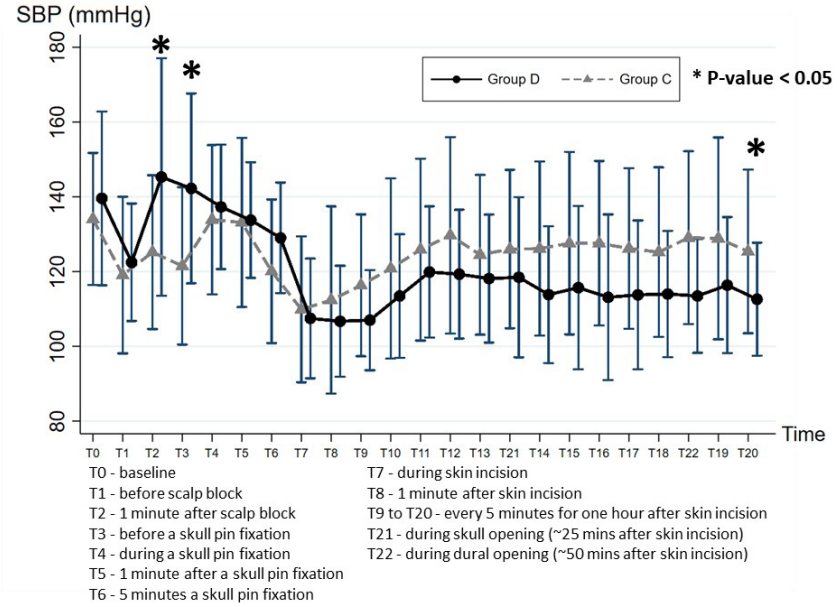

Figure 2. Systolic blood pressure at different time points

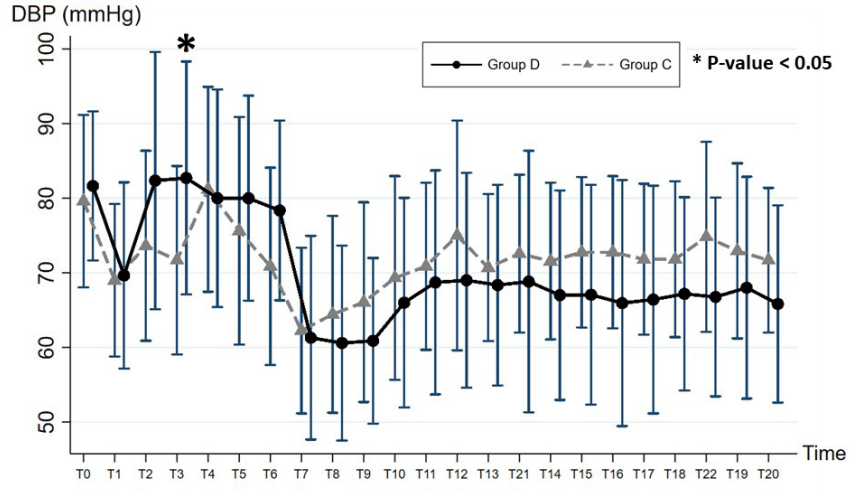

Figure 3. Diastolic blood pressure at different time points

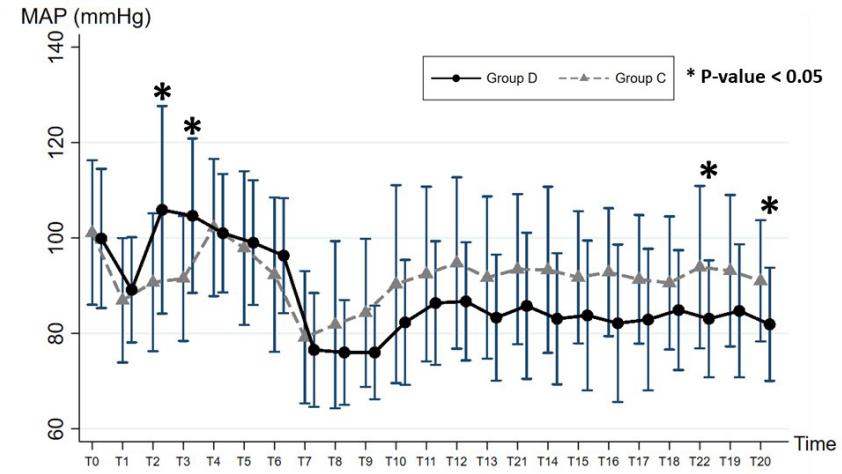

Figure 4. Mean arterial pressure at different time points

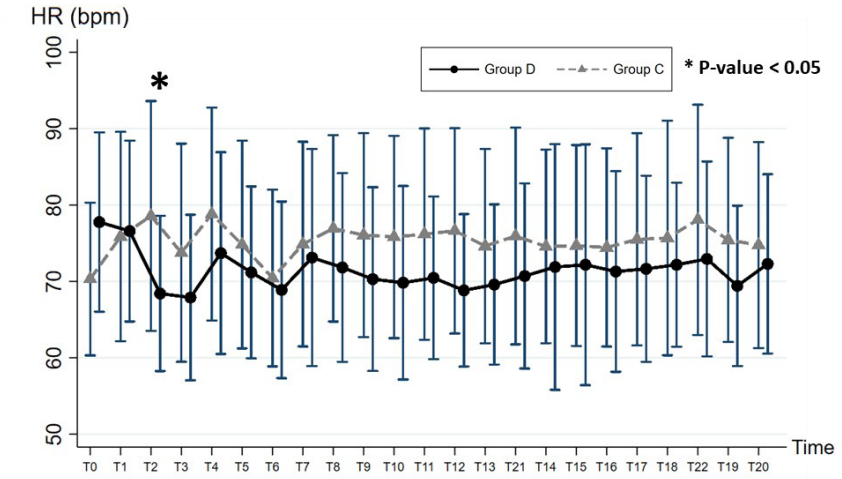

Figure 5. Heart rate at different time points

Table 2. Intraoperative anesthetic requirements

Variable	Group D (n=24)	Group C (n=23)	*p*-value	95%CI
Intraoperative fentanyl use first hour (mcg/kg)	2.63±0.89	3.04±0.96	0.134	(-0.1,1.0)
Intraoperative fentanyl use (mcg/kg)	3.66±1.35	4.61±1.51	0.027	(0.1,1.8)
Intraoperative fentanyl use (mcg/kg/hr)	0.74±0.19	0.75±0.24	0.771	(-0.1,0.1)
Intraoperative propofol use (mg/kg)	29.69±8.32	35.80±10.23	0.030	(0.6,11.5)
Intraoperative propofol use (mg/kg/hr)	5.97±0.82	5.78±1.24	0.548	(-0.8,0.4)

which occurred about 50 minutes after skin incision (T22), but the MAP values of group D from T15 to T22 (which was about 35 minutes after skin incision) were significantly lower than those of group C. (Figure 4)

As to secondary outcomes, intraoperative doses of fentanyl (mcg/kg) and propofol (mg/kg) in group D were significantly lower than those of group C (Table 2). The postoperative tramadol dose, as a rescue drug in the first 24 hours was 1.88 ± 0.25 mg/kg in group D and 2.31 ± 0.20 mg/kg in group C, $p = 0.193$. The incidences of intraoperative hemodynamic adverse events that required medical treatment, including bradycardia, hypotension, and hypertension, were not different between groups, as were the incidences of postoperative adverse hemodynamic events requiring rescue treatment. (Tables 3 and 4)

Table 3. Intraoperative hemodynamic adverse events that required medical treatment

Variable	Group D n=24 (%)	Group C n=23 (%)	*p*-value
Bradycardia	1 (4.17)	1 (4.35)	1.000
Hypotension	6 (25.00)	8 (34.78)	0.534
Hypertension	8 (33.33)	6 (26.09)	0.752

Table 4. Postoperative hemodynamic adverse events that required medical treatment

Variable	Group D n=24 (%)	Group C n=23 (%)	*p*-value
Bradycardia	0 (0.00)	1 (4.35)	0.489
Hypotension	0 (0.00)	0 (0.00)	
Hypertension	1 (4.17)	2 (8.70)	0.609

DISCUSSION

In addition to providing perioperative analgesia for craniotomy, a scalp block has been proven to attenuate the hemodynamic response to skull pinning and skin incision (3, 12, 13) more effectively than routine anesthesia with only intravenous or volatile anesthetic (3, 12). Similarly, the results of our study showed that scalp block with 0.5% bupivacaine in 20 mL attenuated the hypertensive response to noxious stimuli during the first hour of intracranial procedures, including skull pin fixation, craniotomy incision, as well as skull and dural opening. Although the neuroendocrine response has also been previously reported following skull-pin holder fixation (3), stress hormone levels were not investigated in this study.

Regarding locoregional analgesia, dexmedetomidine has been added to several routes of both central and peripheral neural blockade, e.g., epidural, caudal, and spinal, to enhance the duration of both sensory and motor blockade by local anesthetics (14). One prior study demonstrated that adding dexmedetomidine (1 mcg/kg) to 0.25% bupivacaine 20 mL for scalp block was very efficient in obtunding the hemodynamic response to skull pin placement (10). On the contrary, the author could not demonstrate an add-on effect of dexmedetomidine on scalp block with 0.5% bupivacaine when the skull pin was attached. This result is in concordance with a recent study by Sahana et al. (15) which mentions that the addition of dexmedetomidine (1 mcg/kg) to 25 mL of 0.5% ropivacaine for scalp block provided no extra advantage over 25 mL of 0.5% ropivacaine alone in attenuating the hemodynamic response to skull pin placement. In the present study, however, adding dexmedetomidine resulted in much lower BP and HR than that in patients who received scalp block with only 0.5% ropivacaine, at least during the first hour.

The mechanism of action of dexmedetomidine as an alpha2-adrenoceptor agonist in peripheral nerve blocks is not fully understood. Proposed mechanisms include central analgesia, vasoconstriction, and anti-inflammatory effects (16). However, none of these mechanisms can clearly explain the synergistic effect of alpha2-adrenoceptor agonists of dexmedetomidine when added to a local anesthetic in peripheral nerve blocks (14). In the present study, the plasma level of dexmedetomidine was not investigated, so we postulated that the initial hypertensive phase was due to the systemic effect of dexmedetomidine on the alpha2B adrenoceptor mediated vascular response from rapid plasma absorption. However, the subsequent hypotension was not confirmed as being an effect of dexmedetomidine mediated by alpha2A receptor on cardiovascular response and/or locoregional analgesia by enhancing the onset and efficacy of peripheral neural blockade.

Dexmedetomidine prolongs the duration of analgesia via a hyperpolarization-activated cation current that acts more selectively on C-fibers than on A-alpha fibers (17). C fibers are densely innervated in the scalp, which may explain the mechanism. A prior study concluded that the addition of dexmedetomidine (1 mcg/kg) to bupivacaine prolonged the pain-free period, and that a scalp block is a superior technique compared to scalp infiltration with 0.25% bupivacaine and dexmedetomidine (1 mcg/kg) in a 20 mL solution (18). Another study, which added dexmedetomidine 1.5 mcg/kg to levobupivacaine 36 mL for scalp block, reported a prolonged analgesic effect and better hemodynamic control post-craniotomy, despite no data on intraoperative hemodynamics and anesthetic requirements being revealed (19). A recent study by Lekprasert et al. (20) concluded that compared to 0.25% levobupivacaine with adrenaline (1:200,000), preoperative scalp block with added dexmedetomidine 1 mcg/kg increased time to the first analgesic and decreased intraoperative fentanyl use, while postoperative tramadol consumption was not statistically significantly

different between groups, which correlates with our study in which adding dexmedetomidine reduced the amount of fentanyl.

Limitations

There are several limitations in this study. The first is that the plasma level of dexmedetomidine was not investigated, so we postulated that the initial hypertensive phase was due to the systemic effect of dexmedetomidine on the alpha2B adrenergic receptor-mediated vascular response from rapid plasma absorption. Additionally, the subsequent hypotension was not confirmed to be an effect of dexmedetomidine mediated by the alpha2A receptor in the cardiovascular response and/or locoregional analgesia by enhancing the onset and efficacy of peripheral neural blockade. Secondly, authors could not demonstrate whether the scalp block succeeded or failed, and as there was no nociceptive index monitor to guide analgesic drug titration, fentanyl was given subjectively to diminish the hyperdynamic response. Lastly, our intraoperative study period was only one hour after the scalp block, which was insufficient to reveal how long dexmedetomidine affects perioperative hemodynamics in a craniotomy.

CONCLUSIONS

This study demonstrated that hemodynamic responses during the first hour of intracranial surgery are more attenuated with the addition of dexmedetomidine 1 mcg/kg to a scalp block with 0.5% bupivacaine. In addition, adding dexmedetomidine to a scalp block decreases intraoperative fentanyl and propofol requirements during intracranial surgery.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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Review Article

Open Access

Comparative Analysis of the Efficacy and Safety of HIV/AIDS Treatment Strategies: A Comprehensive Review of Clinical Trial Data

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ABSTRACT

This comprehensive review and meta-analysis aimed to evaluate the comparative efficacy and safety of various antiretroviral (ARV) therapy regimens for HIV/AIDS treatment based on clinical trial data over 48 and 96 weeks. We conducted a systematic search across multiple databases, identifying 17 randomized controlled trials that met our inclusion criteria. These studies provided data on 12 different ARV regimens, focusing on integrase strand transfer inhibitor (INSTI)-based, non-nucleoside reverse transcriptase inhibitor (NNRTI)-based, and protease inhibitor (PI)-based treatments. Efficacy was measured by the percentage of participants achieving viral load suppression below 50 copies/mL, while safety was assessed through the incidence of serious adverse events. The analysis revealed significant variability in the efficacy and safety profiles of the ARV regimens studied. INSTI-based treatments, notably elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) and dolutegravir/lamivudine (DTG/3TC), demonstrated the highest levels of viral suppression, maintaining effectiveness at both the 48 and 96-week benchmarks. Notably, a weak positive correlation was identified between the efficacy of these treatments and the incidence of serious adverse events. Despite this correlation, the overall link between a regimen's efficacy and its safety was found to be weak, highlighting the critical importance of tailoring HIV treatment to the individual patient's needs and circumstances. The study underscores the importance of individualizing HIV/AIDS treatment strategies to optimize both efficacy and safety outcomes. While INSTI-based regimens show promise in terms of efficacy, the slightly increased risk of serious adverse events calls for careful consideration in treatment selection and monitoring. Future research should focus on longitudinal studies and the development of predictive models to further refine treatment strategies, helping ensure they are tailored to meet the individual needs of patients living with HIV/AIDS.

KEYWORDS HIV/AIDS, antiretroviral therapy, efficacy, safety, INSTI-based regimens

INTRODUCTION

The global health landscape has been significantly challenged by human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS), affecting millions worldwide. Despite advancements in treatment options, primarily through antiretroviral therapy (ART), the quest for optimizing treatment strategies remains central to improving patient outcomes (1). The dynamic nature of HIV, characterized by its mutation potential, necessitates continuous evaluation of treatment efficacy and safety to adapt to changing patient needs and virus characteristics (2). Current literature provides extensive insights into individual HIV/AIDS treatment strategies but often falls short of offering a comprehensive comparative analysis. Although there have been previous systematic reviews and meta-analyses on the efficacy and safety of HIV/AIDS treatments, this report offers novel insights by comparing a broader range of regimens, including newer integrase strand transfer inhibitor (INSTI)-based therapies over extended periods of 48 and 96 weeks improving the ability of healthcare providers to make more fully informed treatment decisions and highlighting the need for a detailed comparative review of the efficacy and safety of these strategies (3).

Globally, the response to HIV/AIDS has been diverse, with significant advancements in some regions, while others continue to struggle with the epidemic. For instance, recent studies from North America and Europe have shown a promising decrease in HIV transmission rates, attributed to effective ART regimens and preventive measures such as pre-exposure prophylaxis (PrEP) (4). In contrast, Sub-Saharan Africa, despite housing approximately two-thirds of the global HIV positive population, has faced challenges in accessing these advanced treatments, leading to a slower decline in prevalence (5). In Asia, particularly in China, the approach to HIV/AIDS treatment has evolved significantly over the past decade. The Chinese government and healthcare providers have made considerable efforts to improve access to ART, resulting in improved treatment outcomes and reduced HIV transmission rates (6). However, disparities in treatment accessibility and quality still exist, particularly in rural areas and among marginalized communities (7).

The study of ART's efficacy and safety profiles is ongoing, with newer drugs and treatment combinations continually being tested. Recent studies from 2021 to 2024 have further elucidated the benefits and drawbacks of various ART regimens. For instance, recent meta-analyses have highlighted the superior efficacy of INSTIs over other drug classes in achieving viral suppression (8), yet they have raised concerns about their long-term safety and potential side effects. Additionally, updated guidelines and studies from 2021-2024 have emphasized the need for continuous monitoring and adaptation of treatment strategies to manage emerging drug resistance (9).

Moreover, the emergence of HIV drug resistance remains a significant concern, undermining the efficacy of existing treatment strategies. Studies from both developed and developing countries have reported increasing rates of resistance to first-line ART regimens, calling for a reevaluation of current treatment protocols and the development of novel therapeutic options (10). The significance of the present study lies in its direct implications for HIV/AIDS treatment. By providing a detailed comparative analysis of various treatment regimens, this study aims to help healthcare providers make better informed decisions that could improve patient management and outcomes. Specifically, it highlights the efficacy and safety of newer INSTI-based regimens compared to traditional treatments, thereby offering valuable insights for optimizing HIV/AIDS therapy. Additionally, the study identifies gaps in current research and suggests areas for future investigation, particularly in managing drug resistance and increasing long-term treatment sustainability (11).

This study's comprehensive review of clinical trial data, incorporating both international and national literature, underscores the ongoing need to adapt HIV/AIDS treatment strategies in the face of evolving challenges. By comparing the efficacy and safety profiles of various treatment strategies, this research aims to provide actionable insights that can help guide policy and practice, ultimately contributing to the global effort to control and eventually eradicate HIV/AIDS.

METHODS

Search strategy

To ensure a comprehensive collection of data, an extensive literature search was conducted across multiple databases: PubMed, Embase, Cochrane Library, and Web of Science, covering publications from January 2000 to December 2022. The search strategy included both MeSH terms and free-text terms with variations and combinations of "HIV," "AIDS," "ART," "clinical trial," "treatment efficacy," "safety," and "outcome comparison." The search was augmented by scrutinizing the reference lists of selected articles for additional relevant studies (12).

Inclusion and exclusion criteria

The study selection followed predefined inclusion and exclusion criteria to ensure relevance and quality. Inclusion criteria specified randomized controlled trials (RCTs) comparing different HIV/AIDS treatment strategies with outcomes related to efficacy (e.g., viral suppression, $CD4^+$ cell count improvement) and safety (e.g., adverse events, drug resistance). Exclusion criteria were studies not directly comparing treatment strategies, non-randomized trials, observational studies, case reports, reviews, and studies not in English. Additionally, studies focusing on pediatric populations were excluded due to distinct treatment modalities (13).

Data extraction

Data extraction was conducted independently by two researchers using a standardized form designed for this study. This form captured comprehensive details including study identification (author, year), methodology (study design, duration, location), participants (sample size, age, baseline $CD4^+$ count, HIV viral load), treatment strategies compared, outcome measures, and results. Discrepancies in data extraction were resolved through consensus or involvement of a third reviewer if necessary. This meticulous process was followed to maximize the accuracy and reliability of the data used for analysis (14).

Statistical analysis

For the statistical analysis, the study employed meta-analytic techniques using RevMan 5.4 software. The effect sizes were calculated as relative risks (RR) for binary outcomes and mean differences (MD) for continuous outcomes, both with 95% confidence intervals (CIs). Heterogeneity among studies was assessed using the χ^2 test and I^2 statistics, categorizing heterogeneity into low ($I^2 < 25\%$), moderate ($25\% \leq I^2 < 75\%$), and high ($I^2 \geq 75\%$). Based on the heterogeneity results, a fixed-effects model was used for low heterogeneity, while a random-effects model was applied for moderate to high heterogeneity. Sensitivity analysis was conducted to explore the influence of individual studies on the overall results, and publication bias was assessed through funnel plots and Egger's test (15).

Quality assessment

The quality of included studies was rigorously assessed using the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials. This assessment focused on seven domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential sources of bias. Each domain was rated as "low risk," "high risk," or "unclear risk" of bias. This comprehensive evaluation informed the interpretation of the meta-analysis results, providing insights into the reliability of the findings (16).

Ethical considerations

Given the study's design as a systematic review and meta-analysis of published data, ethical approval was not required. However, all procedures were performed in accordance with relevant guidelines and regulations, including adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This adherence underscores the commitment to transparency, reproducibility, and ethical standards in conducting and reporting scientific research (17).

RESULTS

Selection and quality evaluation of studies for a systematic review on HIV antiretroviral therapy efficacy and safety

1. Literature search and study selection

A comprehensive search across multiple databases yielded 2,682 records. After removing duplicates with Zotero, 2,575 records remained.

Initial screening based on titles excluded 2,025 articles that did not meet the study's criteria. Further scrutiny of abstracts and full texts led to the exclusion of an additional 550 articles. Ultimately, 17 studies were included in this systematic review and meta-analysis, covering 12 different antiviral regimens focused on three main classes of antiretroviral (ARV) drugs: integrase strand transfer inhibitors (INSTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) (Figure 1A). The quality of these 17 studies was rigorously assessed using the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials, ensuring robust and reliable conclusions.

The regimens include INSTI-based treatments such as elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF), elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (E/C/F/TDF), bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF), abacavir/dolutegravir/lami-vudine(ABC/DTG/3TC),dolutegravir/lamivudine (DTG/3TC), dolutegravir/emtricitabine/tenofovir disoproxil fumarate (DTG/F/TDF),dolutegravir/emtricitabine/tenofovir alafenamide (DTG/F/TAF), and raltegravir/emtricitabine/tenofovir disoproxil fumarate (RAL/XTC/TDF); NNRTI-based treatments such as efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/F/TDF), anvinovir/ lamivudine/tenofovir disoproxil fumarate (ANV/3TC/TDF), and efavirenz/lamivudine/tenofovir disoproxil fumarate (EFV/3TC/TDF); and the PI-based treatment lopinavir/ritonavir plus lamivudine (LPV/r+3TC). Notably, efavirenz/lamivudine/tenofovir disoproxil fumarate (EFV/3TC/TDF) is the most commonly used national first-line anti-HIV treatment, with efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/F/TDF) and anvinovir/lamivudine/tenofovir disoproxil fumarate (ANV/3TC/TDF) included to establish networked meta-bridging relationships.

Characteristics and quality assessment of included studies

The 17 included studies were all RCTs, comprising 15 studies registered internationally and 2 studies registered in China. Among these, 13 were phase III clinical trials, 3 were phase II, and one study conducted in China (ChiCTR1900024611) did not specify its phase. Quality assessment revealed varying levels of bias risk across studies, depicted in a risk of bias graph (Figure 1B), with green indicating low risk, yellow indicating medium risk, and red indicating high risk. The primary source of high risk was identified as selective reporting,

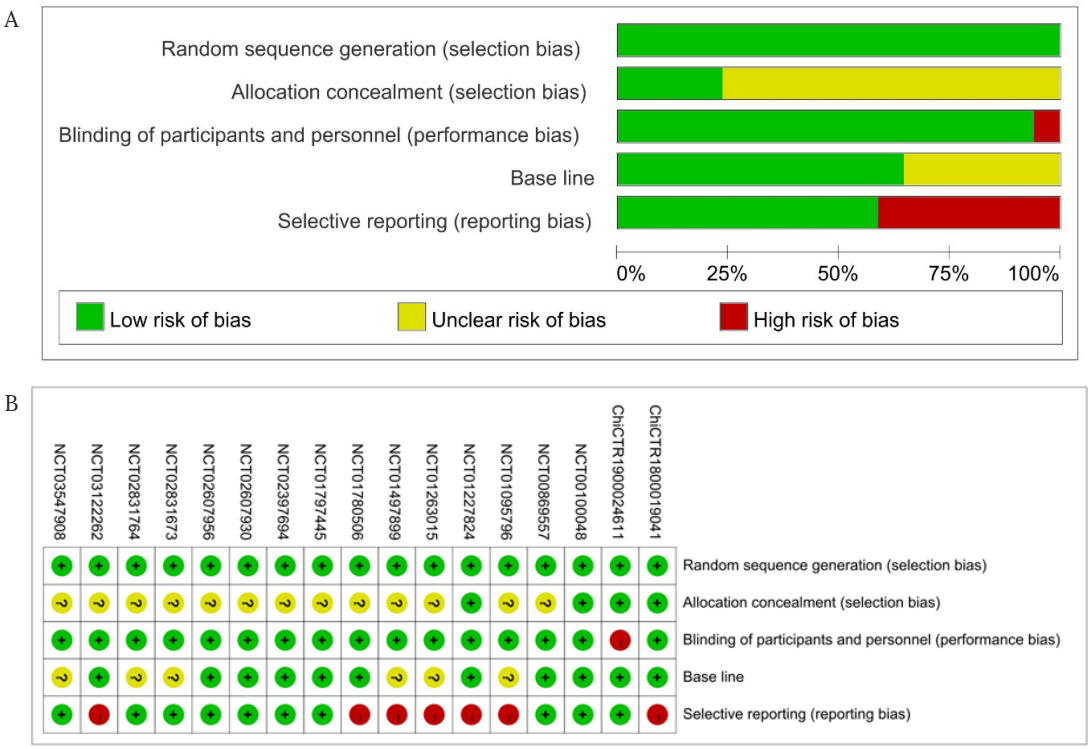

Figure 1. Risk of bias summary (A), Risk of bias assessment for individual studies (B)

given the extensive set of efficacy and safety indicators evaluated, with not all studies reporting in detail on these indicators.

Efficacy and immune response of ARV therapies at the 48-week milestone

1. Efficacy assessment of ARV regimens at the 48-week milestone

Within the scope of our study, Figure 2 delineates the suppression rates of viral load below 50 copies/ml at the 48-week juncture for a spectrum of ART. The data reveals a gradient of efficacy levels, with the E/C/F/TAF regimen leading the cohort, where a noteworthy 90% of patients achieved the desired viral suppression threshold. This high level of efficacy is closely followed by the DTG/3TC and DTG/F/TAF regimens, both demonstrating viral suppression in over 85% of patients. Conversely, regimens such as ANV/3TC/TDF and RAL/XTC/TDF manifest at the lower spectrum of viral suppression efficacy, with rates oscillating around the 70% mark. This disparity in efficacy not only underscores the diverse virological responses elicited by different treatment regimens but also stresses the critical need for individualized therapeutic strategies tailored to patient-specific clinical profiles.

2. Immune response delineated by CD4⁺ count changes at 48 weeks

The Figure 3 illustrates the change in CD4⁺ cell counts at the 48-week benchmark across a spectrum of ART. The vertical dispersion of CD4⁺ cell count changes signifies the immunological response variability among the studied cohort. Each regimen presents a unique profile of immune reconstitution, with some regimens, such as E/C/F/TAF and DTG/F/TAF, demonstrating more substantial median increases indicative of a robust immunological rebound. Conversely, treatments like RAL/XTC/TDF and LPV/r+3TC exhibit relatively modest median increases, highlighting a more constrained immune restoration.

The interquartile range within each box provides insights into the homogeneity of the immune response among patients receiving the same treatment. A narrower interquartile range, as observed in the DTG/3TC regimen, suggests a more consistent response across the patient population, while wider ranges imply a greater variability in treatment outcomes.

The visualization succinctly captures the heterogeneity of immune recovery, suggesting that while some treatments elicit strong and consistent CD4⁺ count surges, others may require additional support or consideration in treatment planning. This detailed depiction of immunological outcomes is crucial for clinicians tailoring treatment strategies and contributes valuable data for longitudinal studies of ARV treatment efficacy.

Long-term efficacy and immune response of ARV therapy over 96 weeks

1. Longitudinal efficacy of ARV treatments in maintaining viral suppression

The longitudinal study of ART revealed varied

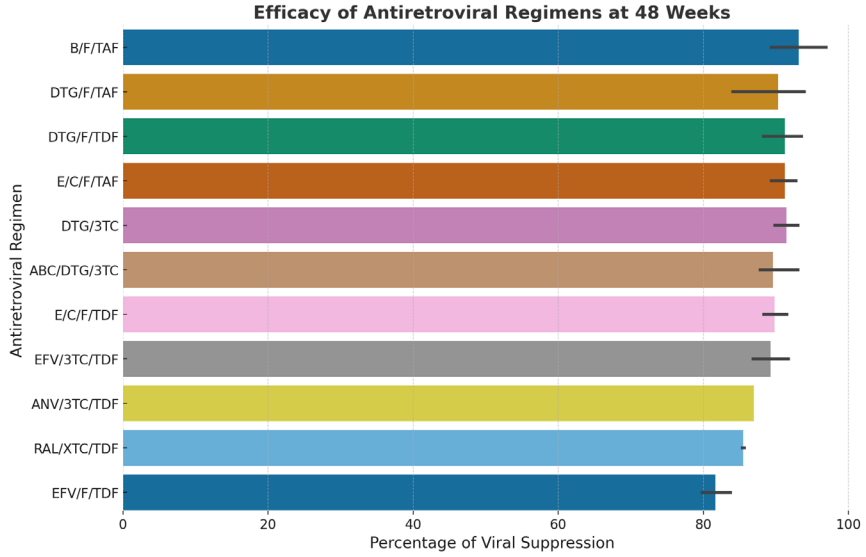

Figure 2. 48-Week viral suppression rates among antiretroviral therapy regimens

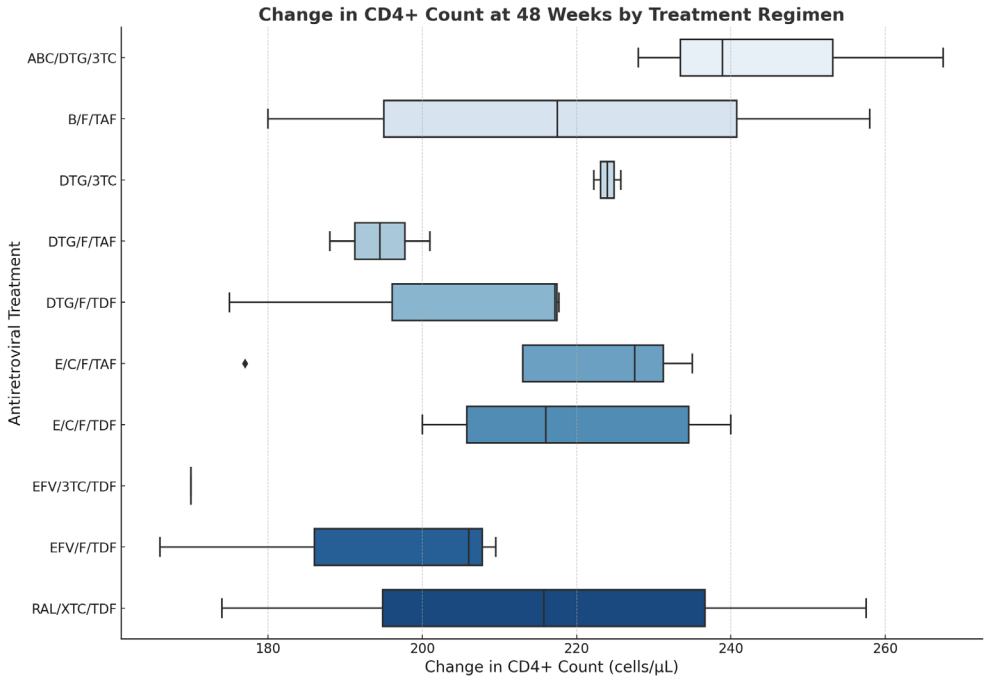

Figure 3. Change in CD4⁺ count at 48 weeks across different antiretroviral treatment regimens

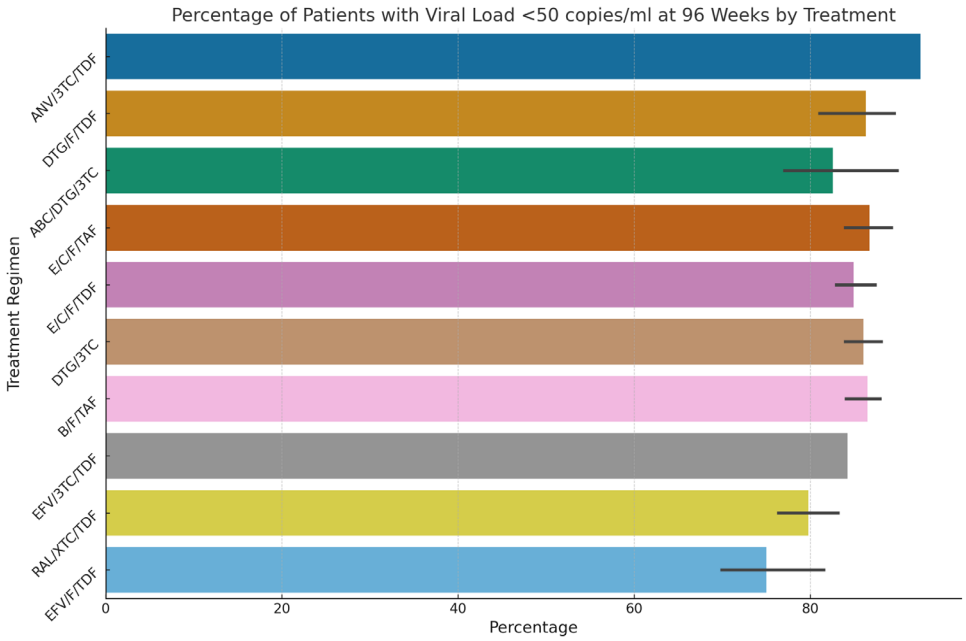

Figure 4. Comparative analysis of 96-week viral suppression rates by antiretroviral regimen

success rates in achieving viral loads of less than 50 copies/mL at the 96-week milestone. Figure 4 and Table 1 present these rates across different treatment regimens, showing a gradient of efficacy. The E/C/F/TAF regimen had the highest efficacy with 84% suppression, followed by ABC/DTG/3TC at 82%. At the lower end, EFV/3TC/TDF had a suppression rate of 65%. These results indicate significant variability in long-term efficacy among different treatment regimens. E/C/F/TAF emerges as the most effective regimen, with the majority of patients achieving the desired viral suppression. ABC/DTG/3TC also shows a high rate of suppression, suggesting strong long-term control of the viral load. In contrast, regimens like EFV/3TC/TDF have a significantly lower proportion of patients attaining similar levels of suppression. This highlights the importance of selecting treatments that offer not just immediate viral suppression but also maintain that suppression over extendedperiods. A chi-square test confirmed significant differences in

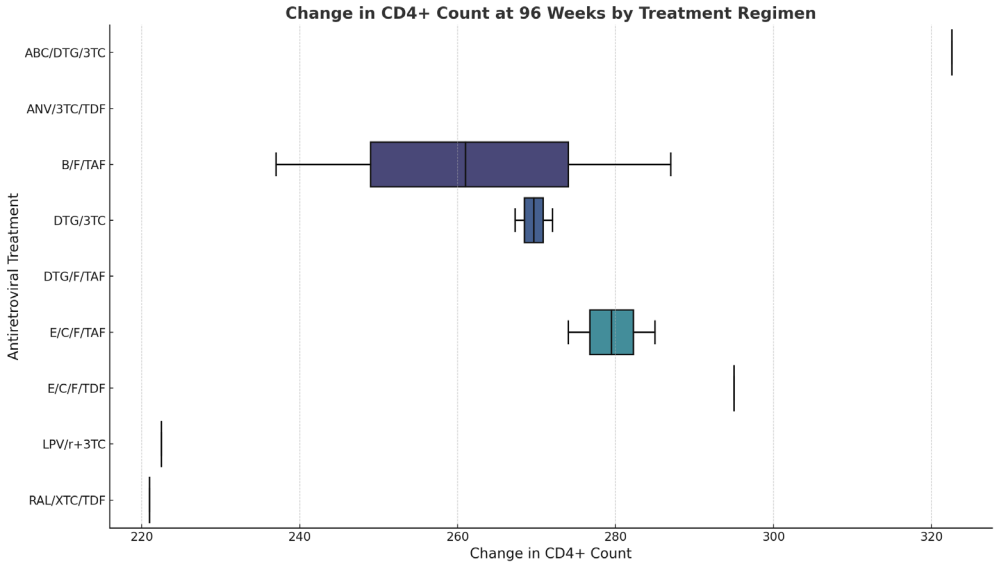

Figure 5. Distribution of CD4⁺ count changes at 96 weeks across antiretroviral treatment regimens

Table 1. Baseline and changes in CD4⁺ cell counts at 48 and 96 weeks in hiv treatment

	Baseline average CD4⁺, cells/mL (SD)	Change in CD4⁺ at 48 weeks	Change in CD4⁺ at 96 weeks
Mean	399.10	221.86	267.67
Median	394.00	227.85	272.00
Std_dev	53.72	27.86	31.15

Decimal digits for mean, median, and standard deviation have been standardized for consistency to facilitate comparison

suppression rates among the treatment groups (χ^2=119.02, p < 0.001). The design of the visualization provides an at-a-glance comparison of each treatment's effectiveness throughout the study, offering a clear view of the enduring nature of these therapies. These findings are pivotal in understanding treatment sustainability and will help inform future therapeutic directions and patient care optimization.

2. Immune response variability in HIV treatment efficacy at 96 weeks

Our analysis extends to the exploration of immune response through changes in CD4⁺ counts, observed at the 96-week milestone across various ARV treatment regimens. Figure 5 and Table 1 delineate the distribution of CD4⁺ count changes, highlighting the variability and central tendencies within each treatment category. Notably, the regimen E/C/F/TAF showcases a broad distribution of immune responses, with a median increase significantly above other regimens, indicative of its potent efficacy in enhancing immune recovery. Conversely, treatments like EFV/3TC/TDF exhibit a more constrained range of CD4⁺ count changes, reflecting a more uniform but modest immune response.

The stratified analysis underscores the disparities in immune recovery potential across treatment regimens, with some demonstrating pronounced increases in CD4⁺ counts, suggestive of superior immune system restoration capabilities. This variability accentuates the critical need for personalized treatment strategies, leveraging detailed insights into both virological suppression and immune system recovery to optimize therapeutic outcomes.

This comprehensive visualization of CD4⁺ count changes serves as a pivotal tool for clinicians and researchers, providing a granular view of the treatment regimens' impact on immune restoration. The analysis underscores the heterogeneity in treatment responses, emphasizing the importance of considering both virological and immunological parameters in the assessment of ART efficacy.

Comparative long-term efficacy of pre-LPV/r+3TC ARV regimens

Our longitudinal analysis of ART efficacies within the pre-LPV/r+3TC cohort reveals significant variances in patient outcomes over 48 and 96 weeks. The synthesized data, as depicted in the Figure 6, demonstrates a range of viral suppression rates, with certain regimens maintaining higher efficacy over time. For instance, the E/C/F/TAF regimen showed an initial suppression rate near 90% at 48 weeks, with a marginal decline to 84% by 96 weeks, suggesting sustained efficacy. In parallel, the E/C/F/TDF regimen exhibited a similar pattern of a slight decrease in suppression from 89% to 82% across the same timepoints. These trends indicate that both regimens possess robust long-term suppressive capabilities. Other treatments, such as B/F/TAF and DTG/3TC, however, experienced a more pronounced decline in suppression rates, which could signal the need for regimen adjustments or closer monitoring. This data informs clinical decisions by highlighting the need for personalized treatment strategies, particularly in cases where long-term viral suppression is a crucial factor in patient care. The analysis underscores the diversity of responses to ARV treatments and the importance of tailoring HIV management to maintain suppression and improve overall patient health outcomes.

Adverse event profiles and their correlation in ARV treatment efficacy

1. Assessment of adverse event profiles in ARV regimen efficacy

The comprehensive evaluation of adverse event profiles among various ARV regimens conducted over pivotal timepoints of 48 and 96 weeks elucidated a landscape marked by variability in patient safety outcomes. Figures 7 and 8 distinctly convey the incidence rates for five essential safety indicators, namely, any adverse events, drug-related adverse events, serious adverse events, adverse events leading to discontinuation, and overall discontinuation rates, each stratified by treatment regimen to underscore contrasts and facilitate nuanced analysis.

For instance, the treatment regimen E/C/F/TAF was observed to maintain a relatively higher incidence of Any Adverse Events consistently across both timepoints, raising considerations for its long-term tolerability. Meanwhile, the DTG/3TC regimen demonstrated a substantially lower frequency of Serious Adverse Events, signifying a safety profile that might be deemed more favorable in clinical practice. Notably, the rates of discontinuation due to adverse events presented considerable variability, underscoring the diverse tolerability across regimens, which becomes a pivotal factor in personalized treatment planning.

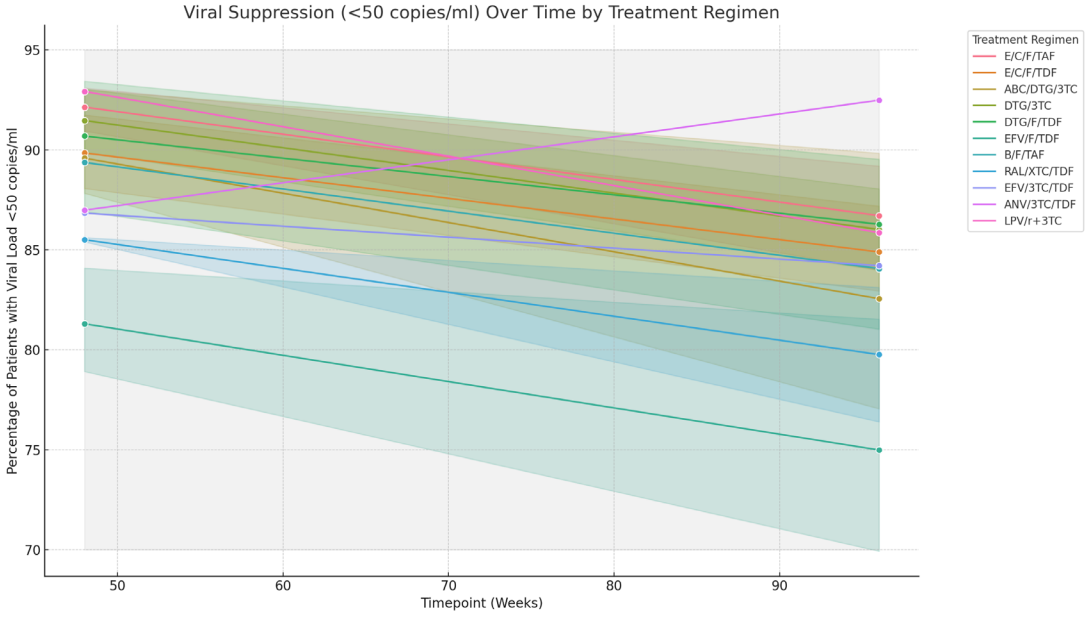

Figure 6. Comparative analysis of viral load suppression across antiretroviral regimens over 48 and 96 weeks

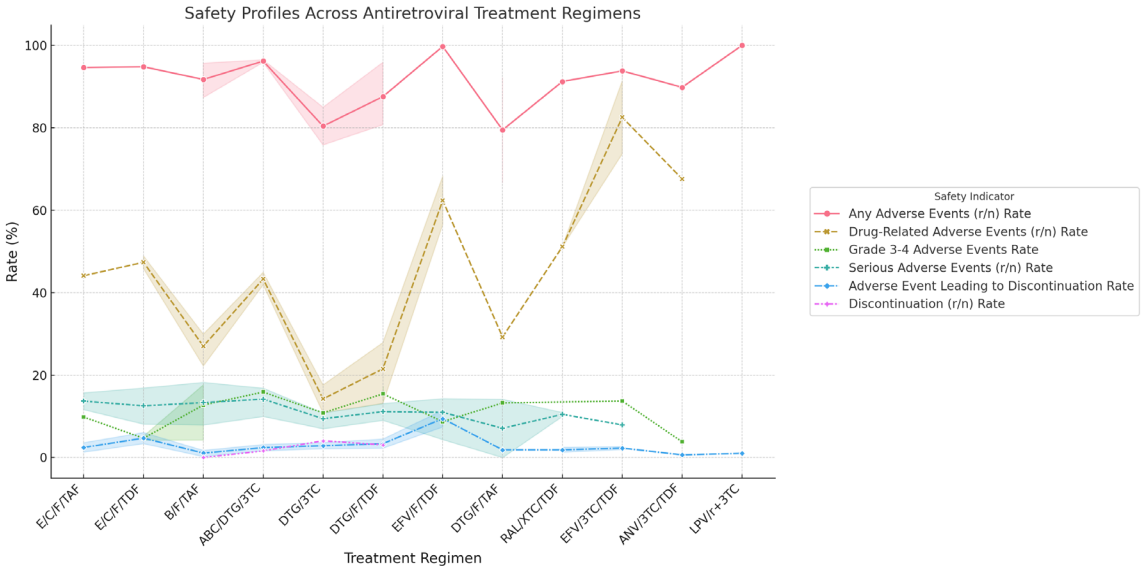

Figure 7. Comparative safety profile of antiretroviral regimens over time

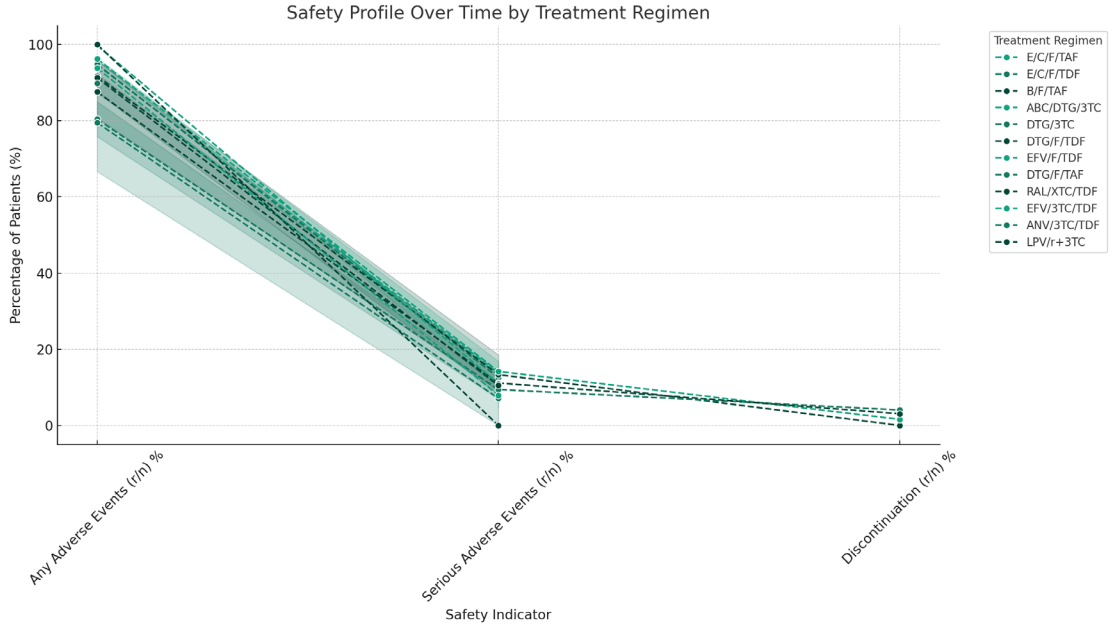

Figure 8. Comparative safety profile of antiretroviral regimens over time

The data, thus, reflect the multifaceted nature of safety profiles, advocating for the customization of therapeutic strategies that prioritize patient well-being alongside treatment efficacy. The insights derived from this analysis accentuate the imperative of ongoing safety monitoring, aiming to refine treatment paradigms and bolster the quality of care in the continuum of HIV/AIDS management, ultimately enhancing patient health outcomes and quality of life.

2. Interrelation of adverse event incidences in ARV treatments

In assessing the safety profile of ART, our analysis has identified a moderate positive correlation between the incidence rates of any adverse events and serious adverse events. Figure 9 illustrates this relationship, with each point representing the paired incidence rates for a given treatment regimen. The average rate of any adverse event stands at approximately 90.18%, indicative of the commonality of adverse effects in treatment. In comparison, the average rate for serious adverse events is significantly lower at around 10.51%, reflecting their less frequent occurrence.

The correlation coefficient of roughly 0.47 suggests that while there is a tendency for regimens with higher overall adverse events to also have higher rates of serious adverse events, this

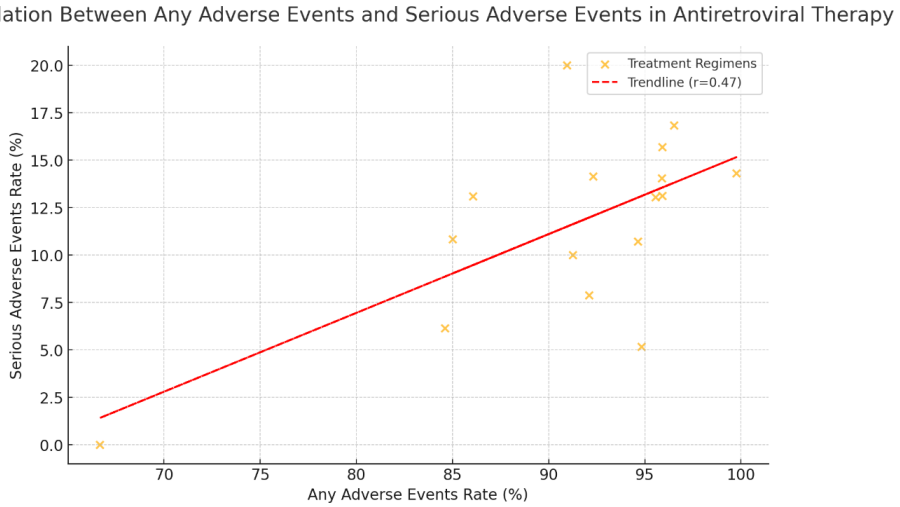

Figure 9. Correlation between any adverse events and serious adverse events in antiretroviral therapy

relationship is not highly pronounced. This points to the possibility of other factors influencing the severity and frequency of adverse events experienced by patients.

These insights not only contribute to our understanding of the safety dynamics associated with ARV treatments but also highlight the need for meticulous monitoring of patients for adverse effects. Further, it underscores the importance of thorough pre-treatment evaluations and post-treatment follow-ups to mitigate the impact of serious adverse events in the management of HIV/AIDS.

Comparative analysis of the efficacy and safety profiles of ART over time

In this comparative study, the efficacy and safety profiles of various ART interventions for HIV treatment over periods of 48 and 96 weeks were analyzed. Efficacy was determined by the percentage of participants achieving viral load suppression below 50 copies/ mL, which serves as the benchmark for successful viral suppression in HIV treatment. Safety was evaluated based on the incidence of serious adverse events. Selected efficacy parameters included viral load suppression and immune recovery indicated by $CD4^+$ count improvement, while safety was assessed through serious adverse events, providing a comprehensive evaluation of treatment effectiveness. Viral suppression directly measures the regimen's ability to control HIV replication, while $CD4^+$ count recovery reflects the immune system's response to treatment. These combined metrics offer a holistic view of the treatment's impact on both viral control and overall immune health. At 48 weeks, data indicated a slight positive correlation between treatment efficacy and the occurrence of serious adverse events, with a correlation coefficient of 0.111. This trend persisted at 96 weeks, with a correlation coefficient of 0.063, suggesting that higher treatment efficacy is slightly associated with an increased risk of serious adverse events. However, the overall relationship between these two metrics remains weak, indicating that while both efficacy and safety are crucial considerations, they do not strongly predict each other within the context of these interventions (Figures 10 and 11). These findings underscore the importance of a balanced approach in the clinical evaluation of ART, taking into account both the benefits of viral suppression and the potential risk of adverse events.

DISCUSSION

Evaluating the efficacy and safety of antiretroviral regimens: insights from a systematic review

The systematic review and meta-analysis conducted in this study comprehensively assess the efficacy and safety of 12 ARV regimens, drawing on data from 17 meticulously chosen RCTs. Our analysis highlights the considerable variability in the efficacy of these ARV regimens, which is particularly evident in the viral suppression rates observed at the 48-week benchmark. The E/C/F/TAF regimen stands out, achieving viral suppression in 90% of participants, signifying

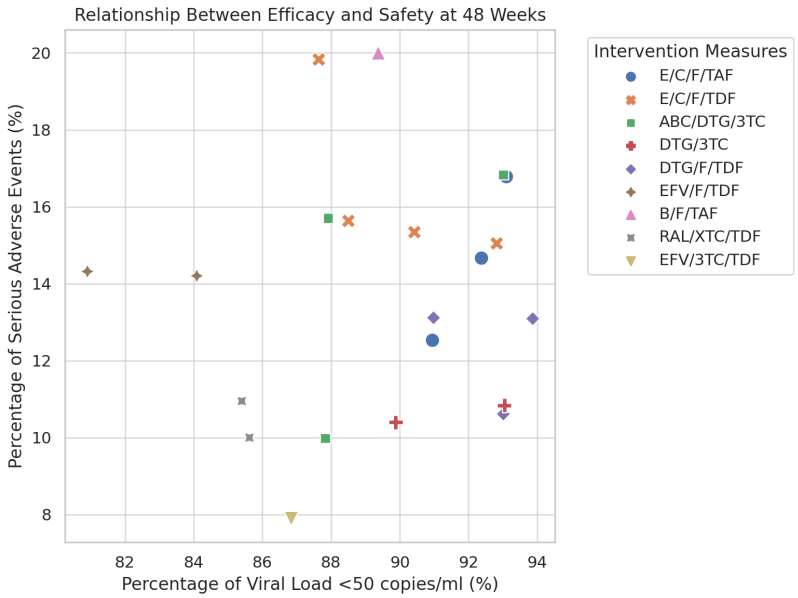

Figure 10. Relationship between efficacy and safety at 48 weeks post-treatment initiation

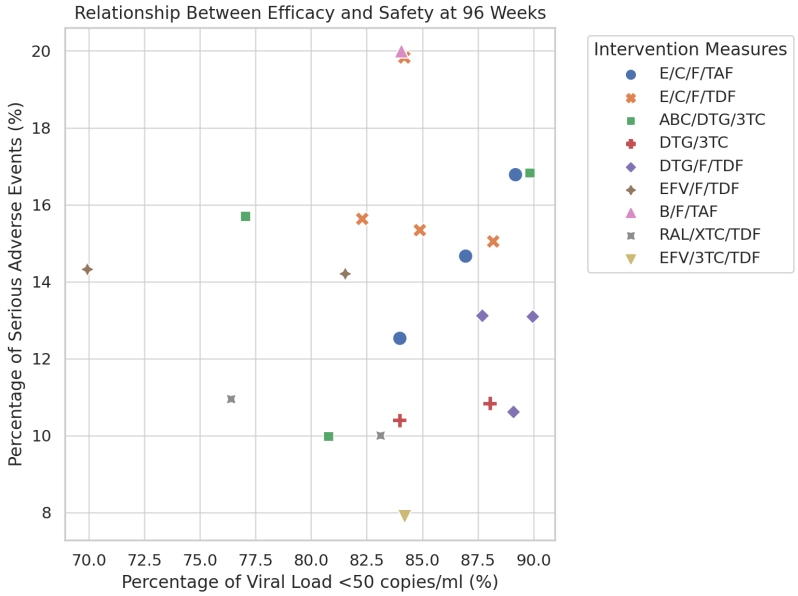

Figure 11. Relationship between efficacy and safety at 96 weeks post-treatment initiation

its potential superiority among the array of treatments studied. This observation is in line with contemporary research, which similarly identifies the high efficacy of INSTI based regimens in securing and maintaining viral suppression (18). Furthermore, the varied immune responses, as reflected in the changes in $CD4^+$ cell counts at both 48 and 96 weeks, underscore the necessity for tailored treatment strategies. The notable immune rebound exhibited by certain regimens compared to others accentuates the need to factor in the individual clinical profiles of patients when formulating treatment plans (19).

The selective reporting bias identified through the quality assessment of included studies represents a potential influence on the interpretation of both efficacy and safety outcomes, echoing the wider call for standardized reporting practices in clinical trials to ensure results' reliability and comparability (20). Additionally, the adverse event profiles linked with different ARV regimens elucidate the intricacies involved in managing side effects whilst aiming for optimal efficacy. Achieving a harmonious balance between efficacy and tolerability forms the foundation of successful long-term HIV management, highlighting the ongoing necessity for research and development

within ARV therapy realms (21). This discussion not only reflects the heterogeneity in ARV regimen efficacy and safety but also the imperative for individualized treatment approaches to accommodate the diverse needs of patients living with HIV.

Long-term efficacy and immune restoration under arv therapy: a comprehensive analysis

Our comprehensive analysis across 96 weeks of ARV treatment highlights significant findings regarding the long-term efficacy and immune response associated with various ARV regimens. The consistent superiority of the E/ C/F/TAF regimen in maintaining viral suppression and facilitating immune restoration underscores its potential as a leading long-term treatment option. This is complemented by the strong performance of ABC/DTG/3TC, which suggests these regimens' importance in achieving durable control over HIV viral loads (22). Conversely, the lower efficacy of EFV/3TC/TDF in sustaining viral suppression points to the need for careful selection of ARV therapies that not only suppress the virus initially but also maintain that suppression effectively over time. This differentiation in long-term outcomes emphasizes the critical nature of regimen selection in the context of HIV treatment sustainability (23).

Furthermore, the analysis of immune response variability, as evidenced by changes in $CD4^+$ counts at 96 weeks, offers valuable insights into the disparate impacts of ARV regimens on immune system recovery. The marked variability across treatments, with some regimens like E/C/F/TAF showing significant immune system enhancement, highlights the nuanced relationship between ARV therapy and immune recovery (24). These findings underline the importance of a holistic treatment approach that considers both virological suppression and immunological health to optimize long-term patient outcomes. A holistic treatment approach in HIV/AIDS management involves not only achieving viral suppression but also ensuring immune recovery, improving the patient's overall health and quality of life, and minimizing long-term adverse effects. Tailoring ARV strategies to balance these aspects is crucial for comprehensive patient care (25).

Longitudinal efficacy of ARV regimens: implications for sustained viral suppression

The longitudinal analysis conducted in our study elucidates the variance in long-term efficacy among pre-LPV/r+3TC ARV regimens, underlining the significance of sustained viral suppression in HIV management. The E/C/F/TAF and E/C/F/TDF regimens exemplify high degrees of durability in their suppressive capacity, with only slight declines in efficacy noted over 96 weeks. These findings suggest a resilient long-term control of the viral load, pivotal for patient care strategies aiming for prolonged suppression. In contrast, regimens such as B/F/TAF and DTG/3TC demonstrate more considerable decreases in suppression rates over time, indicating potential challenges in maintaining optimal viral control with these treatments. This diversity in regimen efficacy over an extended period emphasizes the necessity of individualized treatment plans tailored to ensure sustained viral suppression, a cornerstone in the management of HIV infection. By highlighting these differences, our study contributes valuable insights for clinicians in selecting ART that offer the best chance for long-term success in viral load management (26).

Moreover, the comparative analysis of viral suppression across various regimens provides a clear visual representation of the longitudinal effectiveness of each treatment, serving as a crucial tool for clinicians in making informed decisions regarding HIV treatment strategies. The graphical depiction of suppression rates from 48 to 96 weeks facilitates a deeper understanding of each regimen's performance, aiding in the optimization of HIV care protocols to enhance patient outcomes. Such detailed long-term efficacy data are essential for advancing HIV treatment approaches, underscoring the importance of ongoing research and evaluation of ART to meet the evolving needs of patients living with HIV (27).

Integrated analysis of efficacy and safety in ART

Our comprehensive evaluation of ART across pivotal periods of 48 and 96 weeks underscores the intricate interplay between treatment efficacy and safety, revealing a nuanced balance that necessitates careful clinical consideration. The

observed variability in adverse event rates among different regimens points to the essential role of personalized treatment strategies within the HIV/AIDS management continuum. For instance, the distinct safety profiles of E/C/F/TAF and DTG/3TC regimens—where the former shows a higher incidence of adverse events, and the latter exhibits fewer serious adverse events—highlight the importance of aligning treatment choices with individual patient needs and tolerability considerations. This alignment underscores the necessity for ongoing safety monitoring and the adjustment of treatment paradigms to not only achieve viral suppression but also minimize adverse impacts on patient well-being (28).

Furthermore, the slight positive correlation between the efficacy of treatments and the occurrence of serious adverse events, though weak, suggests that higher efficacy does not automatically imply increased safety risks. Rather, this relationship accentuates the multifactorial nature of treatment outcomes, advocating for an integrated treatment approach informed by both efficacy and safety considerations. The need for meticulous patient monitoring, coupled with comprehensive pre-treatment evaluations and post-treatment follow-ups, becomes evident, aiming to enhance the overall quality of life for individuals living with HIV. As our knowledge and understanding advance, the development of predictive tools and the incorporation of patient-centered outcomes into clinical decision-making will be vital in optimizing HIV treatment strategies, helping ensure a balance between effective viral control and patient safety.

Limitations and future perspectives

This comprehensive review, while offering valuable insights into the comparative efficacy and safety of various HIV/AIDS treatment regimens, is not without its limitations. One such limitation is the inherent variability in the study designs of the included trials, which may affect the generalizability of the findings. Additionally, the slight positive correlation observed between treatment efficacy and the occurrence of serious adverse events, although informative, underscores the need for further research to fully understand the complexities of this relationship. These limitations highlight the importance of advancing methodological approaches in future studies to enhance the robustness and applicability of the findings to diverse patient populations.

Looking ahead, there is a critical need for longitudinal studies that not only examine the immediate impact of ART but also their long-term effects on patient health and quality of life. Future research should also focus on the development of personalized treatment strategies, leveraging advances in genetic and biomarker research to predict individual responses to therapy. Such endeavors will not only address the gaps identified in this review but also propel the management of HIV/AIDS towards more tailored and patient-centered approaches.

CONCLUSIONS

This comprehensive review reveales key insights into the efficacy and safety of ARV regimens, particularly highlighting the superior performance of INSTI-based treatments like E/C/F/TAF and DTG/3TC in achieving sustained viral suppression. Despite a slight positive correlation between efficacy and serious adverse events, our findings underscore the necessity for personalized HIV/AIDS treatment strategies that balance efficacy with safety. These conclusions underscore the importance of careful regimen selection and ongoing patient monitoring to enhance treatment outcomes. Future research aimed at refining predictive models for treatment response is vital for advancing personalized care for individuals with HIV/AIDS. This study contributes to the evolving landscape of HIV/AIDS management, advocating for an approach that prioritizes both the effectiveness of treatment and the well-being of patients.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest related to this study. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of our affiliations or funding bodies.

ADDITIONAL INFORMATION

Author contributions

M.Y.: conceptualization, writing - original draft; Yp.L.: data curation, data analysis; Jy.H.: data curation, data analysis; Sy.Z.: methodology, validation; Jr.Y.: writing - original draft preparation, Writing - review & editing; Zx.Y.: writing - original draft preparation, writing - review & editing; J.Y.: supervision, funding acquisition, project administration, final approval of version to be published. All authors have read and agreed to the published version of the manuscript.

Important abbreviations

INSTIs, integrase strand transfer inhibitors; EFV, Efavirenz; 3TC, Lamivudine; TDF, tenofovir disoproxil fumarate; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; ART, antiretroviral therapy; AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus; RCTs, randomized controlled trials; NRTIs, nucleotide reverse transcriptase inhibitors; NNRTIs, non-nucleotide reverse transcriptase inhibitors; PIs, protease inhibitors; FIs, fusion inhibitors; STRs, single-tablet regimens; ADE, adverse drug event.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Review Article

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Perspectives on OncomiR and TSmiRs in Breast Cancer and Assessment of their Regulatory Network

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ABSTRACT

Breast cancer stands as a primary cause of mortality among women, urging the exploration of novel avenues for early detection. MicroRNAs (miRNAs) emerge as promising biomarkers, acting as both oncogenes and tumor suppressors, thus offering the potential for breakthroughs in early detection. Elevated levels of oncogenic miRNAs (OncomiRs) in cancer foster cell proliferation, migration, and metastasis by suppressing tumor suppressor genes. Inhibiting OncomiRs function presents a promising treatment strategy, where synthetic anti-miRs hinder OncomiRs binding to target RNAs, effectively suppressing cancer cell growth and metastasis. Conversely, decreased expression of Tumor Suppressor miRNAs (TSmiRs) in cancer facilitates malignancy progression by failing to suppress cancer-promoting genes. Circulating microRNAs (miRNAs) have gained considerable interest as promising biomarkers for breast cancer, owing to their distinct properties and involvement in cancer progression. An essential benefit of circulating miRNAs is their presence in bodily fluids like blood, serum, plasma, and breast milk. They exhibit remarkable stability within these fluids, safeguarded against degradation through encapsulation within extracellular vesicles or binding with proteins. This stability renders them appealing candidates for non-invasive biomarker identification. This article provides an overview of miRNA's pivotal role in breast cancer and its clinical significance.

KEYWORDS breast cancer, non-invasive, biomarker, miRNA, serum, prognosis

INTRODUCTION

Breast cancer remains the leading cause of mortality among women, contributing significantly to morbidity and mortality worldwide, despite considerable progress in its treatment (1). GLOBOCAN data from 2020 revealed a distressing figure of 19.3 million reported cancer cases and 10.0 million fatalities linked to the disease. Recent statistics indicate a shift in the most commonly diagnosed cancer, with female breast cancer surpassing lung cancer. Female breast cancer now constitutes approximately 2.3 million cases, representing 11.7% of all cancer cases, and contributes to around 684,996 deaths, accounting for 6.9% of total cancer-related fatalities (2) as shown in Table 1. Recent studies have revealed that emerging nations, notably those in Asia, are experiencing an increase in the prevalence of cancer as shown in Table 2 (3). Early detection of breast cancer increases patients' chances of

Table 1. Worldwide breast cancer incidence in 2020

Population	Units	Crude rate	Age-standardized rate	Cumulative risk %	Mortality	5-year prevalence
Asia	1,026,171	45.3	36.8	5.61	346,009	3,218,496
Europe	531,086	137.2	74.3	11.86	141,765	2,138,117
Northern America	281,591	151.2	89.4	14.78	85,787	1,189,111
Latin America and the Caribbean	210,100	63.2	51.9	8.69	57,984	710,039
Africa	186,598	27.8	40.7	6.53	48,407	429,220
Oceania	25,873	121.4	87.8	14.20	5,044	105,734
TOTAL	22,61,419				684,996	7,790,717

survival (4). Mammography is widely recognized as the most reliable method for breast cancer screening. However, other diagnostic examinations and biopsies are needed because of the high probability of false positives (5). Of a huge study of 702,154 cases of breast cancer in the US, around 2% (2,599/171,829) were found to be true positives, while the remaining 171,829 had defective screening mammography results. Due to the abnormal screening mammography results, most of these women underwent expensive and invasive diagnostic procedures that could have been avoided (6). Therefore, a more accurate breast cancer screening technique needs to be developed. Biomarkers can support the early detection of breast cancer. They can help find specific molecules or genetic abnormalities related to cancer cells (7). Biomarker screening in breast cancer involves reporting tumors and the analysis of DNA, RNA, proteins, and other biomolecules in body fluids and has been shown to be a valuable approach for cancer prognosis, diagnosis, personalized treatment, and predicting drug response. Circulating microRNAs (miRNAs) are now widely recognized as potent biomarkers for a variety of diseases, including cancer (8). Non-coding RNAs (ncRNAs) encompass a diverse array of RNA molecules that do not possess the ability to encode proteins. miRNAs are a notable class of non-coding RNA molecules, typically ranging from 19 to 25 nucleotides in length. These ncRNAs play a crucial role in regulating gene expression by inhibiting mRNA translation or facilitating mRNA degradation. This essential function highlights their significance in cellular processes as shown in Figure 1 (9). Furthermore, miRNAs influence cell proliferation, migration, invasion, and differentiation, and are associated with tumorigenesis. Through their regulatory mechanisms, ncRNAs control oncogenes and tumor suppressor gene expression (10). The dysregulation of oncomiRs and tumor suppressor miRs (TS miRs) in breast cancer holds promise for advancing breast cancer detection, diagnosis, prognosis, and treatment. OncomiRs, which promote oncogenesis by inhibiting tumor suppressor genes, and TS miRs, which counteract oncogenic activity, are emerging as valuable biomarkers for breast cancer screening. Typically, oncomiRs are upregulated, while TS miRs are downregulated in cancer cells. Manipulating the levels of these miRNAs can significantly impact cancer cell behavior. Dysregulated oncomiRs contribute to the uncontrolled growth and survival of cancer cells, playing critical roles in breast cancer metastasis and therapy resistance. Identifying and quantifying these oncomiRs in biological samples like blood or tissue biopsies can offer insights into breast cancer's presence and progression (11). Recent reports suggest that circulating miRNAs have been extensively studied and have shown significant potential as biomarkers for both diagnostic and prognostic purposes. These miRNAs can be detected in bodily fluids such as blood and serum during the early stages of breast cancer, allowing for timely intervention (12). The detection of miRNAs typically involves minimally invasive procedures, which enhance patient comfort and facilitate repeated sampling for longitudinal monitoring of disease progression. Additionally, miRNAs offer the potential for personalized medicine by providing insights into tumor biology and identifying therapeutic targets. Their ability to be multiplexed allows for comprehensive molecular characterization of breast cancer, and advancements in detection technologies have made miRNA analysis more accessible and cost-effective (13).

Table 2. Breast cancer cases in 2020 in Asia

Asia continents	Units				Mortality				Prevalence	
Countries	Number	Rank	(%)	Cumulative risk %	Number	Rank	(%)	Cumulative risk %	Number	Cumulative risk %
Afghanistan	3,173	1	13.9	3.11	1,783	2	11.1	2.07	5,930	31.29
Armenia	1,190	2	12.8	5.54	504	2	8.3	2.20	4,084	260.21
Azerbaijan	2,219	1	13.6	3.72	876	3	8.4	1.47	7,286	143.58
Bahrain	244	1	20.1	4.81	66	2	11.1	1.47	868	144.40
Bangladesh	13,028	3	8.3	1.83	6,783	4	6.2	1.03	31,232	38.35
Bhutan	16	11	2.8	0.60	8	14	1.8	0.36	39	10.79
Brunei Darussalam	137	1	13.9	5.88	29	5	6.7	1.30	499	237.06
Cambodia	1,877	3	10.2	2.44	793	3	6.3	1.07	4,242	49.58
China	4,16,371	3	9.1	4.18	1,17,174	8	3.9	1.16	13,90,095	197.04
Gaza Strip and West Bank	892	1	18.7	5.71	355	2	12.3	2.49	2,390	95.05
Georgia	1,942	1	14.7	6.30	910	2	11.1	2.69	6,917	331.28
India	1,78,361	1	13.5	2.81	90,408	1	10.6	1.49	4,59,271	69.28
Indonesia	65,858	1	16.6	4.83	22,430	2	9.6	1.78	2,01,143	148.11
Iran, the Islamic Republic	16,967	1	12.9	3.67	4,810	5	6.1	1.15	55,915	134.46
Iraq	7,515	1	22.2	5.72	3,019	1	15.3	2.42	20 354	102.46
Israel	4,348	1	15.1	8.46	1,194	2	9.1	1.70	17,745	408.17
Japan	92,024	5	8.9	7.98	17,081	7	4.1	1.11	3,28,716	507.88
Jordan	2,403	1	20.8	6.36	758	2	12.2	2.16	7,363	146.17
Kazakhstan	4,390	2	12.4	4.18	1,654	3	7.9	1.58	16,084	166.44
The Democratic Republic of Korea	5,962	2	10.3	3.49	1,791	6	4.5	1.06	12,040	91.42
Republic of Korea	25,814	3	11.2	6.41	3,009	7	3.4	0.68	86,672	338.52
Kuwait	791	1	20.6	5.74	224	1	13.0	1.83	2,805	169.37
Kyrgyzstan	770	3	10.9	2.61	251	6	5.4	0.92	2,056	62.36
Lao People's Democratic Republic	1,080	2	11.8	3.90	437	4	7.0	1.67	2,583	71.28
Lebanon	1,954	1	16.9	6.23	723	2	11.2	2.33	6,385	188.36
Malaysia	8,418	1	17.3	5.29	3,503	2	11.9	2.24	29,453	187.18
Maldives	83	1	16.7	4.77	26	3	9.8	1.86	248	125.50
Mongolia	188	6	3.3	1.17	62	8	1.4	0.42	589	35.41
Myanmar	6,912	4	9.3	2.29	2,972	6	5.6	1.03	15,875	56.32
Nepal	1,973	3	9.6	1.47	1,049	4	7.7	0.79	4,555	28.85
Oman	558	1	15.0	4.00	195	1	9.6	1.55	1,849	106.49
Pakistan	25,928	1	14.5	4.22	13,725	1	11.7	2.38	60,458	56.39
Philippines	27,163	1	17.7	5.66	9,926	3	10.7	2.02	85,206	156.19
Qatar	218	1	14.7	4.91	57	3	8.1	1.59	776	108.39
Saudi Arabia	3,954	1	14.2	3.01	1,095	2	8.4	0.93	13,653	92.99
Singapore	3,662	1	15.5	8.27	921	4	7.6	2.01	15,306	548.98
Sri Lanka	3,975	1	13.4	2.93	1,682	3	10.1	1.25	13,647	122.44
The Syrian Arab Republic	4,388	1	20.9	6.16	1,946	1	15.0	2.91	9,486	108.53
Tajikistan	738	2	12.9	2.06	279	4	7.3	0.91	1,844	38.97
Thailand	22,158	3	11.6	4.12	8,266	3	6.6	1.39	76,440	213.32
Timor-Leste	119	1	14.6	2.72	48	2	8.9	1.13	294	45.08
Turkey	24,175	2	10.3	4.89	7,161	4	5.7	1.39	83,973	196.64
Turkmenistan	1,025	1	14.9	3.24	450	2	10.4	1.59	2,917	95.27
United Arab Emirates	1,030	1	21.4	6.58	222	1	11.7	1.70	3,746	122.66
Uzbekistan	4,454	1	13.9	2.77	2,067	3	9.9	1.41	13,297	79.28
Viet Nam	21,555	3	11.8	3.69	9,345	4	7.6	1.47	60,753	124.65
Yemen	2,894	1	17.6	3.12	1,638	1	13.5	1.95	4,984	33.67

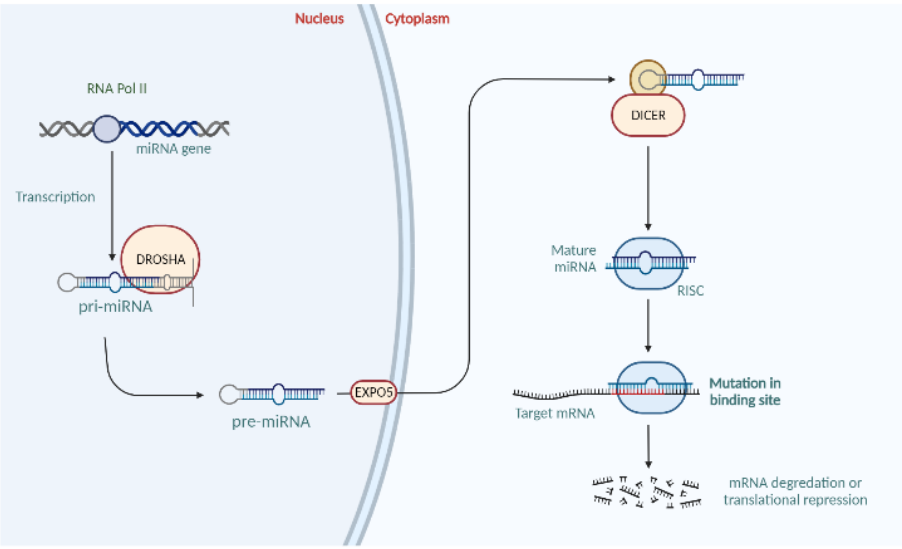

Figure 1. Biogenesis of miRNA

ONCOMIRNAS AS BIOMARKER

OncomiRNAs, also known as oncogenic miRNAs, represent a specific group of microRNAs that have been implicated in the development and advancement of cancer. These specific miRNAs play a role in promoting oncogenesis by exerting influence over various cellular processes, including cell metastasis, proliferation, and apoptosis. As a result, these miRNAs have broad-ranging effects on cancer development and progression. Among cancer cells, OncomiRNAs frequently demonstrate abnormal expression levels when compared to normal cells, and their dysregulation can disrupt gene expression networks relevant to tumorigenesis. OncomiRNAs have gained recognition as promising targets for cancer research in both diagnostic and therapeutic applications. They have achieved this by specifically targeting and modulating the expression of tumor suppressor genes or oncogenes, opening up new possibilities for advancements in the field. Circulating miRNAs, which can be detected in various sources such as tumor tissues, serum, plasma, urine, and patient saliva, hold promise as biomarkers for the early detection and prognostication of breast cancer. Bloodstream miRNAs are released by necrotic and apoptotic cells (9). Like Argonaut 2 (Ago2), miRNAs can circulate cell-free in the bloodstream or encased in membrane vesicles, macrovesicles, or exosomes (14). The comprehensive profiling of miRNAs can identify dysregulated miRNAs throughout breast cancer metastasis and enable the stratification of breast cancer patients for tailored therapeutic interventions. It's important to note that miRNA expression patterns can vary among breast cancer subtypes and individual patients. The dysregulation of TSmiRs and the upregulation of OncomiRNAs play a crucial role in the intricate molecular processes underlying the growth and progression of breast cancer.

TSMIRS IN BREAST CANCER

TSmiRs, although they do not encode proteins, play a crucial role in regulating gene expression and maintaining normal cellular functions. In the context of breast cancer, numerous TSmiRs have been identified, often exhibiting downregulation or functional impairment. This dysregulation results in the aberrant expression of key genes involved in tumor development and progression. The microRNA miR-34a is under direct regulation by the tumor suppressor p53. However, in breast cancer cases, its expression is frequently silenced. By specifically targeting and regulating critical genes involved in cell cycle progression, such as cyclin D1, cyclin E2, and CDK4, miR-34a exerts a powerful influence on cell proliferation. It induces cell cycle arrest and promotes apoptosis, thus playing a significant role in breast cancer pathogenesis. The absence of miR-34a, on the other hand, facilitates tumor growth and confers resistance to apoptosis. miR-34a plays a significant role in regulating both cell cycle progression and apoptosis by directly targeting multiple genes involved in these processes. It directly targets CDK4 and CDK6, which are key regulators of the

cell cycle. Through its inhibitory effects on these genes, miR-34a prompts cell cycle arrest, thereby preventing excessive cell proliferation. Additionally, miR-34a acts by targeting anti-apoptotic genes, including Bcl-2, survivin, and XIAP, thereby facilitating apoptosis and impeding the survival of tumor cells. Several studies have demonstrated that miR-34a exerts inhibitory effects on breast cancer metastasis by selectively targeting genes involved in the epithelial-mesenchymal transition (EMT), a critical process underlying tumor invasion and metastasis. By directly binding to and regulating the expression of transcription factors such as Snail, Slug, and ZEB1, miR-34a effectively counteracts their ability to promote EMT and enhance the metastatic potential of cancer cells. The repression of EMT-related genes by miR-34a hampers the migratory and invasive properties of breast cancer cells. Additionally, miR-34a plays a pivotal role in regulating cancer stem cells (CSCs) in breast cancer, which are characterized by their capacity for self-renewal and initiation of tumor growth.

By specifically targeting important genes, including Notch1, Sox2, and Nanog, miR-34a plays a crucial role in suppressing the stemness properties of CSCs. This targeted regulation effectively reduces the tumorigenic capabilities of CSCs. The decreased expression of miR-34a in breast cancer patients is associated with an unfavourable prognosis, advanced tumor stage, and the presence of lymph node metastasis. As a result, the expression levels of miR-34a hold promising potential as a prognostic biomarker in breast cancer (15). The miR-200 family, which includes miR-200a, miR-200b, miR-200c, miR-141, and miR-429, has gained considerable attention in breast cancer research due to their involvement in multiple aspects of tumor progression and metastasis. These microRNAs play crucial roles in regulating key processes. Furthermore, the miR-200 family has been implicated in the regulation of CSCs in breast cancer. The miR-200 family exerts its regulatory effects by specifically targeting genes, such as BMI1 and Suz12, that are involved in controlling the stemness properties of cancer CSCs. Through this targeting mechanism, the miR-200 family inhibits the characteristics associated with CSCs and diminishes their ability to initiate tumor formation. These findings underscore the importance of the miR-200 family in modulating the behavior of CSCs and highlight its potential as a therapeutic target for suppressing CSC-mediated tumor growth in breast cancer. The miR-200 family has also been implicated in the control of CSCs in breast cancer. In breast cancer, the miR-200 family plays a role in regulating CSCs by targeting specific genes involved in the maintenance of stemness, such as BMI1 and Suz12. Through this mechanism, the miR-200 family inhibits the properties of CSCs and reduces their tumor-initiating potential. These findings highlight the significance of the miR-200 family in the regulation of CSCs and its potential implications for breast cancer treatment strategies. In addition, the aberrant expression of the miR-200 family has been associated with the development of chemoresistance in breast cancer. Particularly, a reduction in the expression of miR-200c has been observed in breast cancer cells that display resistance to chemotherapy. The miR-200 family members exert their influence by targeting genes involved in drug resistance, including ABCG2 and ABCC1. These genes encode ATP-binding cassette transporters that play a crucial role in facilitating the efflux of drugs from cancer cells. Therefore, the dysregulation of the miR-200 family contributes to chemoresistance in breast cancer by modulating the expression of drug efflux transporters. The downregulation of miR-200 family members has been associated with increased expression of drug transporters, leading to the development of drug resistance. Extensive research efforts have been dedicated to investigating the levels of miR-200 family members as potential biomarkers for prognosis and prediction in breast cancer. Decreased expression of miR-200 family members has been correlated with an unfavourable prognosis, heightened aggressiveness of tumors, and an increased risk of metastasis. These findings emphasize the potential of miR-200 family members as valuable prognostic and predictive biomarkers in breast cancer. Moreover, the miR-200 family has demonstrated relevance in predicting treatment response, including resistance to hormonal therapies and chemotherapy. However, it is crucial to acknowledge that the impacts of the miR-200 family in breast cancer can exhibit variability depending on the particular tumor subtype and molecular characteristics. Furthermore,

the interactions between miR-200 family associates and their target genes are intricate, involving multiple signaling pathways (16). Both miR-125a and miR-125b have been recognized as tumor suppressors, displaying the capacity to inhibit cell proliferation and suppress tumor growth. Through their targeted regulation of important genes involved in cell cycle progression, such as CDK6 and E2F3, miR-125a and miR-125b induce cell cycle arrest, effectively restraining tumor cell proliferation. These microRNAs play crucial roles in tumors (17). Notably, miR-214 has been identified as a contributor to tumor growth and metastasis. Its mechanism involves targeting tumor suppressor genes, including PTEN and PDCD4, which results in enhanced cell proliferation, invasion, and migration. Furthermore, miR-214 can enhance the PI3K/AKT signaling pathway, which is closely associated with tumor progression. The regulation of EMT is critical for metastasis, and miR-214 has been identified as a participant in this process in breast cancer. It achieves this by targeting the E-cadherin gene (CDH1), which is responsible for maintaining cell-cell adhesion and suppressing EMT. By inhibiting CDH1, miR-214 disrupts cell adhesion and facilitates the transition to a mesenchymal phenotype. This, in turn, promotes the potential for metastasis (18). Their presence is crucial for tumor development, advancement, and acquiring resistance against therapeutic interventions. Notably, miR-214 has been identified as a regulator of CSCs in breast cancer. It exerts its regulatory effects by targeting important genes involved in maintaining stemness and self-renewal, such as PTEN and p53. Through the modulation of the expression of these genes, miR-214 influences the behavior and functional properties of CSCs in breast cancer. These findings highlight the significance of miR-214 in the regulation of CSCs and its potential as a therapeutic target for breast cancer treatment. Inhibiting these genes, miR-214 can promote CSC characteristics and contribute to tumor aggressiveness. miR-214 has also been connected with the process of drug resistance in breast cancer. It can target genes involved in drug sensitivity, such as PTEN and BIM. Downregulating these genes, miR-214 can confer resistance to chemotherapy and targeted therapies. SOS1 was the target of miR-628, which prevented BC cells from migrating and invading, indicating increasing SOS1 (19). Expression through therapeutic means might be a successful strategy for treating BC metastasis (20). miR-16 functions as a suppressor of various oncogenes implicated in the development of breast cancer. It directly targets genes such as CCND1 (encoding cyclin D1), which promotes cell cycle progression, and BCL2 (encoding anti-apoptotic protein Bcl-2), which inhibits cell death. By downregulating these oncogenes, miR-16 exerts tumor-suppressive effects. miR-16 has demonstrated its ability to target multiple genes involved in angiogenesis, a vital process responsible for tumor progress and metastasis. It targets VEGFA directly and its receptor VEGFR2, thereby suppressing angiogenesis and limiting blood supply to the tumor and playing a key role in the suppression of angiogenesis. Sensitization to chemotherapy is another essential means by which miR-16 enhances breast cancer cells' sensitivity to chemotherapy drugs. Targeting genes related to drug resistance, such as ABCC1 and ABCC5, miR-16 effectively inhibits the function of ATP-binding cassette transporters associated with drug efflux. As a result, the breast cancer cells' sensitivity to chemotherapy drugs is enhanced by reducing the expression of these transporters, i.e., miR-16 alerts breast cancer cells to chemotherapy agents (28). MiRNA-203 has been shown to play a pivotal role in inhibiting EMT in breast cancer cells by targeting critical transcription factors like ZEB1 and Slug (31). ZEB1 and Slug serve as master regulators of EMT, promoting the shift from an epithelial to a mesenchymal phenotype, thus fostering tumor invasion and metastasis. Conversely, miRNA-203 acts as a tumor suppressor by directly targeting and reducing the expression of these transcription factors, consequently impeding the EMT process in breast cancer (43). By inhibiting these genes, miRNA-203 suppresses stemness properties and reduces the tumorigenic potential of CSCs. miRNA-203 is linked to the sensitivity of BC cells to various therapeutic agents. Its dysregulation is involved with resistance to chemotherapy drugs (paclitaxel and doxorubicin). Restoring miRNA-203 expression or modulating its target genes involved in drug resistance may sensitize BC cells to chemotherapy and enhance treatment efficacy (44). miRNA-99a is a regulator of RB1 expression. It directly targets the RB1 mRNA and can downregulate RB1 protein

The references should be listed in numerical order. However, after reference 20, the numbers 21-27, 30, 31, and 31-42 do not appear in the text.

levels by attaching to specific sequences in the 3' (UTR) of the RB1 gene. This targeting results in reduced RB1 activity. By targeting and suppressing RB1 expression, miRNA-99a can potentially pay for the deregulation of the cell cycle and promote breast cancer development (45). miR-31, a tumor suppressor targets multiple oncogenes including RhoA and WAVE3 which are connected in cell migration and invasion. Reduced miR-31 expression enhances tumor cell motility and facilitates the process of metastasis (46). The family of let-7 miRNAs, including let-7a, let-7b, let-7c, let-7d, let-7e, and let-7g, is often downregulated in breast cancer. These miRNAs target various oncogenes, such as HMGA2, KRAS, and c-Myc, which are associated with cell proliferation, differentiation, and metastasis. Reduced let-7 expression contributes to tumor growth and aggressiveness (47). Triple-negative breast cancer (TNBC) is an intrinsic subtype of breast cancer characterized by the absence of ER, PR, and HER2 expression. Within TNBC, certain miRNAs are identified as oncogenic and associated with this subtype. For instance, miR-21 is commonly observed to be upregulated in TNBC and contributes to tumor development, metastasis, and invasion by directing tumor suppressor genes (PTEN and PDCD4). Similarly, miR-155, miR-221/ 222, and miR-10b act as oncogenic in TNBC. Conversely, specific miRNAs function as tumor suppressors in TNBC. Among them, miR-34a, tumor suppressor miRNA is frequently noted to be downregulated in TNBC. It targets genes involved in crucial functions such as cell cycle regulation, apoptosis, and EMT. In TNBC, the miR-200 family members miR-200c, miR-141 and miR-205 have been identified as tumor suppressor microRNAs. They play a crucial role in regulating the process of EMT and have an impact on the metastatic potential of cancer cells. These microRNAs act as key modulators in TNBC, influencing the transition of cancer cells from an epithelial to a mesenchymal phenotype, thereby affecting tumor progression and metastasis (33). A list of expression patterns of TsmiR and their target genes is listed in Table 3.

DIFFERENTIAL EXPRESSION OF CIRCULATING ONCOMIRNAS IN BREAST CANCER

The non-invasive nature of circulating OncomiRNAs makes them particularly appealing as biomarkers for breast cancer. Blood samples or other bodily fluids can be readily obtained, offering a convenient and accessible method for monitoring the status of diseases and evaluating the response to treatment. Changes in the levels of circulating OncomiRNAs during treatment can serve as indicators of treatment response. Alterations in the expression levels of specific OncomiRNAs have been observed in response to various therapies, including chemotherapy, hormone therapy, and targeted therapies. Monitoring these changes can provide valuable information on treatment efficacy and help guide personalized treatment decisions (Table 4).

Emerging research has shed light on the release of miRNAs from apoptotic or necrotic cells into various body fluids such as blood, plasma, serum, breast milk, saliva, and urine. These studies have unveiled the presence of miRNAs in these bodily fluids, highlighting their potential as biomarkers for various diseases and conditions. As a result, there may be a good chance to employ these circulating biomarkers to monitor BC as well as the various stages of this fatal disease. Recent research has demonstrated that serum is a more favourable option among bodily fluids for regulating the expression of miRNAs. This preference arises from the higher concentrations of miRNAs found in serum, which could be attributed to the impact of the clotting process (48). In a study conducted by Huiping Li et al. a signature consisting of miR-16-5p, miR-17-3p, miR-451a, and miR-940 levels was identified. This signature showed significant associations with neutral response rates, time to disease progression, and overall survival in three separate cohorts of HER2+ metastatic breast cancer patients undergoing initial treatment with trastuzumab (49). These findings suggest that a serum miRNA signature has the potential to serve as an indicator of therapeutic efficacy in HER2+ metastatic breast cancer patients receiving trastuzumab treatment. In another study by Natsuko Satomi-Tsushita et al. a combination of miRNAs was identified to assess the response to eribulin in metastatic breast cancer. This combination included miR-296-3p, miR-575, miR-3160-5p, miR-4710, miR-4755-3p, miR-4483, miR-5698, and miR-8089 (50). Further, hsa-miR-3184-5p and hsa-miR-6784-5p have been recognized as key regulators of BC and sensitive serum biomarkers (51).

Table 3. The expression pattern of TsmiR and their target in breast cancer

TsmiR annotation	Targets	Pathways	Function	References
miR-34a-3p	HIF1-α	p53	Migration, invasion, proliferation	15
miR-125b-5p	ST14	VDR	Proliferation invasion and migration	17
miR-628-3p	SOS1	Src MEK1/2	Prevents invasion and migration	20
miR-206	CDK4	NF-κB	Stops TNBC tumorigenesis	21
miR-26b-5p	CDK6	glycolytic	Aids in G0/G1 cell cycle arrest and prevents cellular growth	22
miR-26a-5p	ST8SIA4	NF-κB/PI3K/Akt	Prevents BC progression	23
miR-124-3p	STAT3 MGAT5	Wnt/β-catenin PI3K/ AKT/	Prevents BC cell proliferation and invasion	24
miR-205-5p	TG2	TGFβ1, Wnt, β-catenin NF-κB	Decreases invasion and BC bone metastasis	25
miR-21-3p	CYP1A1	MAT2B	Prevents proliferation	26
miR-29b-3p	TET1 TDG	AKT signalling Wn-t/β-catenin	Facilitate cell growth, proliferation, and apoptosis	27
miR-100-3P	mTOR	Stat5a IL-1ra	Proliferation migration and invasion	27
miR-512-5p	JAG1	Notch2	Proliferation, invasion, migration	28
miR-34a-5p	TGFBR2	TGF-β	Invasion and metastasis	28
miR-16-5p	TGF-β	Wnt/β- catenin ERK	Apoptosis ,invasion and migration.	29
miR-148a-5p	DNMT1 Wnt10b	Wnt/β-catenin	Proliferation and migration	30
miR-204-5p	JAK2	STAT3 BCl-2	Proliferation and apoptosis	34
miR-296-5p	PLK1	MS2bp	Growth, Invasion, Metastasis	35
miR-15a-5p	CCNE1	sONE eNOS	Growth inhibition, suppression of migration	36
miR-22-3p	Twist1	EMT	Migration, invasion, proliferation	37
miR-30b-5p	ITGB3 , IL-8, L-11, CDH11 CTGF	PI3K,	Metastasis , differentiation Proliferation, apoptosis, invasion	38
miR-143-3p	MAPK3, KRAS	RECK signalling	Tumorigenesis, development, metabolism, invasion, proliferation, apoptosis, and metastasis	39
miR-195-5p	MFN2	mTORC2 Akt	Proliferation , migration, and invasion	40
miR-497-5p	PTEN	YAP1	Proliferation	41
miR-26a-5p	HMGA1	Wnt/β- catenin	Invasion and migration	42
miR-126-3p	VEGF-A	PI3K signal	Apoptosis, proliferation, and angiogenesis	43

According to the Xiaoqin Li et al. study, breast cancer patients had a higher blood range of the microRNAs miR-9-5p and miR-148a-3p than normal controls (52). Interestingly, miR-17-5p did not show important differences between the two groups. The study revealed that HER2-positive breast cancer patients had notably higher levels of miR-9-5p in their blood compared to HER2-negative breast cancer patients. Guo et al. conducted a study where they observed significantly decreased levels of miR-455-3p and increased levels of miR-1915-3p in the serum of breast cancer patients. Moreover, patients with infiltrating carcinoma metastases demonstrated elevated levels of miR-1915-3p and lower levels of miR-455-3p compared to those with carcinoma in situ or without lymph node metastasis (53). Another study by Cardinali et al comparing breast cancer patients to healthy controls found that breast cancer patients had significantly elevated levels of four miRNAs in plasma (miR-20b-5p, miR-92a-5p, miR-106a-3p, and miR-106a-5p) and four miRNAs in serum (miR-19b-3p, miR-20b-5p, miR-92a-3p, and miR-106a-5p). These findings contrasted with individuals with benign breast tumors as well as age- and sex-matched healthy

Table 4. The expression pattern of differential expression of Circulating OncomiRNAs in breast

miRNA	Regulation in breast cancer	Functions	Signaling pathways
miR-16-5p	Down-regulated	Tumor suppressor	Apoptosis, cell cycle regulation, PI3K/AKT
miR-17-3p	Up-regulated	Oncogenic, promotes proliferation	PI3K/AKT, TGF-β signaling
miR-451a	Down-regulated	Tumor suppressor	AMPK/mTOR pathway, cell migration
miR-940	Up-regulated	Oncogenic, enhances invasion and migration	Wnt/β-catenin, PI3K/AKT
miR-296-3p	Down-regulated	Tumor suppressor, involved in angiogenesis	PI3K/AKT, VEGF signaling
miR-575,	Up-regulated	Promotes cell proliferation and survival	PI3K/AKT, MAPK, JAK/STAT
miR-3160-5	Up-regulated	Involved in tumor progression	TGF-β, Wnt/β-catenin, Notch
miR-4710	Up-regulated	Influences cell migration and invasion	FAK/SRC, Rho GTPases, Integrin
miR-4755-3p	Up-regulated	Involved in cell growth	mTOR, Ras/Raf/MEK/ERK, Hippo
miR-4483	Up-regulated	Involved in tumorigenesis	NF-κB, Hedgehog, TGF-β
miR-5698	Up-regulated	Implicated in cell proliferation	EGFR, STAT3, NF-κB
miR-8089	Up-regulated	Invasion and migration	MMPs, EMT signaling, AKT/mTOR
hsa-miR-3184-5p	Up-regulated	Tumor suppressor, regulates cell cycle	p53 signaling
hsa-miR-6784-5p	Up-regulated	Tumor suppressor, involved in apoptosis	p53 signaling, PI3K/AKT, MAPK pathways
miR-9-5p	Up-regulated	Promotes metastasis, epithelial-mesenchymal transition (EMT)	Notch signaling, E-cadherin repression
miR-148a-3p	Up-regulated	Tumor suppressor, inhibits metastasis	TGF-β signaling, Wnt/β-catenin
miR-17-5p	Up-regulated	Oncogenic, promotes proliferation	PI3K/AKT, TGF-β signaling
miR-455-3p	Down-regulated	Tumor suppressor, inhibits proliferation and invasion	Wnt/β-catenin, EMT regulation
miR-1915-3p	Up-regulated	Promotes metastasis, regulates apoptosis	PI3K/AKT, apoptosis pathways
miR-20b-5p	Up-regulated	Promotes cell proliferation and survival	PI3K/AKT, MAPK pathways
miR-92a-5p	Up-regulated	Promotes angiogenesis and cell proliferation	Notch signaling, cell cycle regulation
miR-106a-3p	Up-regulated	Promotes cell cycle progression and invasion	TGF-β signaling, E2F signaling
miR-106a-5p	Up-regulated	Promotes cell proliferation and metastasis	PI3K/AKT, E2F signaling
miR-19b-3p	Up-regulated	Promotes cell proliferation and inhibits apoptosis	PI3K/AKT, Wnt/β-catenin
miR-92a-3p	Up-regulated	Promotes cell proliferation and inhibits apoptosis	Notch signaling, cell cycle regulation
miR-21	Down-regulated	Promotes proliferation, invasion, and metastasis	PI3K/AKT, NF-κB, and MAPK pathways
miR-497-5p	Up-regulated	Tumor suppressor, inhibits cell proliferation	PI3K/AKT, cell cycle regulation
miR-1246	Up-regulated	Promotes cell proliferation, invasion, and metastasis	p53 signaling, Wnt/β-catenin
miR-1307-3p	Up-regulated	Involved in tumor progression and metastasis	Cell cycle regulation
miR-4634	Up-regulated	Involved in cancer cell proliferation	PI3K/AKT, NF-κB, and MAPK pathways, Notch signaling,
miR-6861-5p	Up-regulated	Involved in tumor progression	PI3K/AKT, NF-κB, and MAPK pathways, Notch signaling,
miR-6876-5p	Up-regulated	Involved in cancer progression	PI3K/AKT, NF-κB, and MAPK pathways
miR-1246	Up-regulated	Promotes cell proliferation, invasion, and metastasis	p53 signaling, Wnt/β-catenin, Notch signaling,
miR-1307-3p	Down-regulated	Involved in tumor progression and metastasis	cell cycle regulation
let-7a	Up-regulated	Tumor suppressor, inhibits cell proliferation	RAS signaling, HMGA2
miR-574-5p	Up-regulated	Promotes inflammation and tumor progression	JAK/STAT, PI3K/AKT, and NF-κB pathways
miR-155		Promotes inflammation, cell proliferation, and survival	JAK/STAT, PI3K/AKT, and NF-κB pathways

individuals (54). Additionally, Bingjie Cai et al. found higher expression of serum miRNA-21 in breast cancer patients. Increased levels of circulating miR-21 were associated with advanced tumor stage, poor prognosis, and lymph node metastasis in breast cancer (53). The researchers concluded that serum miRNA-21 shows promise as a non-invasive biomarker for breast cancer, based on the aforementioned findings. Zhong et al. conducted a study revealing elevated expression of miR-497-5p in the serum of breast cancer patients. However, in cell lines and tissue samples from the same patients, miR-497-5p was found to be downregulated (55). Another comprehensive analysis performed by Loke et al. involved the study of 4630 serum samples. The results identified a five-miRNA signature comprising miR-1246, miR-1307-3p, miR-4634, miR-6861-5p, and

miR-6876-5p (56). This signature demonstrated high accuracy in detecting breast cancer, including its early stages, thereby highlighting its potential as a robust diagnostic tool. Furthermore, a study conducted by Sheng-kai demonstrated that breast cancer patients exhibit decreased expression of let-7a and an increased range of miR-574-5p, miR-155, and MALAT1 in their serum (57).

REGULATORY NETWORK OF ONCOMIRNAS IN EARLY BREAST CANCER

Oncogenic miRNAs are essential for the growth of breast cancer. The key oncogenic miRNAs involve angiogenesis, metastasis, invasion, cell migration, and apoptosis inhibition. According to a clinical investigation, the overexpression of miR-17, which is activated by the oncoprotein c-Myc, is connected to increased cell proliferation, lower overall survival, and progressive clinical stage in breast cancer patients (58). According to a study by Luengo-Gil, miR-20a has been found to enhance angiogenesis and stimulate the growth of glomeruloid microvasculature in breast cancer. This effect is likely attributed to the overexpression of VEGFA, a key factor involved in angiogenesis (59). Another study by Mehrgou, A. highlights the crucial role of miR-21 overexpression in promoting cell proliferation and contributing to a more severe phenotype in pregnancy-associated breast cancer (60). Furthermore, Yang et al. discovered that overexpressing miR-181a and miR-181b facilitates the formation of cellular spheres, regulates the cell cycle, enhances cell proliferation, and promotes resistance to chemotherapy (61). A list of expression patterns of OncomiRNAs and their target genes is shown in Table 5 (16, 44, 59, 62-83). To gain a deeper understanding of the biological and molecular roles of specific miRNAs, a comprehensive literature survey was conducted. The mirWalk database, accessible at http://mirwalk.umm.uni-heidelberg.de/, was employed to predict the target genes associated with the top 10 upregulated and downregulated miRNAs. From this analysis, a total of 215 target genes were predicted for the upregulated miRNAs, while 118 target genes were identified for the downregulated miRNAs as shown in Figures. 2 and 3. To further investigate the functional characteristics of these target genes, a Gene Ontology (GO) analysis was performed. This analysis aimed to categorize the upregulated target genes based on their involvement in biological processes and molecular functions. The ClueGO plug-in, integrated within the Cytoscape platform, was utilized for this purpose. A statistical significance threshold ($p < 0.05$) was applied, along with Bonferroni step-down analysis, to ensure reliable results as shown in Table 6. This comprehensive analysis is instrumental in the identification of potential therapeutic targets and biomarkers for breast cancer diagnosis, prognosis, and the development of personalized treatment strategies for patients.

The GO term GO:0090201 is not directly connected to BASP1, BCL2, HES1, JAG1, NOTCH1, or NOTCH2 and reflects the control of cytochrome c release from mitochondria. Although these proteins and genes have various cellular functions, they do not specifically play a role in the release of cytochrome c. It is important to note that certain proteins, including BCL2, are indeed connected in the regulation of cytochrome c release. BCL2 is a protein known for its anti-apoptotic function, as it inhibits the release of cytochrome c from mitochondria. This effect is achieved through interactions with pro-apoptotic proteins like BAX and BAK, which control the release of cytochrome c. Conversely, HES1, JAG1, NOTCH1, and NOTCH2 are components of the Notch signaling pathway, which is involved in cell fate determination and development. These elements contribute to the intricate regulatory processes of cellular functions. Although the Notch pathway is not directly associated with the regulation of cytochrome c release, it is involved in other cellular processes and gene expression regulation. GO:0016241, the regulation of macroautophagy, a cellular process that involves the degradation and recycling of cellular components through the formation of autophagosomes, is represented. It is regulated by a complex interplay of various genes and proteins. AKT1 is known to modulate autophagy through its downstream targets and signaling pathways. BNIP3L is a helpful regulator of autophagy and is implicated in the induction of mitophagy, a selective form of autophagy that targets damaged mitochondria for degradation. MTOR forms complexes with other proteins and functions as a central node in the signaling pathways that control autophagy. It negatively regulates autophagy, inhibiting the formation of autophago-

Table 5. The expression pattern of OncomiRNAs and their target in breast cancer

OncomiRNAs annotation	Targets	Pathways	Function	Reference
hsa-miR-200a-3p	TP53INP1	YAP1 TP53INP1	Suppresses apoptosis	16
hsa-miR-203a-5p	Akt2/ SOCS3	p53	Proliferation, apoptotic	44
hsa-miR-20a-5p	BECN1, ATG16L	Autophagy lysosome pathway Genomic	Genomic damage and tumour growth Metastasis growth, and proliferation	59
hsa-miR-20b-5p	Tumor suppressor PTEN	PI3K AKT mTOR	Invasion, metastasis, proliferation, EMT,	62
hsa-miR-29a-3p	TET1	STAT3 JAK	migration	63
hsa-miR-105-5p	GOLIM4	Exosome delivery to epithelial barrier cells	Proliferation and metastasis	64
hsa-miR-106b-5p	SIX1 SMAD7	TGF-β	Tumor-initiating and EMT	65
hsa-miR-155-5p	SOCS1 MMP16	TGF-β and STAT3	Chemoresistance, proliferation and metastasis, progression, cell cycle	66
hsa-miR-181a-5p	SOCS3 PIAS3	STAT JAK signalling	Differentiation, apoptosis, cell cycle regulation, proliferation	67
hsa-miR-196a-5p	CCA	β-catenin axis HAND1 Wnt	Proliferation and migration	68
hsa-miR-210-3p	GPD1L CYG	HIF-1alpha-dependent pathway	Invasion ,cell proliferation, and migration	69
hsa-miR-374a-5p	WIF1, PTEN, WNT5A	Wnt/β-catenin signaling	Metastasis	70
hsa-miR-375	PI3K	MAPK signalling	Metastasis	71
hsa-miR-504-3p	CDK6	CDK6 to mediate the ERK signalling pathway	Migration	72
hsa-miR-21-5p	PTEN, Cdc25, PDCD4 Maspin, TPM1	-PDCD4	EMT, invasion, metastasis , migration, and proliferation	73
hsa-miR-181b-3p	CBX7 Bim	DNA damage repair pathway	Chemoresistance Sphere formation, and proliferation	74
hsa-miR-301a-3p	PTEN	AKT/mTOR Wnt/ β -catenin PI3K/	Invasion, metastasis , and proliferation.	75
hsa-miR-10b-5p	E-cadherin	Akt EMT TWIST-1P13K	Proliferation, invasion, and metastasis	76
hsa-miR-373-5p	CD44	AKT PI3K	Migration, invasion, and metastasis	77
hsa-miR-495-3p	E-cadherin, JAM-A, and REDD1; repression of JAM-A	AKT mTOR Wnt/ β -catenin PI3K	Migration, EMT, invasion and metastasis, and cell migration	78
hsa-miR-520a-3p	CD44	Wnt/ β -catenin	Migration and invasion	79
hsa-miR-9-5p	Cyclin D1 E-cadherin	Wnt/ β -catenin	Angiogenesis and metastasis Migration, invasion	80
hsa-miR-93-5p	PTEN; LATS2	Akt PI3K pathway,	Metastasis and angiogenesis	81
hsa-miR-200a-3p	YAP1	EMT- EGF	Suppresses apoptosis	82
hsa-miR-301a-3p	ESR1	ER signalling	Invasion	83

somes. The PI3K/AKT/mTOR signaling pathway, which adversely regulates autophagy, is known to be activated by PIK3CA. TBK1 participates in the control of autophagy, particularly in reaction to viral infections and inflammation. TP53 can also modulate autophagy, either promoting or inhibiting it depending on the context. AKT1, BNIP3L, MTOR, PIK3CA, TBK1, and TP53 are all associated with the various signaling pathways and cellular processes that modulate autophagy, highlighting

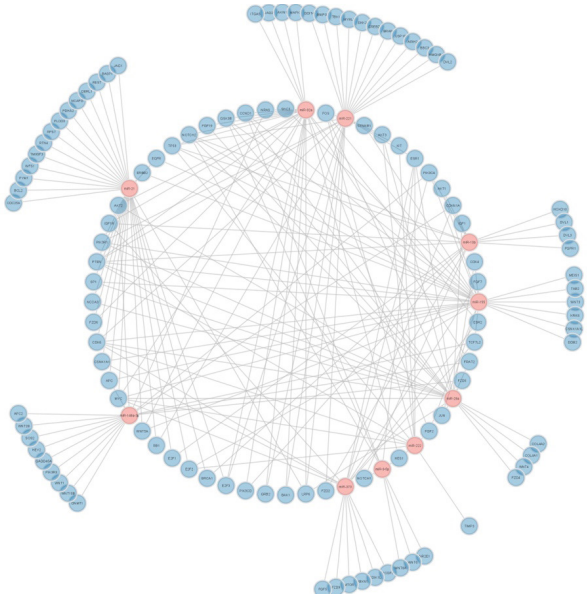

Figure 2. Upregulation miRNA-Targets interaction network analysis

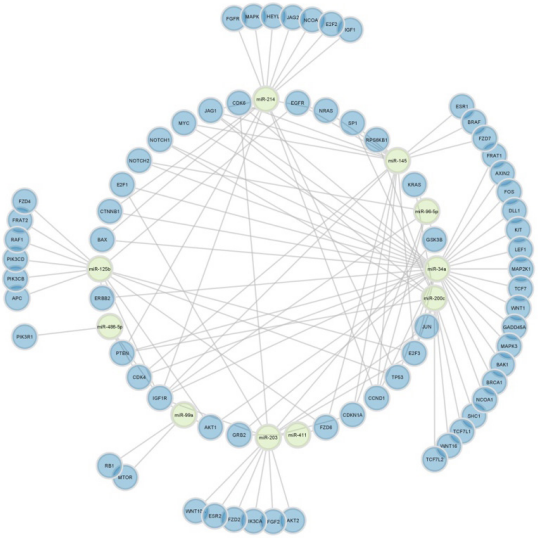

Figure 3. Downregulation miRNA-Target interaction network analysis

Table 6. List of gene ontology terms for predicted upregulated miRNA-target genes

GO ID	GO Terms	No. of Genes	*p*-value
GO:0061515	Myeloid cell development	3	0.05
GO:0048599	Oocyte development	4	0.05
GO:0016241	Regulation of macroautophagy	4	0.05
GO:0090201	Negative regulation of release of cytochrome c from mitochondria	6	0.05
GO:0030316	Osteoclast differentiation	3	0.05
GO:0030510	Regulation of BMP signaling pathway	5	0.05
GO:0090288	Negative regulation of cellular response to growth factor stimulus	5	0.05
GO:1902106	Negative regulation of leukocyte differentiation	5	0.05
GO:0043388	Positive regulation of DNA binding	4	0.05
GO:2001244	Positive regulation of intrinsic apoptotic signaling pathway	4	0.05
GO:0072132	Mesenchyme morphogenesis	4	0.05

the complexity and multifaceted nature of autophagy regulation. GO:0030510 represents the regulation of the BMP (bone morphogenetic protein) signaling pathway, which is associated with several cellular processes, including embryonic development, tissue homeostasis, and cell differentiation. This GO term describes the processes and factors that modulate the activity and output of the BMP signaling pathway. HES1, NOTCH1, and NOTCH2 are all elements of the Notch signaling pathway, which interacts with and modulates BMP signalling. Notch signaling can crosstalk with BMP signaling to regulate cellular responses and developmental processes. HES1 is a downstream transcriptional effector of Notch signaling and can influence the activity of the BMP pathway. WNT1 and WNT5A are members of the Wnt family of secreted glycoproteins. It is well established that Wnt signaling pathways interact with and control BMP signaling in a context-dependent manner. WNT1 and WNT5A can modulate BMP signaling by influencing the expression of BMP receptors, antagonists, or downstream effectors. GO:1902106 represents the negative regulation of leukocyte differentiation. This term describes the processes and factors that inhibit or suppress the differentiation of leukocytes, which are a type of white blood cell involved in immune responses. CDK6, CTNNB1, ERBB2, MYC, and PIK3R1 are associated with the negative regulation of leukocyte differentiation. These genes represent factors that can modulate signaling pathways and gene expression programs involved in the differentiation of leukocytes, potentially inhibiting or suppressing the differentiation process. Breast cancer cells can directly interact with leukocytes and manipulate their differentiation and function. This can occur through the secretion of specific factors or by modulating signaling pathways involved in leukocyte differentiation. Although the specific gene ontology term "negative regulation of leukocyte differentiation" may not be directly associated with breast cancer, it is important to recognize that the immune system and leukocytes play crucial roles in the tumor microenvironment and the body's immune response against cancer. These factors significantly contribute to the complex interplay between the immune system and breast cancer, highlighting the impact of leukocyte differentiation and function on the development and progression of the disease. Tumors can release various factors like cytokines, growth factors, and immune checkpoint molecules such as PD-L1 that suppress the immune response and inhibit leukocyte differentiation. GO:0043388 represents the positive regulation of DNA binding. This term describes processes or factors that enhance or promote the binding of DNA by proteins, transcription factors, or other DNA-binding molecules. CTNNB1, HES1, IGF1, and RB1 are associated with the promotion of DNA binding by transcription factors or other DNA-binding molecules, thereby influencing gene expression and cellular processes.

BBC3 is a gene that is transcriptionally activated by TP53 (tumor protein p53) and plays a significant role in positively regulating the intrinsic apoptotic pathway, as well as responding to DNA damage and various stress signals. TP53, also known as p53, can exert a positive regulatory effect on the intrinsic apoptotic pathway by facilitating the transcription of pro-apoptotic genes, including BBC3, while inhibiting the expression of anti-apoptotic genes. Through its involvement in initiating the intrinsic apoptotic pathway, TP53 serves as a critical component in regulating programmed cell death. GO:0072132 represents mesenchyme morphogenesis. This term describes the processes and factors involved in the formation and association of mesenchymal tissues during growth and tissue remodelling. EY2 is known to interact with various signaling pathways, including the Notch signaling pathway, to influence mesenchymal cell behaviour and tissue morphogenesis. MYC can influence mesenchyme morphogenesis by modulating gene expression programs that control cell behaviour and tissue remodelling during development. NOTCH1 is involved in mesenchyme morphogenesis by regulating the behavior and differentiation of mesenchymal cells through its interaction with other signaling pathways and transcription factors. In summary, the genes HEY2, MYC, NOTCH1, and WNT5A are associated with mesenchyme morphogenesis indicate elements that affect how genes are expressed and how cells behave, and tissue remodeling during the formation and organization of mesenchymal tissues. GO:0048599 represents oocyte development. This term describes the processes and factors involved in the development, maturation, and

differentiation of oocytes, which are the female reproductive cells involved in reproduction and embryonic development. BCL2, CTNNB1, IGF1, and WNT4 are associated with oocyte development.

These genes play crucial roles in regulating the growth, maturation, and differentiation of oocytes. They are involved in a wide range of cellular processes, including apoptosis, gene expression, and signaling pathways, contributing significantly to various aspects of oocyte development. Their involvement contributes significantly to the development and maturation of oocytes during reproductive processes. GO:0061515 represents myeloid cell development, encompassing the intricate processes underlying the differentiation and proliferation of various immune cells, including monocytes, macrophages, granulocytes, and dendritic cells. While breast cancer predominantly arises from epithelial cells, the tumor microenvironment and immune response, notably involving myeloid cells, intricately influence disease progression. Genes like KIT and MEIS1 are pivotal in regulating critical facets of myeloid progenitor cell growth, survival, and differentiation. Specifically, KIT contributes broadly to these processes, while MEIS1 plays a more specialized role in the specification and maturation of myeloid progenitor cells, orchestrating gene expression alongside other transcription factors and co-factors to promote myeloid cell differentiation. NOTCH2 further regulates the transition of myeloid progenitors into mature myeloid cells, such as monocytes and macrophages. Conversely, genes like BCL2, CTNNB1, IGF1, and WNT4 are predominantly associated with oocyte development, delineating pathways crucial for folliculogenesis and ovarian function, rather than myeloid cell differentiation. They stand for elements that are crucial to the development, maturation, and differentiation of oocytes. These genes control cellular processes that aid in the growth and maturation of oocytes throughout reproductive processes, including apoptosis, gene expression, and signaling pathways (84).

CONCLUSIONS

This review aims to offer a comprehensive and updated understanding of breast cancer, with a focus on its current epidemiology, prognostic biomarkers, and potential therapeutic strategies. Given the increasing incidence and mortality rates of breast cancer over recent decades, miRNAs have emerged as clinically relevant in diagnosis, prognosis, and treatment. Targeting genes regulated by OncomiRNAs and TS-miRNAs elucidates key processes like proliferation, apoptosis, and metastasis. TS miRs play essential roles in maintaining normal cellular functions by inhibiting processes such as cell proliferation and invasion. The loss of specific TS miRs in breast cancer is associated with increased tumor aggressiveness and poorer prognosis. Dysregulated in cancer, these genes often belong to pivotal pathways like PI3K/AKT/mTOR and MAPK/ERK. OncomiRNAs promote tumorigenesis by altering gene expression in these pathways, driving aggressive cancer behavior. Gene ontology analysis categorizes miRNA-regulated genes based on biological processes and molecular functions, shedding light on breast cancer pathogenesis. However, this review may lack coverage of the exploration of specific breast cancer subtypes or mechanisms. Generalizing miRNA's significance across all breast cancer subtypes may overlook the disease's heterogeneity. Further research on tissue- or circulating- specific miRNAs as biomarkers in breast cancer holds promise for improved diagnosis and prognosis. Thus, findings from these studies underscore the potential utility of miRNAs in clinical practice.

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ADDITIONAL INFORMATION

Authors contributions

JCH: Reviewed and compiled the paper, con-

ceived and designed the protocol, reviewed relevant papers, and contributed to the manuscript compilation. GLP: Assisted in comprehending the bioinformatic tools integrated into the paper and contributed to understanding the role of miRNA in breast cancer, which aided in the manuscript& compilation.

Availability of data and materials

The authors affirm that the data and materials are accessible and transparent.

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