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EDITORIAL STATEMENT

The First Issue of Journal of Medicine and Urban Health

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It is with great pride that we present the inaugural issue of the *Journal of Medicine and Urban Health (JMUH)*, marking a new era in our legacy as the *Vajira Medical Journal: Journal of Urban Medicine*. This transformation signifies a timely expansion of the Journal's vision—to serve not only as a reputable scientific publication, but also as a bridge for Thai researchers to connect and collaborate with the international research community under our new identity.

We are honored to welcome a newly appointed editorial board composed of leading experts from Thailand and around the world. Their collective expertise will guide our commitment to publishing impactful, peer-reviewed research across a wide range of disciplines—including clinical and basic sciences, public health (especially in urban settings), health policy, and medical innovation.

Our goal is to position the journal as a prominent international platform that contributes to medical and public health knowledge and informs policies relevant to health—particularly in urban contexts. We also aspire to be indexed in Scopus and other high-visibility international databases in the coming years, ensuring the widest possible reach for our authors' work.

As Editor-in-Chief, I invite researchers worldwide to contribute to and engage with the *JMUH*. Together, we aim to advance knowledge that improves medical and public health outcomes for populations globally, especially in urban environments.

Reference

1. Hanprasertpong J. Editorial statement: the last issue of Vajira Medical Journal: Journal of Urban Medicine. Vajira Med J 2025;69(4):e277499. doi: 10.62691/vmj.2025.277499.

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SPECIAL ARTICLE

Evolution of Systemic Therapies in Endometrial Cancer: From Cytotoxic Chemotherapy to Immunotherapy, Targeted Therapies, and Antibody–Drug Conjugates

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ABSTRACT

Molecular classification in endometrial cancer (EMC) has become central to treatment decision-making. An advance in molecular classification has transformed the therapeutic landscape of EMC, particularly in patients with high-risk, advanced, or metastatic disease. This coincided with a new era of personalized treatment with targeted therapies, immunotherapy in particular, immune checkpoint inhibitors (ICIs). Several studies have demonstrated the benefits of combination strategies incorporating chemotherapy, targeted therapies, and ICIs with or without tyrosine kinase inhibitor, followed by maintenance therapy. This approach has resulted in clinically meaningful improvements in progression-free survival and, in selected populations, overall survival, with the most pronounced benefit observed in mismatch repair (MMR)–deficient tumors. This review summarizes current evidence from pivotal phase II-III trials evaluating ICIs combined with chemotherapy, ICIs with poly adenosine diphosphate ribose polymerase inhibitors, and targeted agents including trastuzumab, bevacizumab, and selinexor as first- and second-line treatment for EMC. Studies of antibody-drug conjugates, novel therapeutic agents designed to selectively deliver cytotoxic drugs and thereby reduce the systemic toxicity associated with chemotherapy, were also included. Treatment recommendations are summarized within the context of MMR status, p53 abnormalities, human epidermal growth factor receptor 2/neu expression, and other emerging molecular biomarkers.

Keywords: antibody–drug conjugates, endometrial cancer, immunotherapy, precision oncology, targeted therapy

INTRODUCTION

Endometrial cancer (EMC) is the most common gynecologic cancer in developed countries and second most common gynecologic cancer in Thailand.[1] Most patients seek medical consultation in early-stage disease due to abnormal uterine bleeding which is the most common symptom. Early-stage disease is often curable with surgery. If indicated with risk features, radiation therapy is the mainstay of adjuvant treatment.

Chemotherapy either in combination with radiation therapy or chemotherapy alone is considered for the patients with higher risk. For advanced and recurrent diseases, systemic treatment is generally required and relied primarily on chemotherapy, most commonly platinum- and taxane-based regimens.[2] However, chemotherapy offered only limited durability of response and poor outcomes for patients with high-risk, advanced, or recurrent disease.

Over the past decade, advances in molecular classification and tumor biology of EMC have been demonstrated. The Cancer Genome Atlas (TCGA) Research Network reported a biologically heterogeneous nature and a broad spectrum of clinical behavior of many cancers including EMC.[3] Molecular classification has fundamentally altered the understanding of EMC biology and subsequent refinement into clinically applicable molecular subgroups. This has also transformed the therapeutic landscape from generalized systemic treatment with chemotherapy to personalized therapy with targeted therapies, immune checkpoint inhibitors (ICIs), and antibody–drug conjugates (ADCs).

Targeted therapies focus on tailoring treatment according to specific molecular abnormalities of cancer, thereby increasing specificity and reducing damage to normal tissues. Immunotherapy, on the other hand, enhances the function of the immune system in controlling and eliminating cancer cells in appropriately selected patients. ADCs represent a new frontier in EMC treatment by combining precise molecular targeting with potent cytotoxic payloads, aiming to improve the efficiency of cancer cell eradication while minimizing effects on normal cells.

The integration of these novel agents has led to meaningful improvements in progression-free survival (PFS) and, in selected populations, overall survival (OS). This review summarizes the evolution of systemic therapy in EMC, from traditional chemotherapy to biomarker-driven precision medicine.

We discuss pivotal clinical trials supporting first-line and subsequent-line use of targeted agents, ICIs, and ADCs, with emphasis on molecular stratification, clinical outcomes, and future directions. A detailed critical appraisal of each studies/ trials is beyond the scope of this review and will be addressed in our upcoming work.

CONTENT OF REVIEW

Chemotherapy for EMC

Initial systemic therapy for advanced or recurrent EMC was based on single-agent chemotherapy, particularly doxorubicin, which showed modest activity in early Gynecologic Oncology Group (GOG) studies during the 1980s–1990s.[4] Efforts to improve outcomes led to evaluation of combination regimens. GOG-122 demonstrated that doxorubicin plus cisplatin chemotherapy significantly improved PFS and OS compared with whole abdominal irradiation in advanced-stage disease, establishing combination chemotherapy as standard treatment.[5] Subsequent intensification with the triplet regimen of paclitaxel, doxorubicin, and cisplatin (TAP) in GOG-177 resulted in superior objective response rate (ORR), PFS and OS compared with doxorubicin–cisplatin, but at the cost of substantial neurotoxicity.[6] Subsequent trial GOG-209 showed that carboplatin plus paclitaxel was non-inferior to TAP in OS with significantly reduced toxicity.[7] This benchmark trial has led carboplatin plus paclitaxel as the preferred first-line chemotherapy regimen for advanced or recurrent EMC.

Molecular classification and risk stratification of EMC

Based on the TCGA findings of biologic molecular characteristics, genomic alterations, and gene mutations, EMC is classified into four molecular subgroups. These are: *Polymerase Epsilon (POLE)*-mutated, mismatch repair–deficient (MMRd), p53-abnormal, and no specific molecular profile (NSMP). These subtypes have distinct immunogenicity and prognostic outcomes. Notably, because *POLE* mutation acts as a driver mutation, multiple molecular abnormalities (multiple classifiers) may coexist. *POLE* mutation may be found together with MMRd and/or *TP53* mutation (p53abn) in approximately 10-20% of cases. In such cases, prognosis should be determined by the presence of *POLE* mutation. MMRd may also coexist with *TP53* mutation; although data remain limited, prognosis should be determined according to MMRd status.[8]

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Both the International Federation of Gynaecology and Obstetrics (FIGO)8 and the European Society of Gynaecological Oncology (ESGO)/ the European Society for Radiotherapy and Oncology (ESTRO)/ the European Society of Pathology (ESP) guidelines[2] recommend molecular testing as an adjunct to standard histopathologic evaluation whenever feasible. Molecular testing can be performed on preoperative biopsy/ curettage specimens or on hysterectomy specimens.

In early-stage EMC, *POLE*-mutated and p53-abnormal statuses are to be annotated and modify the anatomical stage.[8] Molecular classification is particularly important in high-grade endometrioid carcinoma (grade 3) which exhibits significant heterogeneity in clinical behavior and molecular characteristics. Early-stage tumors with *POLE* mutation have an excellent prognosis, whereas tumors with p53abn or NSMP tumors that are estrogen receptor (ER)–negative are associated with poor prognosis.[9,10]

In advanced stage or recurrent disease, the expression of MMRd and p53-abnormal certainly impact the therapeutic intervention. MMRd tumors exhibit high neoantigen load and immune infiltration, rendering them highly sensitive to ICIs, whereas p53-abnormal tumors often benefit from antiangiogenic or human epidermal growth factor receptor 2 (HER2)-targeted approaches.

ESGO, ESTRO, ESP have jointly made a recommendation of EMC treatment based on prognostic risk group incorporating FIGO staging, location of cancer, surgical pathological and molecular features.[2]

Targeted therapies, immunotherapy, ADCs for EMC

Targeted therapies and ICIs with or without poly adenosine diphosphate ribose polymerase (PARP) inhibitors have been tested in many clinical trials as first- or second-line of treatment for EMC. As first-line treatment, the drugs were combined with chemotherapy, mainly paclitaxel and carboplatin, followed by maintenance therapy after completion of chemotherapy. Tyrosine kinase inhibitors were also tested in combination with ICIs, substituting for the original chemotherapy. These agents were also included in many trials as second-line of EMC treatment.

I. First-line targeted therapy and immunotherapy in EMC patients

Clinical studies evaluating these agents as first-line treatment are summarized in Table 1 and discussed below.

1. ICIs combined with chemotherapy followed by ICI with or without PARP inhibitor maintenance

Four main randomized phase III trials—RUBY, NRG-GY018, AtTEnd, and durvalumab and olaparib (DUO-E)—have evaluated ICIs combined with carboplatin–paclitaxel as first-line therapy in high-risk, advanced, or metastatic EMC, including carcinosarcoma. Collectively, the studies support the use of ICIs combined with carboplatin–paclitaxel followed by ICIs maintenance as first-line treatment in high-risk, advanced, or metastatic EMC—particularly in MMRd tumors, where substantial PFS and emerging OS benefits are observed (e.g., RUBY PFS at 24 months: 61.4% vs. 15.7%; hazard ratio (HR) 0.28). In mismatch repair-proficient (MMRp) tumors, ICIs provide consistent PFS benefit, though OS benefit remains less clear. PD-L1 inhibitors such as atezolizumab improve PFS (especially in MMRd disease), but OS benefit has not been clearly demonstrated. Details are as follows:

1.1 Dostarlimab (RUBY Part 1 / European Gynecological Oncology Trial (ENGOT)-EN6-NSGO / GOG-3031)

The RUBY trial comprised two parts. Part 1 evaluated immunotherapy alone and has been published,[11,12] while Part 2 evaluates immunotherapy combined with a PARP inhibitor. Part 1 study randomized 494 patients with stage III–IV or first recurrent EMC to receive dostarlimab 500 mg or placebo intravenously, in combination with carboplatin–paclitaxel every 3 weeks for 6 cycles.[11,12] This was followed by maintenance treatment with dostarlimab 1000 mg or placebo every 6 weeks for up to 3 years.

The results showed significantly improved PFS at 24 months and OS at 36 months in the patients who had dostarlimab compared to placebo: 36.1% vs. 18.1% (HR 0.64) and 54.9% vs. 42.9% (HR 0.69), respectively. The survival benefits with dostarlimab were evidenced regardless of MMR/ microsatellite stable (MSS) status, albeit lower extent of benefits in the MMRp/MSS group. The greatest benefit was observed in patients with MMRd/high microsatellite instability (MSI-H) tumors, with the PFS at 24 months and OS at 36 months of 61.4% vs. 15.7% (HR 0.28) and 78.0% vs. 46.0% (HR 0.32), respectively. The outcomes for the patients with MMRp/MSS tumors

Table 1 Studies Evaluating ICIs and Targeted Therapies as First-Line Treatment for EMC

Study (ref)	Patient	Biomarker Status	Treatment	Outcome (study vs. control) Data presented as median unless specified otherwise
RUBY part1/ ENGOT-EN6-NSGO/ GOG-3031 (part 1) phase III trial (NCT03981796)[11,12]	N = 494 Measurable stage III-IVA, stage IVB, or RR-EC/CS (CT-free ≥ 6 m) 1L for stage III-IV 1L/2L for RR	MMRd/ MSI-H vs. MMRp/MSS	1) TC Q3W x 6 cycles with Dos 500 mg IV Q3W x 6 cycles then Dos 1000 mg IV Q6W to 3 yrs or until PD/ toxicity 2) TC (as arm 1)	All: 24-m PFS 36.1 vs. 18.1% (HR 0.64, 95% CI 0.51-0.80, p < 0.001) 36-m OS 54.9 vs. 42.9% (HR 0.69, 95% CI 0.54-0.89, p = 0.002) MMRd/MSI-H: 24-m PFS 61.4 vs. 15.7% (HR 0.28, 95% CI 0.16-0.50, p < 0.001) 36-m OS 78.0 vs. 46.0% (HR 0.32, 95% CI 0.17-0.63, p < 0.001) MMRp/MSS: 24-m PFS 28.4 vs. 18.8% (HR 0.76, 95% CI 0.59-0.98) 36-m OS 48.6 vs. 41.9% (HR 0.79, 95% CI 0.60-1.40, p = 0.049)
KEYNOTE-868/ NRG-GY018 phase III trial (NCT03914612)[13]	N = 816 Measurable stage III- IVB, RR-EC (CT-free ≥ 12 m) 1L for stage III-IV 1L/ 2L for RR	MMRd vs. MMRp	1) TC Q3W x 6-8 cycles with Pembro 200 mg IV Q3W x 6-8 cycles, then Pembro 400 mg IV Q6W x 14 cycles 2) TC (as arm 1)	MMRd: 12-m PFS 74% (NA) vs. 38% (median 7.6 m) (HR 0.30, 95% CI 0.19-0.48, p < 0.001) MMRp: PFS 13.1 m vs. 8.7 m (HR 0.54, 95% CI 0.41-0.71, p < 0.001)
KEYNOTE-B21/ ENGOT-en11/ GOG-3053 (NCT04634877)[14]	N = 1095 Stage I, II, non-endometrioid with MI or Stage I, II, abnormal p53/TP53 with MI or Stage III or IVA, any histology	MMRd vs. MMRp	1) TC Q3W x 6 cycles with Pembro 200 mg IV Q3W x 6-8 cycles, then Pembro 400 mg IV Q6W x 6 cycles vs. 2) TC (as arm 1)	All: PFS NR (22%) vs. NR (22%) (HR 1.02, 95% CI 0.79-1.32, p = 0.570) MMRd: PFS NR vs. NR (HR 0.31, 95% CI 0.14-0.69) MMRp: PFS NR vs. NR (HR 1.20, 95% CI 0.91-1.57)
AtTEnd/ENGOT-en7 phase III trial (NCT03603184)[15]	N = 551 Measurable stage III-IV or RR-EC/CS • 1L for all	MMRd vs. MMRp	1) TC Q3W x 6-8 cycles with Atezolizumab 1200 mg IV Q3W x 6-8 cycles then Atezolizumab 1200 mg IV Q3W until PD or toxicity vs. 2) TC (as arm 1)	All: PFS 10.1 vs. 8.9 m (HR 0.74, 95% CI 0.61-0.91, p = 0.022) OS 38.7 vs. 30.2 m (HR 0.82, 95% CI 0.63-1.07, p = 0.048) MMRd: PFS NA vs. 6.9 m (HR 0.36, 95% CI 0.23-0.57, p < 0.001) OS NA vs. 25.7 m (HR 0.41, 95% CI 0.22-0.76) MMRp: PFS 9.5 vs. 9.2 m (HR 0.92, 95% CI 0.73-1.1.6) OS 31.5 vs. 28.6 m (HR 1.00, 95% CI 0.74-1.35)

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Table 1 Studies Evaluating ICIs and Targeted Therapies as First-Line Treatment for EMC (cont.)

Study (ref)	Patient	Biomarker Status	Treatment	Outcome (study vs. control) Data presented as median unless specified otherwise
DUO-E phase III trial (NCT04269200)[16,17]	N = 718 Measurable stage III or IV or RR-EC/CS (CT-free > 12 m), 1L for stage III-IV 1L/2L for RR	MMRd vs. MMRp	1) TC Q3W x 6-8 cycles (**Control**) vs. 2) TC (as I) + Du 1,120 mg IV Q3W x 6-8 cycles, then Du 1,500 mg IV Q4W until PD or toxicity (**Du**) vs. 3) TC (as I) + Du 1,120 mg IV Q3W x 6-8 cycles, then Du 1,500 mg IV Q4W + Olaparib 300 mg tablets bid until PD or toxicity (**DO**)	All: 12-m PFS 61.5% vs. 48.5% vs. 41.1% DuO vs. Control: HR 0.55, 95% CI 0.43-0.69, p < 0.0001 Du vs. Control: HR 0.71, 95% CI 0.57-0.89, p = 0.003 12-m OS 87.7% vs. 84.2% vs. 79.7% DuO vs. Control: HR 0.59, 95% CI 0.42-0.83, p = 0.003 Du vs. Control: HR 0.77, 95% CI 0.56-1.07, p = 0.120) MMRd: 12-m PFS 70.0% vs. 67.9% vs. 43.3% DuO vs. Control: HR 0.41, 95% CI 0.21-0.75 Dur vs. Control: HR 0.42, 95% CI 0.22-0.80 12-m OS 89.2% vs. 91.2% vs. 74.4% DuO vs. Control: HR 0.28 95% CI 0.10-0.68 Du vs. Control: HR 0.34 95% CI 0.13-0.79 MMRp: 12-m PFS 59.4% vs. 44.4% vs. 40.8% DuO vs. Control: HR 0.57, 95% CI 0.44-0.73 Dur vs. Control: HR 0.77, 95% CI 0.60-0.97 12-m OS 87.3% vs. 82.5% vs. 81.0% DuO vs. Control: HR 0.69 95% CI 0.47-1.00 Du vs. Control: HR 0.91 95% CI 0.64-1.30
LEAP-001/EN-GOT-en9 phase III trial (NCT03884101)[20]	N = 842 Stage III-IV or RR-EC (CT-free ≥ 6 m) 1L for stage III-IV, 1L/2L for RR	MMRp	1) TC Q3W x 6-8 cycles vs. 2) Lenva 20 mg oral OD + Pembro 200 mg IV Q3W until PD or toxicity	All: PFS 12.5 vs. 10.2 m (HR 0.91, 95% CI 0.76-1.09) OS 37.7 vs. 32.1 m (HR 0.93, 95% CI 0.77-1.12) MMRp: PFS 9.6 vs. 10.2 m (HR 0.99, 95% CI 0.82-1.21) OS 30.9 vs. 29.4 m (HR 1.02, 95% CI 0.83-1.26)
Fader et al. (Phase II)[21, 22]	N = 61 Stage III-IV or RR-EC 1L for all	HER2/neu	TC Q3W x 6 cycles + Trastuzumab 6 mg/kg IV (8 mg/kg first cycle) Q3W until PD or toxicity vs.TC (as arm 1)	PFS 12.9 vs. 8.0 m (HR 0.46, 90% CI 0.28-0.76, p = 0.005) OS 29.6 vs. 24.4 m (HR 0.58, 90% CI 0.34-0.99, p = 0.046).
GOG-86P (NCT00977574)[31]	N = 494 Measurable stage III-IVA or stage IVB or RR-EC (CT-free ≥ 6 m) 1L for all	p53abn	1) Bev IV and TC IV Q3W x 6 cycles, then Bev IV Q3W until PD or toxicity 2) Temsirolimus IV Day1 and 8 + TC IV Q3W x 6 cycles then Temsirolimus IV Day 1, 8, and 15 Q3W until PD or toxicity 3) Bev IV + IxaC IV Q3W x 6 cycles, then Bev IV Q3W until PD or toxicity	PFS Bev* vs. Temsirolimus: 12.5 vs. 8.2 m; HR 0.48, 95% CI 0.31-0.75) Bev/TC vs. Temsirolimus/TC: HR 0.55, 95% CI 0.32-0.94) Bev/IxaC vs. Temsirolimus/TC: HR 0.43, 95% CI 0.26-0.71) OS Bev* vs. Temsirolimus: HR 0.61, 95% CI 0.38-0.98 *Bev referred to data from both arm 1 and arm 3.

Table 1 Studies Evaluating ICIs and Targeted Therapies as First-Line Treatment for EMC (cont.)

Study (ref)	Patient	Biomarker Status	Treatment	Outcome (study vs control) Data presented as median unless specified otherwise
SIENDO/EN-GOT-EN5/GOG-3055 Phase III trial[25,26]	N = 263 Stage IV or RR-EC completed > 12 w of taxane-platinum, with PR/CR 1L for stage IV 1L/2L for RR	p53wt MMRd/ MMRp	Selinexor 80 mg or placebo oral once weekly (2:1)	All: PFS 5.7 vs. 3.8 m (HR 0.76, 95% CI 0.54-1.08, p = 0.126) p53wt: PFS 28.4 vs. 5.2 m (HR 0.44, 95% CI 0.27-0.73) p53wt/MMRp: PFS 39.5 vs. 4.9 m (HR 0.36, 95% CI 0.19-0.71) p53wt/MMRd: PFS 13.1 vs. 3.7 m (HR 0.49, 95% CI 0.18-1.34)

Abbreviations: 1L, first-line; 2L, second-line; Bev, bevacizumab; CI, confidence interval; CT, chemotherapy; CS, carcinosarcoma; Dur, durvalumab; DuO, durvalumab and olaparib; Dos, dostarlimab; ENGOT, European Gynecological Oncology Trial; EMC, endometrial cancer; HR, hazard ratio; IxaC, ixabepilone and carboplatin; Lenva, lenvatinib; MMRd, mismatched repair deficient; MMRp, mismatched repair proficient; MI, myometrial invasion; NSMP; NA, not available; NR, not reach, NSMP, no specific molecular profile; OS, overall survival; p53wt, p53 wild type; pembro, pembrolizumab; PD, progressive disease; PFS, progression-free survival; PR/CR, partial response/complete response; RR, recurrence; TC, paclitaxel and carboplatin

were also improved, albeit more modest, with the corresponding PFS and OS of 28.4% vs. 18.8% (HR 0.76) and 48.6% vs. 41.9% (HR 0.79), respectively.

1.2 Pembrolizumab

1) KEYNOTE-868 / NRG-GY018

This phase III trial enrolled 816 patients with advanced EMC (stage III–IVA with measurable disease, stage IVB, or recurrent disease with or without measurable disease). This is the only first-line chemoimmunotherapy trial which excluded subjects with uterine carcinosarcomas. Patients were stratified into MMRd (n = 225) and MMRp (n = 591) cohorts.[13] The patients were randomized 1:1 to receive pembrolizumab 200 mg or placebo with carboplatin–paclitaxel every 3 weeks for 6 cycles (up to 10 cycles in selected patients), followed by maintenance treatment with pembrolizumab 400 mg or placebo every 6 weeks for up to 2 years.

Significantly improved PFS benefits from pembrolizumab over chemotherapy alone were demonstrated regardless of MMR status. Among the patients with MMRp tumors, median PFS of the patients who received pembrolizumab was significantly longer vs. control: 13.1 vs. 8.7 months; HR 0.54. Higher degree of benefits was found in those with MMRd tumors, the corresponding 12-month PFS were 74% vs. 38%. Median PFS was not reached in the pembrolizumab group versus 7.6 months in the control group (HR 0.30).

2) KEYNOTE-B21 / ENGOT-en11 / GOG-3053

This phase III trial enrolled 1,095 patients with stage I–II disease with myometrial invasion and non-endometrioid histology or p53/TP53 abnormalities, or stage III–IVA disease with no residual disease after surgery.[14]

The patients were randomized to receive pembrolizumab or placebo, with carboplatin–paclitaxel for 6 cycles, followed by pembrolizumab or placebo every 6 weeks for 6 additional cycles. No difference in PFS was observed overall (22% in both arms). However, prespecified subgroup analysis demonstrated improved PFS in the MMRd subgroup treated with pembrolizumab (HR 0.31), reinforcing the clinical benefit of ICIs in MMRd EMC. Longer follow-up is ongoing to further clarify the benefits.

1.3 Atezolizumab (AtTEnd / ENGOT-en7)

In this trial, 551 patients with advanced (stage III–IV) or first recurrent EMC were randomized 2:1 to receive atezolizumab 1200 mg or placebo with carboplatin–paclitaxel every 3 weeks for 6-8 cycles, followed by maintenance atezolizumab or placebo every 3 weeks until disease progression.[15]

No difference in ORR was observed (75% vs. 74.6%). Nevertheless, the median PFS and OS of all populations were significantly longer with atezolizumab: 10.1 vs. 8.9 months; HR 0.74 for PFS and 38.7 vs. 30.2 months; HR 0.82 for OS. The benefits were observed only in the MMRd group, with median PFS and median OS not reached in those receiving atezolizumab vs. 6.9 months (HR 0.36) and 25.7 months (HR 0.41) in the placebo group. No statistically significant differences in PFS or OS of the patients with MMRp tumors were observed.

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1.4 DUO-E / GOG-3041 / ENGOT-EN10

This phase III trial randomized 718 patients with advanced or first recurrent EMC to receive carboplatin–paclitaxel alone or added with durvalumab 1120 mg every 3 weeks for 6 cycles before durvalumab maintenance 1500 mg every 4 weeks or added with durvalumab before durvalumab and olaparib 300 mg tablets twice daily maintenance.[16,17]

The results of all population showed 12-month PFS was significantly higher in all patients who had durvalumab than chemotherapy alone: 48.5% vs. 41.1% (HR 0.71). The benefits were observed in both MMRp subgroup (modest improvement of 12-month PFS: 44.4% vs. 40.8%; HR 0.77) and especially in MMRd subgroup (12-month PFS of 67.9% vs. 43.3%; HR 0.42).

2. ICIs combined with chemotherapy followed by ICIs plus PARP inhibitor maintenance Therapy

Advanced and metastatic EMC frequently harbors mutations in *PTEN*, *TP53*, and other genes involved in homologous recombination DNA repair (HRD). Recent studies, including DUO-E and RUBY Part 2, have evaluated the role of PARP inhibitors combination with ICIs as maintenance therapy following ICIs combined with chemotherapy in EMC.

2.1 DUO-E / GOG-3041 / ENGOT-EN10

The DUO-E trial also explored whether adding olaparib to durvalumab as maintenance therapy could further improve outcomes beyond those described in Section 1.4.

In patients receiving durvalumab plus olaparib as maintenance therapy, both PFS and OS were significantly improved compared with chemotherapy alone (HR 0.55). When comparing maintenance strategies following chemotherapy plus durvalumab by MMR status, both durvalumab alone and durvalumab plus olaparib demonstrated closely align PFS benefits, although direct statistical comparison was not performed (HR 0.42 vs. HR 0.41, respectively) in the MMRd subgroup. However, in MMRp subgroup, there was a trend toward improved PFS (HR 0.57) from durvalumab plus olaparib compared with durvalumab alone (HR 0.77).

Post hoc analyses evaluating the highly heterogeneous MMRp subgroup—characterized by overlapping biomarker expression (67% PD-L1 positive, 59% *TP53* mutation, 21% HRD, 8% *BRCA* mutation, and 27% serous carcinoma)—demonstrated that durvalumab plus olaparib combined with chemotherapy improved PFS compared with chemotherapy alone across all biomarker-defined subgroups.[18]

2.2 Dostarlimab plus niraparib (RUBY Part 2 / ENGOT-EN6-NSGO / GOG-3031)

This study compared dostarlimab plus chemotherapy followed by maintenance dostarlimab plus niraparib compared to placebo plus chemotherapy followed by placebo. The experimental arm was associated with longer PFS in the intention-to-treat population (median 14.5 vs. 8.3 months; HR 0.60) and the MMRp/MSS cohort (median 14.3 vs. 8.3 months; HR 0.63).[19]

3. ICIs combined with tyrosine kinase inhibitors

3.1 Pembrolizumab plus Lenvatinib (LEAP-001 / ENGOT-en9)

This phase III trial randomized 842 patients with advanced (stage III–IV) or first recurrent EMC who had not previously received first-line chemotherapy to have pembrolizumab 200 mg intravenously every 3 weeks plus lenvatinib 20 mg orally once daily until disease progression vs. carboplatin–paclitaxel chemotherapy every 3 weeks for up to 7 cycles.[20]

After a median follow-up of approximately 38 months, no significant differences in PFS or OS were observed in the overall population. However, in the MMRd subgroup (n = 200), median PFS was significantly longer with pembrolizumab plus lenvatinib (31.8 vs. 9.0 months; HR 0.62).

4. Targeted therapies combined with chemotherapy followed by targeted maintenance

4.1 Trastuzumab (NCT01367002)

Serous carcinoma and carcinosarcoma of the endometrium frequently overexpress HER2/neu, providing a rationale for treatment with trastuzumab, a monoclonal antibody targeting the extracellular domain of HER2/neu.

A randomized phase II trial in patients with advanced-stage or first recurrent with HER2/neu-positive uterine serous carcinoma compared carboplatin–paclitaxel plus trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks intravenously) to carboplatin–paclitaxel alone.[21,22] Treatments continued until disease progression.

The study found an addition of trastuzumab significantly improved both PFS (12.9 vs. 8.0 months; HR 0.46) and OS (29.6 vs. 24.4 months; HR 0.58). Trastuzumab combined with chemotherapy was well tolerated, with manageable toxicity.

4.2 Bevacizumab (GOG-86P)

A phase II trial evaluated bevacizumab in patients with advanced (stage III–IV) or recurrent EMC who had not previously received chemotherapy.[23] Patients were assigned into 3 arms of treatment:

1) Paclitaxel/carboplatin/bevacizumab 2) Paclitaxel/carboplatin/temsirolimus, and 3) Ixabepilone/carboplatin/ bevacizumab. Bevacizumab (arms 1 and 3) or temsirolimus (arm 2) was continued as maintenance therapy.

The ORRs were similar across all three arms. However, OS in the patients who had paclitaxel/carboplatin/bevacizumab (arm 1 and arm 3) were superior compared with temsirolimus (and compared with historical controls from GOG-209). Subsequent analyses focusing on *TP53* mutation status demonstrated that among patients with p53-abnormal tumors (n = 108), bevacizumab significantly improved with HR of 0.48 for PFS and HR of 0.61 for OS compared to the patients who had temsirolimus. No significant survival benefit was observed in patients with *TP53* wild-type tumors.[24]

4.3 Selinexor (SIENDO / ENGOT-EN5 / GOG-3055)

Selinexor is a targeted Exportin 1 (XPO1) inhibitor that blocks nuclear export of tumor suppressor proteins, including p53, thereby promoting selective apoptosis and inhibiting DNA damage repair mechanisms.

The SIENDO phase III trial[25] randomized 263 patients with metastatic (stage IV) or recurrent EMC to receive selinexor or placebo following platinum-based chemotherapy. In the overall population, selinexor did not significantly improve outcomes. However, in patients with p53 wild-type tumors, median PFS was significantly prolonged with selinexor (39.5 vs. 4.9 months; HR 0.36).[26]

An additional phase III trial (ENGOT-EN20/GOG-3083/ XPORT-EC-042) is currently ongoing to further evaluate selinexor in p53 wild-type EMC.

5. ADCs

Until now, there are no studies using ADCs in first-line treatment. An ongoing clinical study is evaluating the investigational anti–trophoblast cell surface antigen 2 (Trop-2) antibody–drug conjugate sacituzumab tirumotecan (Sac-TMT; SKB264/MK-2870) in combination with immunotherapy as first-line maintenance therapy for patients with MMRp EMC (NCT06952504), with enrollment initiated in May 2025.[27]

Summary of first-line targeted therapies and immunotherapy

The integration of immunotherapy and targeted therapies into first-line treatment has significantly improved outcomes for patients with advanced EMC. Molecular profiling is essential for optimizing treatment selection. Treatment selection should be guided by clinical risk and molecular classification2:

1) **Low-risk and intermediate-risk disease:** Surgery alone; no adjuvant immunotherapy or targeted therapy required.

2) **High-risk disease:** Chemotherapy with consideration of combination of ICIs (e.g., dostarlimab, pembrolizumab), followed by ICI maintenance, with or without radiotherapy.

3) **Advanced, metastatic, or unresectable disease:** Treatment should be guided primarily by MMR status and molecular features:

- *MMRd tumors:* ICIs (dostarlimab, pembrolizumab, or durvalumab) plus carboplatin–paclitaxel followed by ICI maintenance.
- *MMRp tumors:* ICIs plus carboplatin–paclitaxel followed by ICI with/without PARP inhibitor maintenance (e.g. dostarlimab, pembrolizumab, atezolizumab, or durvalumab, durvalumab + olaparib)
- *HER2/neu-positive tumors:* Carboplatin–paclitaxel plus trastuzumab, followed by trastuzumab maintenance.
- *p53-abnormal tumors:* Consider bevacizumab-containing regimens.
- *TP53 wild-type tumors:* Consider XPO1 inhibitors (Selinexor) as maintenance therapy.

Ongoing trials investigating novel combinations and biomarkers will further refine personalized therapeutic strategies in this disease.

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II. Second-line targeted therapies and immunotherapy in EMC patients

Immunotherapy is now recognized as the standard first-line treatment for patients with EMC, and its utilization continues to increase. The role of these agents in patients with recurrent or progressive disease as second-line treatment had also been studied. Single-agent ICIs are effective in MSI-H/MMRd tumors, while the combination of pembrolizumab and lenvatinib has become a standard option for MMR-proficient disease after platinum failure. The indication for such therapy, however, should be reconsidered in the context of the patient's prior first-line treatment, which will be discussed in subsequent sections.

Patients with no prior immunotherapy

Whenever feasible, debulking of newly developed lesions or biopsy is recommended to reassess the current microenvironment tumor. In cases where re-biopsy is not possible, archival primary tumor tissue or prior pathological results may serve as alternative sources to guide treatment selection. Table 2 shows specific therapeutic agents and corresponding clinical studies and are detailed below.

1. ICIs monotherapy

1.1 Pembrolizumab (KEYNOTE-158)

This was a phase II trial involving multiple types of solid tumors in patients who had previously received at least one line of chemotherapy. Participants were administered pembrolizumab (200 mg intravenously every 3 weeks) and continued treatment until disease progression or completion of a maximum of 35 cycles. The key findings related to EMC are as follows:

1) KEYNOTE-158 (Cohort D, K)

The cohorts relevant to EMC included Cohort D (EMC) and Cohort K Data from 94 patients with advanced or recurrent EMC from Cohorts D (EMC) and Cohort K (Other Advanced Solid Tumors, excluding Colorectal Cancer, with MSI-H status) with MMRd or MSI-H tumors, and 96 patients from Cohort D with MMRp/MSS tumors.[28,29] The two groups were not directly compared. The results demonstrated the efficacy of pembrolizumab in patients with advanced or recurrent EMC who were positive for MMRd protein or MSI-H following disease progression after prior chemotherapy, and who are not candidates for curative treatment with surgery or radiation. The ORR was 50%, with a median PFS of 13.1 months and a median OS of 65.4 months among those with MMRd/MSI-H group, and 7%, with a median PFS of 2.1 months, and a median OS of 11.1 months among those with MMRp/MSS group.

Adverse events of Grade 3 or higher were observed in 14% of the MSI-H/MMRd population, with no incidence of Grade 5 adverse events.

2) KEYNOTE-158 high tumor mutational burden (TMB-high) subgroup

This prespecified analysis used data from 1,066 solid tumors in patients with progressive disease from prior treatment, comprising 102 with high tumor mutational burden (TMB-high) and 688 with non-TMB-high.[30] This included 15 TMB-high and 67 non-TMB-high EMC patients.

The study showed TMB-high cancers had a favorable ORR to pembrolizumab (29%) compared to the non-TMB-high group (6%). However, no statistical comparison was made. Adverse events of Grade 3 or higher were observed in 13% and Grade 5 in 1% of the total population.

1.2 Dostarlimab (GARNET trial)

This phase I/II trial included patients with advanced or recurrent EMC who had previously received at least one platinum-containing chemotherapy regimen.[31] A total of 314 patients were enrolled (161 patients in the MMRp/MSS group and 153 patients in the MMRd/MSI-H group). Patients were treated with Dostarlimab (500 mg intravenously (IV) every 3 weeks for 4 cycles, followed by 1000 mg IV every 6 weeks) and continued treatment until disease progression. The ORR were 45.5% for MMR/MSI-H group and 15.4% for MMRp/MSS group.

Adverse events of Grade 3 or higher were observed in 17.6% of the MMRd/MSI-H group and 20.5% of the MMRp/MSS group. No incidence of Grade 5 adverse events was reported.

2. Tyrosine kinase inhibitor monotherapy (Lenvatinib)

This phase II trial investigated Lenvatinib in 133 patients with advanced or recurrent EMC who had previously received at least one platinum-containing chemotherapy regimen.[32] Patients in the study received Lenvatinib at a dose of 24 mg orally once daily. The ORR for the entire study population was 14.3%, showing little difference between the endometrioid subtype (15%) and the non-endometrioid subtype (14%). Key efficacy metrics included a duration of response lasting greater than or equal to 23 weeks in 37.6% of patients, a mean PFS of 5.6 months, and a median OS of 10.6 months. Regarding

Table 2 Studies Evaluating ICIs, Antibody-Drug Conjugates, and Targeted Therapies as Second-Line or Later Treatment for EMC

Study (ref)	Patient (all had advanced or recurrent EC)	Biomarker status	Treatment	Outcome (study +/- control) (PFS and OS presented as median unless specified otherwise)
KEYNOTE-158 (Phase II)[28-30]	N = 94 progressed after standard Rx	MMRd/ MSI-H	Pembro 200 mg Q3W up to 35 cycles	MMRd: ORR 50% (95% CI, 40-61) PFS 13.1 m (95% CI, 4.3-25.7) OS 65.4 m (95% CI, 29.5-NR)
	N = 1066	TMB-high	Pembro 200 mg Q3W up to 35 cycles	TMB-high: ORR 29% (95% CI, 21-39)
GARNET (Phase I/II)[31]	N = 314 progressed after standard Rx	MMRd/ MMRp	Dos 500 mg Q3W x 4 cycles then 1000 mg Q6W until PD	MMRp/MSS: ORR 15.4% (95% CI, 10.1-22) MMRd/MSI-H: ORR 45.5% (95% CI, 37.1-54)
Vergote et al. (Phase II)[32]	N = 133 prior 1 platinum-based CT	All population	Lenva 24 mg OD in a 28-day cycle	ORR 14.3% (95% CI: 8.8-21.4) SD: ≥ 23 weeks: 23.3% Clinical benefit: 37.6% (95% CI: 29.3-46.4) PFS: 5.6 m (95% CI: 3.7-6.3) OS: 10.6 m (95% CI: 8.9-14.9)
Study 309/ KEYNOTE-775 (Phase III)[33]	N = 827 prior ≥ 1 platinum-based CT	MMRd/ MMRp	Pembro 200 mg Q3W + Lenva 20 mg QD until PD (Pembro up to 35 cycles) Doxo 60 mg/m2 q 3 weeks, or paclitaxel 80 mg mg/m2 IV q wk (1 week off)	MMRp: PFS 6.7 vs. 3.8 m; HR 0.60 (95% CI, 0.50-0.72) OS 18.0 vs. 12.2 m; HR 0.70 (95% CI, 0.58-0.83) ORR 32.4% vs. 15.1% All comers: PFS 7.3 vs. 3.8 m; HR 0.56 (95% CI, 0.48-0.66) OS 18.7 vs. 11.9 m; HR 0.65 (95% CI, 0.55-0.77) ORR 33.8% vs. 14.7% MMRd: PFS 10.7 vs. 3.7 m; HR 0.39 (95% CI, 0.25-0.60) OS 31.9 vs. 8.6 m; HR 0.43 (95% CI, 0.28-0.68)
DESTINY-PanTumor02 (Phase II)[35]	N= 267 prior ≥ 1 systemic treatment or no satisfactory alternative options	HER2 IHC	Trastuzumab deruxtecan 5.4 mg/kg Q3W until PD	EMC: ORR 57.5% (95% CI, 40.9-73.0) PFS 11.1 m (95% CI, 7.1-NR) All cancersFer: ORR 37.1% (95% CI, 31.3-43.2) PFS 6.9 m (95% CI, 5.6-8)

Abbreviations: 1L, first-line; 2L, second-line; Bev, bevacizumab; CI, confidence interval; CMT, chemotherapy; CS, carcinosarcoma; Dos, dostarlimab; HR, hazard ratio; Lenva, lenvatinib; MMRd, mismatched repair deficient; MMRp, mismatched repair proficient; MSI-H, high microsatellite instability; MSS, microsatellite stable; NR, not reached; ORR, overall response rate; OS, overall survival; p53wt, p53 wild type; Pembro, pembrolizumab; PD, progressive disease; PFS, progression-free survival; TMB, tumor mutational burden

safety, a high incidence of adverse events of Grade 3 or higher occurring in 59% of patients were reported.

3. ICIs combination with tyrosine kinase inhibitor

3.1 Pembrolizumab and lenvatinib (Study 309 / KEYNOTE-775)

This phase III trial randomized 827 patients with advanced or recurrent EMC, previously treated with at least one platinum-based chemotherapy regimen, in a 1:1 ratio to receive either Lenvatinib (20 mg orally once daily) plus Pembrolizumab (200 mg IV every 3 weeks, up to 35 cycles) vs. investigator's choice chemotherapy (Doxorubicin or Paclitaxel).[33]

The study found that patients treated with Lenvatinib combined with Pembrolizumab showed superior efficacy over chemotherapy for advanced

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EMC patients previously treated with platinum. In overall population, median PFS and OS were longer compared to the chemotherapy group: 7.3 months vs. 3.8 months (HR = 0.56) for PFS, and 18.7 months vs. 11.9 months (HR = 0.65) for OS across the entire population. Among the patients with MMRp tumor, longer PFS with Lenvatinib + Pembrolizumab (6.7 months) compared to chemotherapy (3.8 months, HR = 0.60), and significantly longer OS (18 months vs. 12.2 months, HR = 0.70). A more substantial benefit was demonstrated in those with MMRd tumor: significantly longer PFS (10.7 months vs. 3.7 months, HR = 0.39) and dramatically longer OS (31.9 months vs. 8.6 months, HR = 0.43) with Lenvatinib + Pembrolizumab compared to chemotherapy. Adverse events of Grade > 3 were high in both arms, with 90.1% in the combination arm and 73.7% in the chemotherapy arm, and Grade 5 AEs occurred in 6.4% and 5.2%, respectively.

An exploratory analysis[34] in the subset of 71 patients who completed the full 35 cycles of combination therapy and continued Lenvatinib monotherapy after the completion of Pembrolizumab therapy. The analysis revealed continuous treatment provided sustained clinical benefit. For the entire cohort (30 MMRp and 41 MMRd patients), median PFS was 34.1 months, with 2-year and 3-year PFS of 68.3% and 49.3% respectively. The corresponding 2-year and 3-year OS rates were 100% and 89%. The benefit was also demonstrated among the patients with MMRp tumor: median PFS was 34.1 months, with 2-year and 3-year PFS of 66.7% and 46.2% respectively. The corresponding 2-year and 3-year OS were 100% and 84.3%. However, the safety profile showed that Grade > 3 AEs occurred in 80.5% of the total patients who continued Lenvatinib monotherapy. This exploratory data supports the concept of ongoing clinical benefit when continuing Lenvatinib.

4. ADCs

4.1 DESTINY-PanTumor 02

This phase II trial evaluated trastuzumab deruxtecan (T-DXd) in 267 patients, including 40 EMC patients, with HER2-expressing solid tumors (according to 2016 CAP/ASCP/ACSO guidelines for HER2 scoring in gastric cancer) who had received at least one prior chemotherapy regimen.[35] Patients received T-DXd at a dose of 5.4 mg/kg intravenously every 3 weeks until disease progression was detected.

The study demonstrated a favorable ORR across all solid tumors with HER2 expression (immunohistochemistry (IHC) 3+/2+), with particularly high benefit observed in endometrial, ovarian, cervical, bladder, and biliary tract cancers. Across all solid tumor types, the ORR was 37.1%, and the median PFS was 6.9 months. In the EMC group, the ORR was 57.5%. Specifically, within this population, the ORR for HER2 IHC 3+ patients was 84.6%, and the median PFS was 11.1 months.

Regarding safety, the incidence of Grade > 3 adverse events was 40.8% of the total population. An adverse event of special interest was interstitial lung disease or pneumonitis, which occurred in 10.5% of all patients, with a 1.1% incidence of death related to this adverse event.

4.2 Other ADCs

Clinical activity has also been reported with other Trop-2 ADCs. Datopotamab deruxtecan (Dato-DXd) demonstrated antitumor activity in patients with advanced solid tumors, including EMC, in the phase II TROPION-PanTumor03 study.36 In addition, sacituzumab govitecan showed clinical efficacy in heavily pretreated EMC in the phase II basket trial TROPiCS-03.[37]

Ongoing phase III trials are expected to further define the role of Trop-2 ADCs in this disease, including the ASCENT-GYN-01 study evaluating sacituzumab govitecan (NCT06486441) and trials investigating sacituzumab tirumotecan (MK-2870), such as MK-2870-020/TroFuse-020/GOG-3101/ENGOT-cx20 (NCT06459180).

5. Targeted therapies combined with hormonal treatments

Other treatment approaches in EMC include an emerging subgroup of ER–positive disease, which may be amenable to hormonal therapy. Although hormonal treatments are not the primary focus of this review, several phase II studies have explored the combination of endocrine therapy with targeted agents. In the randomized phase II PALEO trial, the cyclin D kinase 4 (CDK4)/6 inhibitor palbociclib combined with endocrine therapy was evaluated in patients with ER-positive endometrioid EMC that was either primary metastatic or relapsed after at least one prior systemic therapy. With a median follow-up of 21.9 months, the median PFS was 8.3 months in the combination arm compared with 3.1 months with endocrine therapy alone.[38]

Similarly, a single-arm phase II study evaluated

abemaciclib plus letrozole in recurrent ER-positive EMC, demonstrating an ORR of 30% and a median PFS of 9.1 months.[39] In addition to CDK4/6 inhibition, targeting the PI3K pathway has also been explored. A phase II study combining the mTOR inhibitor everolimus with letrozole reported an ORR of 32%, with particularly favorable responses observed in patients with endometrioid histology and catenin beta 1 mutations.[40]

Despite these encouraging results, there remains a clear need for phase III validation to define the role of combined hormonal and targeted therapies in EMC, particularly in the context of evolving treatment paradigms and increasing incorporation of molecular classification into clinical decision-making.

Patients with prior immunotherapy

The hypothesized mechanisms of resistance to immunotherapy include genetic alterations, such as beta-2 microglobulin or Janus kinases1/2, changes in the tumor microenvironment characterized by increased vascular endothelial growth factor (VEGF) activity, and an escalation of T-cell inhibitory pathways.

Treatment strategies to address immunotherapy resistance include the use of new agents, such as Werner syndrome helicase (WRN) inhibitors, which are designed to exploit the vulnerability of MMRd cancer cells by inhibiting the WRN protein (crucial for DNA repair), leading to an accumulation of DNA damage and replication stress, while MSS cells are not sensitive to this effect. Other strategies involve combination therapies (ICI + others), such as combining a PD-1 inhibitor with an anti-VEGF agent or a PARP inhibitor, using dual checkpoint blockade, or performing immunotherapy re-challenge (re-use of the same ICI), especially if the patient previously responded well and treatment was discontinued for more than 6 months.[41]

Clinical evidence for rechallenge comes from two retrospective studies. One report involved 8 patients with advanced MMRd EMC who progressed after first-line Pembrolizumab, where second-line treatment with Pembrolizumab plus Lenvatinib achieved an ORR of 75% (CR 12.5%, PR 62.5%).[42] Another study of 11 EMC patients (8 MMRd, 3 MMRp) previously treated with an ICI showed an ORR of 54.6% when given a second-line ICI-based regimen.[43]

Despite these encouraging efficacy signals, safety data for second-line immunotherapy after prior ICI remains limited, as studies on rechallenge have reported severe (grade 3-4) immune-related adverse events, including endocrine AEs and colitis. Consequently, implementing immunotherapy in this patient cohort requires careful consideration of the current limitations in the existing literature. Treatment initiation should be guided by a thorough, individualized assessment of each patient's risk-benefit profile, ideally taking into account putative biomarkers which predict responsiveness to immunotherapy rechallenge.

Summary of second-line targeted therapies, immunotherapy, and ADCs

Treatment is tailored according to molecular features; hence, molecular study should be performed if not prior available.

- MSI-H/MMRd: Consider ICIs e.g. Dostarlimab, Pembrolizumab
- TMB-H: Consider ICI (Pembrolizumab)
- MMRp: Consider Pembrolizumab and Lenvatinib
- HER2 (IHC 3+): Consider HER2-directed ADC i.e. Trastuzumab deruxtecan

To date, no solid evidence from clinical trial to test the role of immunotherapy rechallenge.

CONCLUSION

Systemic therapy for EMC has evolved from uniform chemotherapy to a precision-based approach integrating targeted agents, immunotherapy, PARP inhibitors, tyrosine kinase inhibitors, and ADCs. Molecular classification now underpins therapeutic decision-making and has led to substantial improvements in outcomes for patients with advanced disease. Continued translational research and well-designed clinical trials will further advance personalized care in this rapidly evolving field.

Conflict of Interest

All authors declare no conflicts of interest.

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209-49. doi: 10.3322/caac.21660.
2. Concin N, Matias-Guiu X, Cibula D, Colombo N, Creutzberg CL, Ledermann J, et al. ESGO-ESTRO-ESP guidelines for the management of patients with endometrial carcinoma: update 2025. Lancet Oncol 2025;26(8):e423-35. doi: 10.1016/S1470-2045(25)00167-6.
3. Cancer Genome Atlas Research N, Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, et al. Integrated genomic characterization of endometrial carcinoma. Nature 2013;497(7447):67-73. doi: 10.1038/nature12113.
4. Tangjitgamol S, Kavanagh J. Cytotoxic trials by the Gynecologic Oncology Group. In: Ayhan A, Reed N, Gultekin M, Dursun P, editors. Textbook of gynaecological oncology. Ankara: Gunes Publisher; 2012. p. 769-79.
5. Randall ME, Filiaci VL, Muss H, Spirtos NM, Mannel RS, Fowler J, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a gynecologic oncology group study. J Clin Oncol 2006;24(1):36-44. doi: 10.1200/JCO.2004.00.7617.
6. Fleming GF, Brunetto VL, Cella D, Look KY, Reid GC, Munkarah AR, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a gynecologic oncology group study. J Clin Oncol 2004;22(11):2159-66. doi: 10.1200JCO.2004.07.184.
7. Miller DS, Filiaci VL, Mannel RS, Cohn DE, Matsumoto T, Tewari KS, et al. Carboplatin and paclitaxel for advanced endometrial cancer: final overall survival and adverse event analysis of a phase III trial (NRG Oncology/GOG0209). J Clin Oncol 2020;38(33):3841-50. doi: 10.1200/JCO.20.01076.
8. Berek JS, Matias-Guiu X, Creutzberg C, Fotopoulou C, Gaffney D, Kehoe S, et al. FIGO staging of endometrial cancer: 2023. J Gynecol Oncol 2023;34(5):e85. doi: 10.1002/ijgo.14923.
9. Leon-Castillo A, de Boer SM, Powell ME, Mileshkin LR, Mackay HJ, Leary A, et al. Molecular classification of the PORTEC-3 trial for high-risk endometrial cancer: impact on prognosis and benefit from adjuvant therapy. J Clin Oncol 2020;38(29):3388-97. doi: 10.1200/JCO.20.00549.
10. Vermij L, Jobsen JJ, Leon-Castillo A, Brinkhuis M, Roothaan S, Powell ME, et al. Prognostic refinement of NSMP high-risk endometrial cancers using oestrogen receptor immunohistochemistry. Br J Cancer 2023;128(7):1360-8. doi: 10.1038/s41416-023-02141-0.
11. Mirza MR, Chase DM, Slomovitz BM, dePont Christensen R, Novak Z, Black D, et al. Dostarlimab for primary advanced or recurrent endometrial cancer. N Engl J Med 2023;388(23):2145-58. doi: 10.1056/NEJMoa2216334.
12. Powell MA, Bjorge L, Willmott L, Novak Z, Black D, Gilbert L, et al. Overall survival in patients with endometrial cancer treated with dostarlimab plus carboplatin-paclitaxel in the randomized ENGOT-EN6/GOG-3031/RUBY trial. Ann Oncol 2024;35(8):728-38. doi: 10.1016/j.annonc.2024.05.546.
13. Eskander RN, Sill MW, Beffa L, Moore RG, Hope JM, Musa FB, et al. Pembrolizumab plus chemotherapy in advanced endometrial cancer. N Engl J Med 2023;388(23):2159-70. doi: 10.1056/NEJMoa2302312.
14. Van Gorp T, Cibula D, Lv W, Backes F, Ortac F, Hasegawa K, et al. ENGOT-en11/GOG-3053/KEYNOTE-B21: a randomised, double-blind, phase III study of pembrolizumab or placebo plus adjuvant chemotherapy with or without radiotherapy in patients with newly diagnosed, high-risk endometrial cancer. Ann Oncol 2024;35(11):968-80. doi: 10.1016/j.annonc.2024.08.2242.
15. Colombo N, Biagioli E, Harano K, Galli F, Hudson E, Antill Y, et al. Atezolizumab and chemotherapy for advanced or recurrent endometrial cancer (AtTEnd): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2024;25(9):1135-46. doi: 10.1016/S1470-2045(24)00334-6.
16. Baurain J-F, Chon HS, Pepin JT, Sundborg M, Golde M, Kim B-G, et al. Durvalumab plus carboplatin/paclitaxel followed by durvalumab with or without olaparib as a first-line treatment for endometrial cancer: overall survival and additional secondary efficacy end-points by mismatch repair status in the DUO-E/GOG-3041/ENGOT-EN10 trial. Gynecol Oncol 2024;190 Suppl 1:S62-3. doi: 10.1016/j.ygyno.2024.07.092.
17. Westin SN, Moore K, Chon HS, Lee JY, Thomes Pepin J, Sundborg M, et al. Durvalumab plus carboplatin/paclitaxel followed by maintenance durvalumab with or without olaparib as first-line treatment for advanced endometrial cancer: the phase III DUO-E trial. J Clin Oncol 2024;42(3):283-99. doi: 10.1200/JCO.23.02132.
18. Westin S, Moore K, Chon HS, Pepin JT, Salinas E, Starks D, et al. Durvalumab plus carboplatin/paclitaxel followed by

durvalumab with/without olaparib in endometrial cancer: exploratory analyses of biomarker/histological heterogeneity and efficacy in the DUO-E mismatch repair proficient subpopulation. Int J Gynecol Cancer 2024;34 Suppl 3: A4-5. doi: 10.1136/ijgc-2024-IGCS.5.

19. Mirza M, Ghamande S, Hanker L, Black D, Raascou-Jensene N, Gilbert L, et al. Dostarlimab plus chemotherapy followed by dostarlimab plus niraparib maintenance therapy among patients with primary advanced or recurrent endometrial cancer in the ENGOT-EN6-NSGO/GOG-3031/RUBY trial. Gynecol Oncol 2024;190 Suppl 1:S6. doi:10.1016/j.ygyno.2024.07.016.
20. Marth C, Moore RG, Bidzinski M, Pignata S, Ayhan A, Rubio MJ, et al. First-line lenvatinib plus pembrolizumab versus chemotherapy for advanced endometrial cancer: a randomized, open-label, phase III trial. J Clin Oncol 2025;43(9):1083-100. doi: 10.1200/JCO-24-01326.
21. Fader AN, Roque DM, Siegel E, Buza N, Hui P, Abdelghany O, et al. Randomized phase II trial of carboplatin-paclitaxel compared with carboplatin-paclitaxel-trastuzumab in advanced (stage III-IV) or recurrent uterine serous carcinomas that overexpress Her2/Neu (NCT01367002): updated overall survival analysis. Clin Cancer Res 2020;26(15):3928-35. doi: 10.1158/1078-0432.CCR-20-0953.
22. Fader AN, Roque DM, Siegel E, Buza N, Hui P, Abdelghany O, et al. Randomized phase II trial of carboplatin-paclitaxel versus carboplatin-paclitaxel-trastuzumab in uterine serous carcinomas that overexpress human epidermal growth factor receptor 2/neu. J Clin Oncol 2018;36(20):2044-51. doi: 10.1200/JCO.2017.76.5966.
23. Aghajanian C, Filiaci V, Dizon DS, Carlson JW, Powell MA, Secord AA, et al. A phase II study of frontline paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, or ixabepilone/carboplatin/bevacizumab in advanced/recurrent endometrial cancer. Gynecol Oncol 2018;150(2):274-81. doi: 10.1016/j.ygyno.2018.05.018.
24. Leslie KK, Filiaci VL, Mallen AR, Thiel KW, Devor EJ, Moxley K, et al. Mutated p53 portends improvement in outcomes when bevacizumab is combined with chemotherapy in advanced/recurrent endometrial cancer: an NRG oncology study. Gynecol Oncol 2021;161(1):113-21. doi: 10.1016/j.ygyno.2021.01.025.
25. Vergote I, Perez-Fidalgo JA, Hamilton EP, Valabrega G, Van Gorp T, Sehouli J, et al. Oral selinexor as maintenance therapy after first-line chemotherapy for advanced or recurrent endometrial cancer. J Clin Oncol 2023;41(35):5400-10. doi: 10.1200/JCO.22.02906.
26. Makker V, Perez-Fidalgo JA, Valabrega G, Hamilton E, Van Gorp T, Sehouli J, et al. Long-term follow-up of efficacy and safety of selinexor maintenance treatment in patients with TP53wt advanced or recurrent endometrial cancer: a subgroup analysis of the ENGOT-EN5/GOG-3055/SIENDO study. Gynecol Oncol 2024;185:202-11. doi: 10.1016/j.ygyno.2024.05.016.
27. Eminowicz G, Alexandre J, Sanchez LMM, Braicu I, Madry R, Taskiran C, et al. 1221TiP GOG-3119/ENGOT-en29/TroFuse-033: a phase III, randomized study of sacituzumab tirumotecan (sac-TMT) + pembrolizumab (pembro) vs pembro alone as first-line (1L) maintenance therapy for mismatch repair-proficient (pMMR) endometrial cancer (EC). Ann Oncol 2025;36 Suppl 2:S790. doi: 10.1016/j.annonc.2025.08.1856.
28. O'Malley DM, Bariani GM, Cassier PA, Marabelle A, Hansen AR, Acosta AJ, et al. Pembrolizumab in microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) and non-MSI-H/non-dMMR advanced endometrial cancer: phase 2 KEYNOTE-158 study results. Gynecol Oncol 2025;193: 130-5. doi: 10.1016/j.ygyno.2024.12.020.
29. O'Malley DM, Bariani GM, Cassier PA, Marabelle A, Hansen AR, De Jesus Acosta A, et al. Pembrolizumab in patients with microsatellite instability-high advanced endometrial cancer: results from the KEYNOTE-158 study. J Clin Oncol 2022;40(7):752-61. doi: 10.1200/JCO.21.01874.
30. Marabelle A, Fakih M, Lopez J, Shah M, Shapira-Frommer R, Nakagawa K, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 2020;21(10):1353-65. doi: 10.1016/S1470-2045(20)30445-9.
31. Oaknin A, Pothuri B, Gilbert L, Sabatier R, Brown J, Ghamande S, et al. Safety, efficacy, and biomarker analyses of dostarlimab in patients with endometrial cancer: interim results of the phase I GARNET Study. Clin Cancer Res 2023;29(22):4564-74. doi: 10.1158/1078-0432.CCR-22-3915.
32. Vergote I, Powell MA, Teneriello MG, Miller DS, Garcia AA, Mikheeva ON, et al. Second-line lenvatinib in patients with recurrent endometrial cancer. Gynecol Oncol 2020;156(3): 575-82. doi: 10.1016/j.ygyno.2019.12.039.
33. Makker V, Colombo N, Casado Herraez A, Monk BJ, Mackay H, Santin AD, et al. Lenvatinib plus pembrolizumab in previously treated advanced endometrial cancer: updated efficacy and safety from the randomized phase III study 309/KEYNOTE-775. J Clin Oncol 2023;41(16):2904-10. doi: 10.1200/JCO.22.02152.
34. Colomba E, Lorusso D, Mackay H, Moore R, Yonemori K, Kim YM, et al. Outcomes for patients (pts) with advanced endometrial cancer (aEC) who completed pembrolizumab (pembro) and continued lenvatinib (LEN) in the phase III Study 309/KEYNOTE-775. Ann Oncol 2023;34 Suppl 2:S512-3. doi: 10.1016/j.annonc.2023.09.1927.
35. Meric-Bernstam F, Makker V, Oaknin A, Oh DY, Banerjee S, Gonzalez-Martin A, et al. Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: primary results from the DESTINY-PanTumor02 Phase II Trial. J Clin Oncol 2024;42(1):47-58. doi: 10.1200/JCO.23.02005.
36. Oaknin A, Ang JE, Rha SY, Yonemori K, Kristeleit R, Lin CC, et al. 714MO datopotamab deruxtecan (Dato-DXd) in patients with endometrial (EC) or ovarian cancer (OC): results from the phase II TROPION-PanTumor03 study. Ann Oncol 2024;35:S547-8. doi:10.1016/j.annonc.2024.08.775.
37. Santin AD, Corr BR, Spira A, Willmott L, Butrynski J, Tse KY, et al. Efficacy and safety of sacituzumab govitecan in patients with advanced solid tumors (TROPiCS-03): analysis

in patients with advanced endometrial cancer. J Clin Oncol 2024;42(29):3421-9. doi: 10.1200/JCO.23.02767.
38. Mirza MR, Bjørge L, Marmé F, Christensen RD, Gil-Martin M, Auranen A, et al. Palbociclib plus letrozole in estrogen receptor-positive advanced/recurrent endometrial cancer: double-blind placebo-controlled randomized phase II ENGOT-EN3/PALEO trial. Gynecol Oncol 2025;192:128-36. doi: 10.1016/j.ygyno.2024.12.003.
39. Konstantinopoulos PA, Lee EK, Xiong N, Krasner C, Campos S, Kolin DL, et al. A phase II, two-stage study of letrozole and abemaciclib in estrogen receptor-positive recurrent endometrial cancer. J Clin Oncol 2023;41(3):599-608. doi: 10.1200/JCO.22.00628.
40. Slomovitz BM, Jiang Y, Yates MS, Soliman PT, Johnston T, Nowakowski M, et al. Phase II study of everolimus and letrozole in patients with recurrent endometrial carcinoma. J Clin Oncol 2015;33(8):930-6. doi: 10.1200/JCO.2014.58.3401.
41. Podder V, Coleman RL, Eskander RN, Flint M, Monk BJ, Slomovitz BM. Checkpoint inhibitor rechallenge in advanced endometrial cancer: revisiting the immune landscape beyond first-line therapy. Int J Gynecol Cancer 2025;35(11):102124. doi: 10.1016/j.ijgc.2025.102124.
42. Rose PG, Feldman M, Podzielinski I, Petty AP, Vargas R. Activity of pembrolizumab and lenvatinib in mismatch repair deficient (dMMR) endometrial cancer patients who have failed pembrolizumab monotherapy: a case series. Gynecol Oncol Rep 2023;50:101303. doi: 10.1016/j.gore.2023.101303.
43. Morton M, Marcu I, Levine M, Cosgrove C, Backes F, O'Malley D, et al. Evaluation of efficacy and adverse events after second immunotherapy exposure in endometrial and cervical carcinoma. Obstet Gynecol 2023;142(2):360-3. doi: 10.1097/AOG.0000000000005243.

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ORIGINAL ARTICLE

Meaning in Life Among Urban Palliative Patients in Thailand

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ABSTRACT

Objective: Explore the prevalence and factors influencing the sense of meaning in life among palliative care patients.

Materials and Methods: A mixed method study was conducted using the Meaning in Life Questionnaire to assess the presence and search for meaning among palliative patients. Demographic data, including age, sex, and medical history, were descriptively analyzed. In-depth interviews were performed to explore the personal interpretations of the meaning of life of the patients, and qualitative data was analyzed using content analysis.

Results: A total of 107 palliative care patients participated in the study, comprising 41.1% males and 58.9% females. The findings revealed that 76.6% of the participants reported experiencing a sense of meaning in life, which was highly individualized. Although the concept of life's meaning varies from person to person, commonalities can still be observed. Through content analysis, these personal interpretations were categorized into eight key themes: family (77.6%), occupation (21.5%), society (15.9%), religion (11.2%), health (9.3%), finance (6.5%), education (4.7%), and specific life issues (16.8%).

Conclusion: A sense of meaning in life is integral to the well-being of palliative patients, and the family is the most influential factor. Holistic and person-centered palliative care interventions must integrate spiritual and existential dimensions to improve the quality of life of patients during their final stages.

Keywords: meaning in life, mixed methods study, palliative care, quality of life, spirituality

INTRODUCTION

The elucidation of the concept of meaning in life poses a profound intellectual challenge. Viktor Emil Frankl, lauded as the progenitor of logotherapy, stated in "The Unheard Cry for Meaning (1985)" that the meaning of life is "an individual's response to life's call in a specific situation". Moreover, he argued that the essence of meaning in life lies in an individual's subjective evaluation of elements that hold significance within their existence. This essence serves as a potent motivator for life's endeavors, cultivating mental fortitude that acts as an essential bulwark in the face of adversity. Of paramount importance is the understanding that meaning in life is an intensely personal and idiosyncratic phenomenon, unique to each individual.[1]

Within the palliative care domain, the concept of spirituality has been meticulously analyzed. In this

context, meaning in life emerges as an intrinsic component of spirituality.[2] Understanding the profound meaning in life acts as a catalyst for the cultivation of psychological resilience and an enhanced quality of life.[3] Consequently, people who grasp the essence of meaning in their lives are substantially more inclined to enrich their existence fully and participate in a more profound end-of-life experience. This stands in stark contrast to those who grapple with the void left by the absence of such understanding.[4,5]

Urbanization has significantly altered lifestyles, requiring people to adapt their values to fit modern society. Rapid urban growth has introduced new challenges and problems that affect quality of life through physical, economic, and social changes.[6] Because this study was conducted at the Siriraj Palliative Care Center, located in Bangkok, and thus represents an urban population, certain contextual differences may exist when compared to rural populations, for example, differences in access to healthcare services, family structure, cultural values, and social support systems. Therefore, the findings of this study are mainly representative of patients in an urban setting.

Since there have been limited studies in Thailand examining the incidence and nature of meaning in life among palliative care patients especially within the context of urban society, this study is designed to address this knowledge gap for the aim of 1) determining the prevalence of palliative care patients who have found meaning in their lives and 2) exploring the various ways in which each individual understands this deeply personal aspect of life. Based on consultations with experts in palliative care, we hypothesize that approximately 50% of this patient population derive meaning primarily through family, socioeconomic status, or education. We hope that this understanding will help healthcare teams provide personalized support and guidance, assisting patients in finding peace and dignity as they near the end of their lives. Additionally, the detailed findings about meaning in life can serve as a helpful guide for others who are still searching for their own sense of purpose and significance.

METERIALS AND METHODS

This study used a convergent parallel mixed methods design, integrating quantitative and qualitative methodologies to comprehensively explore meaning in life among palliative patients. Conducted at Siriraj Palliative Care Center between September 2021 and September 2022, the research was approved by the Institutional Review Board of Siriraj Hospital, Mahidol University (COA: Si 682/2021). Written informed consent was obtained from all participants before data collection.

The study focused on individuals aged 18 years or older with medically diagnosed incurable chronic diseases, a life expectancy of one year or less, and good communication skills, which means the ability to understand the meaning of others and to express one's own thoughts and feelings clearly to ensure meaningful participation. The research was conducted in a hospital-based palliative care center in an urban setting, where patients received comprehensive palliative care services. These services included outpatient and inpatient care, ward consultations, and home visits, all provided by a multidisciplinary team comprising palliative care specialists, nurses, psychologists, music therapists, and traditional Thai medicine practitioners. The care was delivered in accordance with established standards, integrating both clinical expertise and holistic approaches which may differ from rural settings where services are often incomplete, for example, the absence of a dedicated palliative care ward or the lack of specialist physicians and a multidisciplinary care team.

Based on expert estimates that approximately 50% of patients in this population have a profound understanding of life's meaning, the sample size was determined using a 95% confidence level with an acceptable error margin of 0.1. Accounting for a 10% safety margin for potential participant attrition, the final required sample size was 107 individuals.

This study integrated quantitative survey data and qualitative interview data to provide a holistic understanding of patients' experiences. The quantitative component used the Meaning in Life Questionnaire (MLQ), originally developed by Steger et al., to assess two dimensions of meaning in life: (1) Presence of Meaning, the extent to which individuals perceive their lives as meaningful and (2) Search for Meaning, the extent to which individuals actively seek meaning in life. The MLQ is a 10-item self-report instrument scored on a 7-point Likert scale (ranging from 1 = 'Absolutely Untrue' to 7 = 'Absolutely True'). It has been validated in more than 30 languages, including Thai,[7] demonstrating high reliability (α = 0.75), discrimination values ranging from 0.39 to 0.73, and

strong convergent validity with other psychological measures. A total score greater than 25 on the presence of meaning subscale is considered indicative of having meaning in life.[8]

To complement the survey data, semi-structured in-depth interviews were conducted. These interviews included all 10 items from the MLQ, supplemented by open-ended questions about what 'meaning in life' personally means to the participants, and asked them to rank the importance of each aspect. The aim was to explore participants' personal interpretations and experiences regarding meaning in life.

The interviews were recorded on audio tape, transcribed verbatim, and analyzed using thematic content analysis. Two independent researchers (XX and YY) systematically coded the interview transcripts. Any discrepancies in coding were resolved through discussion until consensus was reached, with a third senior researcher available for adjudication if necessary. Manual coding was performed without the use of specialized qualitative software.

Quantitative data were analyzed using descriptive statistics, including frequencies and percentages, to describe the prevalence and distribution of variables. All statistical analyses were conducted using IBM SPSS Statistics, version 28. This process ensured methodological rigor and enhanced the credibility of both quantitative and qualitative findings.

RESULTS

In this study, 107 palliative patients were examined using both quantitative and qualitative methods. The patient population consisted of 41.1% men and 58.9% women, with a mean age of 61 years. and diagnosed with cancer (98.1%). Most participants had a Palliative Performance Scale score of 40-60 (59.8%). Socioeconomic issues were relatively uncommon, with the majority reporting no problems (72.9%); however, financial burden (17.8%) was the most frequently reported issue. Regarding occupation, participants were diverse, with the largest groups being private business owners (20.6%) and contract workers (17.8%), while 13.1% were government officers and 14.0% retired. The majority practiced Buddhism (98.1%), with a small proportion identifying as Muslim (1.9%). Details are presented in **Table 1.**

Table 2 presents the descriptive statistics of each item of the Meaning in Life Questionnaire (MLQ) items. The mean scores and standard deviations are

Table 1 Demographic Characteristics of Participants (n = 107)

Variable	Category	Number	%
Gender			
	Male	44	41.1
	Female	63	58.9
Age			
	22-60 years	49	45.8
	61-89 years	58	54.2
Diagnosis			
	Cancer	105	98.1
	Non-cancer	2	1.9
Palliative Performance Scale (PPS score)			
	Group 1 (10-30)	18	16.8
	Group 2 (40-60)	64	59.8
	Group 3 (70-100)	25	23.4
Socioeconomic Issues			
	Caregiver burden	3	2.8
	Family conflict	3	2.8
	Financial burden	19	17.8
	No caregiver	3	2.8
	Multiple problems	1	0.9
	None	78	72.9
Occupation			
	Government officer	14	13.1
	State enterprise employee	3	2.8
	Private employee	6	5.6
	Private business	22	20.6
	Retired	15	14.0
	Farmer/Gardener	5	4.7
	Freelancer	3	2.8
	Contract worker	19	17.8
	Student	1	0.9
	Housewife	7	6.5
	None/Unemployed	12	11.2
Religion			
	Buddhism	105	98.1
	Islam	2	1.9

Table 2 Descriptive Statistics of Each Meaning in Life Questionnaire (MLQ) Items (n = 107)

Items	Mean	SD
1. I understand my life's meaning.	5.89	1.57
2. I am looking for something that makes my life feel meaningful.	3.27	2.33
3. I am always searching for something that makes my life feel significant.	3.21	2.25
4. I have a good sense of what makes my life meaningful.	6.08	1.35
5. I have discovered a satisfying life purpose.	5.69	1.63
6. My life has a clear sense of purpose.	5.27	2.06
7. I am searching for meaning in my life.	3.23	2.36
8. I am seeking a purpose or mission for my life.	3.05	2.32
9. My life has no clear purpose. (reverse coded)	5.12	2.03
10. I am always looking to find my life's purpose.	3.45	2.10

Abbreviation: SD, standard deviation

reported to reflect the degree of agreement with each statement among participants. Higher mean scores indicate stronger agreement, whereas larger standard deviations reflect greater variability in responses.

Among the participants, 76.6% reported experiencing a profound sense of meaning in life, while 23.4% did not report a significant sense of meaning. The highest mean score was observed for the item "I have a good sense of what makes my life meaningful" (M = 6.08, SD = 1.35), suggesting that most participants were able to clearly identify factors that make their lives meaningful. Similarly, items related to presence of meaning, such as "I have discovered a satisfying life purpose" (M = 5.69, SD = 1.63) and "My life has a clear sense of purpose" (M = 5.27, SD = 2.06), also demonstrated high scores. This suggests that a majority of palliative patients find meaning in their lives despite their terminal illness. When examining the desire to seek meaning, the data indicated that 68.2% of the participants did not express a desire to actively search for meaning. However, 31.8% of the participants indicated an ongoing interest in seeking deeper meaning, demonstrating a dynamic relationship between the presence of meaning and the active pursuit of purpose, even at the end of life.

Qualitative analysis, which involved content analysis of in-depth interviews, uncovered eight major themes that were central to the patients' sense of meaning in life. Illustrative dialogues for each theme are presented in **Table 3**. These themes were as follows: Family: 77.6% of the participants identified family as a significant source of meaning, emphasizing the importance of taking care of loved ones, nurturing family bonds and ensuring family members' happiness and wellbeing. Occupation: 21.5% of the participants highlighted their work, professional life, or past occupation as an important source of meaning. For some, the act of providing for others, pursuing meaningful careers, or continuing to contribute to their work until the end of life was significant. Society: 15.9% of the participants derived meaning from social connections and the role they played in society. This included participating in community activities, helping others, and feeling a sense of belonging. Religion: 11.2% of the patients placed importance on spiritual and religious practices, including prayer, attending religious services, and seeking comfort in their faith during their illness. Health: 9.3% of the patients expressed that their health, or the effort to maintain it, was an important factor in the meaning of their lives, emphasizing the significance of physical well-being and self-care. Financial aspects: 6.5% of the patients identified financial stability as a key concern, with thoughts of ensuring the financial security of their families or dealing with the financial challenges posed by their illness. Education: 4.7% noted that education, either through their own experiences or

Table 3 Examples of Participants' Dialogues across Different Groups

Theme	%	Example Dialogues
Family	77.6	Ensuring that family members live together happily and enjoy a good quality of life.
		Spending time with family members.
Occupation	21.5	Having the opportunity to do work that one loves.
		Occupying a managerial or supervisory role.
Society	15.9	Doing good deeds and not causing trouble or harm to others in society.
		Having the opportunity to give back to and help the community.
Religion	11.2	Practicing Dharma, chanting, and observing moral precepts.
		Understanding the principles of birth, aging, sickness, and death.
Health	9.3	Having a healthy body, being able to take care of oneself, and not being a burden to others.
		Regaining the ability to walk.
Financial	6.5	Having enough money, living comfortably, and being debt-free.
		Building wealth and achieving a lifestyle that includes owning a house and a car.
Education	4.7	Pursuing further studies in philosophy.
		Continuously seeking knowledge and pursuing further education in fields of personal interest.
Specific issues	16.8	Having the opportunity to travel to various places.
		Sharing life experiences and teaching others to help them avoid wasting time.

Multiple responses allowed.

through the education of their children, provided a source of meaning and fulfillment. Specific Personal Concerns: 16.8% of the participants identified personal life experiences or challenges, such as overcoming adversity, savoring simple pleasures like good food, or reflecting on the impact of their lives on others. These themes were expressed differently between individuals, highlighting the personal and individualized nature of meaning.

Family was by far the most frequently mentioned and emotional theme, indicating that the connections people share with their loved ones remain a core source of meaning even in the face of terminal illness. Through the combination of survey data and in-depth qualitative insights, this study presents a multifaceted understanding of meaning in life among palliative patients, providing valuable insight into how they derive purpose and significance from different aspects of their lives.

DISCUSSION

Palliative care plays a vital role in improving the quality of life for patients facing life-threatening illnesses, not only by addressing their physical symptoms but also by recognizing and responding to their psychological, social, and spiritual needs.[9,10] It is especially important for individuals dealing with advanced incurable conditions, where existential and spiritual distress may emerge, making the understanding of life's meaning crucial to their emotional and psychological resilience.[11-13] This study underscores the significance of spirituality in the context of palliative care, demonstrating its association with improved resilience, quality of life, and better coping mechanisms in patients near the end of life.

The findings of this study align with prior research that has explored the connection between spirituality and the concept of meaning in life. A robust sense of purpose has been shown to be protective against mental and emotional distress, including feelings of hopelessness, depression, and anxiety.[14,15] Furthermore, the presence of meaning in life among patients receiving palliative care is often related to the preservation of interpersonal relationships and a sense of belonging to a social or family unit.[16] Our study confirms that a significant portion of palliative

patients in the Siriraj Palliative Care Center expressed having a profound sense of meaning, with family relationships emerging as a central theme. This finding reflects the broader literature, which highlights the importance of familial bonds as a source of meaning in life, particularly during the final stages of existence.[17,18] The role of family within an urban context, as shown in our findings, is consistent with previous research indicating that elderly individuals living in urban areas often define their purpose in life through maintaining physical and mental health to remain self-dependent, witnessing the success of the younger generation, and living in a way that benefits others.[19] However, this study differs in terms of its target population. Other study explained that this is because family significantly influences the sense of meaning in life, exerting both a direct effect on one's life meaning and an indirect effect through positive personality traits. Personality is associated with the sense of meaning in life, and this personality is fundamentally shaped by the family as one's initial life environment.[20] Moreover, one study from Philippines found that meaning in life had also moderate positive correlations with family closeness.[21]

Data from this study further illustrate that not all patients actively search for meaning in their lives, with 31.8% expressing a desire for it. This finding resonates with existing research suggesting that while some patients are actively engaged in spiritual or existential quests, others may find themselves in a state of resignation or lack of interest, especially in the face of physical decline and imminent mortality.[22] As revealed in the qualitative analysis, the sources of meaning for palliative patients are deeply personal and vary significantly from individual to individual. For some, occupation, health, and societal roles play central roles, while others may find meaning in religious or spiritual practices.[11,13,18]

Our study also reflects the findings of cross-cultural studies, where differences in perceived meaning of life were associated with various cultural, educational and psychosocial factors.[13,18] These studies demonstrate that meaning in life can be influenced by individual circumstances, such as the level of education, marital status, and even psychological distress caused by illness. Our findings confirm that the pursuit of meaning is not universal but is shaped by personal experiences and external circumstances.

Ultimately, our study reaffirms the critical role of meaning in life within the scope of palliative care. By recognizing the multifaceted and deeply personal nature of meaning, healthcare providers can offer more personalized care, ensuring that the spiritual and emotional needs of patients are addressed.

However, this scholarly inquiry, by the dint of its design and scope, has limitations. First, the inclusion criteria that circumscribed the participation of palliative patients may limit the generalizability of the findings to the broader population of individuals receiving palliative care. Moreover, the evidentiary foundation upon which this study rests emanates from a subset of patients who were capable of communication and self-reflection, potentially excluding those with cognitive impairments or more severe physical deterioration. As a result, the data may not comprehensively encapsulate the multitudinous facets of the existential spectrum encountered by all palliative patients. It is incumbent upon stakeholders to recognize these limitations while striving to optimize the pertinence and contributions of this research effort. Future studies should aim to include a more diverse range of patient profiles and care settings to enrich the understanding of meaning-making in end-of-life care.

CONCLUSION

Meaning in life is an important factor in the spiritual dimension and associated with enhancing people's quality of life. This study represents an urban population. It was observed that a significant proportion of patients reported experiencing a sense of meaning in life, primarily derived from family relationships. Other sources of life meaning such as occupation, society, religion, health, finance, and education were reported in declining frequency.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author Contributions

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Formal analysis: P.C., T.N.

Funding acquisition: T.N.

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Methodology: P.S., T.N.

Project administration: T.N.

Resources: -

Software: P.C.

Supervision: T.N.

Validation: P.S., T.N.

Visualization: -

Writing – original draft preparation: P.C.

Writing – review & editing: P.S., T.N.

Data Availability Statement

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Devoe D. Viktor Frankl's logotherapy: the search for purpose and meaning. Inq J 2012;4(07):1-3.
2. Puchalski CM, Vitillo R, Hull SK, Reller N. Improving the spiritual dimension of whole person care: reaching national and international consensus. J Palliat Med 2014;17(6):642-56. doi: 10.1089/jpm.2014.9427.
3. Albers G, Echteld MA, de Vet HC, Onwuteaka-Philipsen BD, van der Linden MH, Deliens L. Content and spiritual items of quality-of-life instruments appropriate for use in palliative care: a review. J Pain Symptom Manage 2010;40(2):290-300. doi: 10.1016/j.jpainsymman.2009.12.012.
4. van der Kaap-Deeder J, Soenens B, Van Petegem S, Neyrinck B, De Pauw S, Raemdonck E, et al. Live well and die with inner peace: the importance of retrospective need-based experiences, ego integrity and despair for late adults' death attitudes. Arch Gerontol Geriatr 2020;91:104184. doi: 10.1016/j.archger.2020.104184.
5. Echlin KN, Rees CE. Information needs and information-seeking behaviors of men with prostate cancer and their partners: a review of the literature. Cancer Nurs 2002;25(1):35-41. doi: 10.1097/00002820-200202000-00008.
6. Nathalang S. Urban middle class and the quality of life development: the case study of northern and western outskirts of Bangkok and periphery. J Soc Dev Manag Strategy 2019;21(1):167–86.
7. Reawtaisong P, Supwirapakorn W. The effects of logotherapy on meaning in life of the elderly with cancer. J Police Nurses 2017;9(1):47-58.
8. Steger MF, Frazier P, Oishi S, Kaler M. The meaning in life questionnaire: assessing the presence of and search for meaning in life. J Couns Psychol 2006;53(1):80-93. doi: 10.1037/0022-0167.53.1.80.
9. Davis MP, Hui D. Quality of life in palliative care. Expert Rev Qual Life Cancer Care 2017;2(6):293-302. doi: 10.1080/23809000.2017.1400911.
10. Meier DE, Brawley OW. Palliative care and the quality of life. J Clin Oncol 2011;29(20):2750-2. doi: 10.1200/JCO.2011.35.9729.
11. Bernard M, Strasser F, Gamondi C, Braunschweig G, Forster M, Kaspers-Elekes K, et al. Relationship between spirituality, meaning in life, psychological distress, wish for hastened death, and their influence on quality of life in palliative care patients. J Pain Symptom Manage 2017;54(4):514-22. doi: 10.1016/j.jpainsymman.2017.07.019.
12. Chochinov HM. Dignity in care: the human side of medicine [internet]. 2022 [cited 2025 Dec 3]. Available from: https://academic.oup.com/book/44814
13. Goyarrola R, Lipsanen J, Saarelainen SM, Suviranta R, Rahko E, Lamminmäki A, et al. Spiritual well-being correlates with quality of life of both cancer and non-cancer patients in palliative care - further validation of EORTC QLQ-SWB32 in Finnish. BMC Palliat Care 2023;22(1):33. doi: 10.1186/s12904-023-01153-0.
14. Yoon DP, Lee EK. The impact of religiousness, spirituality, and social support on psychological well-being among older adults in rural areas. J Gerontol Soc Work 2007;48(3-4):281-98. doi: 10.1300/j083v48n03_01.
15. Ano GG, Vasconcelles EB. Religious coping and psychological adjustment to stress: a meta-analysis. J Clin Psychol 2005;61(4):461-80. doi: 10.1002/jclp.20049.
16. Gravier AL, Shamieh O, Paiva CE, Perez-Cruz PE, Muckaden MA, Park M, et al. Meaning in life in patients with advanced cancer: a multinational study. Support Care Cancer 2020;28(8):3927-34. doi: 10.1007/s00520-019-05239-5.
17. Majerníková L, Obročníková A. Relationship between the quality of life and the meaning of life in cancer patients. Nursing in the 21st Century 2017;16(2):13-4. doi: 10.1515/pielxxiw-2017-0012.
18. Gijsberts MHE, Liefbroer AI, Otten R, Olsman E. Spiritual care in palliative care: a systematic review of the recent european literature. Med Sci (Basel) 2019;7(2):25. doi: 10.3390/medsci7020025.
19. Khaw T, Balthip K, Laimek S, Youngwanichseth S. Perception of purpose in life among elderly in urban areas. J Res Nurs Midwifery Health Sci 2024;44(2):29-41.
20. Liu Z. Exploring the influence of family environment and positive personality on the sense of meaning in life. J Educ Humanit Soc Sci 2023;8:1540-5. doi: 10.54097/ehss.v8i.4516.
21. Fabella FET. A study on meaning in life in relation to family closeness, strength of faith, community involvement and social media activity. World J Adv Res Rev 2022;16(1):406-16. doi: 10.30574/wjarr.2022.16.1.1056.
22. Breitbart W, Rosenfeld B, Gibson C, Pessin H, Poppito S, Nelson C, et al. Meaning-centered group psychotherapy for patients with advanced cancer: a pilot randomized controlled trial. Psychooncology 2010;19(1):21-8. doi: 10.1002/pon.1556.

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ORIGINAL ARTICLE

The Role of Mitotic Count and Ki-67 Index in Identifying Likely Benign Salivary Gland Tumors to Avoid Overtreatment

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ABSTRACT

Objective: This study evaluated and compared the utility of mitotic count and Ki-67 index in distinguishing benign and malignant salivary gland tumors. The primary objective was to identify optimal cut-off points for these proliferative indices to help guide diagnosis and avoid overtreatment in cases where definitive histomorphology is challenging, especially in small biopsy specimens.

Materials and Methods: A total of 88 salivary gland tumor specimens were evaluated, including 56 benign and 32 malignant cases. Mitotic count and Ki-67 index were quantified for all cases. The diagnostic performance of each marker was assessed by determining sensitivity, specificity, the area under the receiver operating characteristic curve and the Area Under the Curve (AUC).

Results: Benign tumors exhibited consistently low mitotic counts (average < 1) and Ki-67 indices (average < 2.00%). In contrast, malignant tumors showed significantly higher values. A mitotic count ≥ 2 and a Ki-67 index ≥ 5.00% were determined as optimal cut-off points. The Ki-67 index (AUC = 0.76) demonstrated a higher sensitivity (68.80%) than the mitotic count (50.00%), performing slightly better than the mitotic count (AUC = 0.73).

Conclusion: Diagnosing benign and malignant salivary gland tumors based on morphology alone in small biopsies can be challenging. A mitotic count ≥ 2 and a Ki-67 index ≥ 5.00% are linked with malignancy, and these proliferation markers serve as valuable adjuncts to improve diagnostic accuracy and guide appropriate patient management. This approach is particularly useful in preventing overtreatment.

Keywords: benign and malignant salivary gland tumors, Ki-67 index, mitotic count

INTRODUCTION

Salivary gland masses encompass a wide variety of tumor types, ranging from benign to malignant neoplasms. Tumors of the parotid gland are the most common, with an estimated annual incidence of 1-3 cases per 100,000 individuals. The majority of these are benign neoplasms (77.00-80.00%), with pleomorphic adenoma (PA) being the most frequent. Malignant salivary gland tumors (MSGTs) are relatively rare, with an incidence of approximately 1-2 cases per 100,000 per year, accounting for about 20.00-30.00% of all salivary gland tumors globally.[1-4] In certain Asian populations, including Thailand, the incidence may be slightly lower, with MSGTs representing only 2.00-3.00% of all head and neck neoplasms.[5]

Despite their lower incidence, MSGTs are associated with poorer clinical outcomes, including a higher risk of local recurrence and distant metastasis, necessitating aggressive treatment such as extensive surgical resection and adjuvant radiotherapy.[6] These interventions can significantly impair patient quality of life, particularly when complications such as facial nerve injury occur in parotid gland surgery.[7] Therefore, accurate and early diagnosis is essential for appropriate therapeutic management and optimizing clinical outcomes.

A significant diagnostic challenge in salivary gland pathology lies in the limited nature of small biopsy specimens. These procedures often obtain only a small and potentially unrepresentative portion of the lesion, which is problematic when distinguishing between benign and malignant tumors due to their overlapping morphological features. For instance, benign tumors like myoepithelioma and basal cell adenoma (BCA) can closely resemble their malignant counterparts, such as myoepithelial carcinoma (MC), basal cell adenocarcinoma (BCAC), epithelial-myoepithelial carcinoma (EMC), and adenoid cystic carcinoma (AdCC). Even salivary duct carcinoma (SDC) or carcinoma (Ca) ex PA in its intraductal phase may be difficult to distinguish from benign apocrine metaplasia in PA.

Although molecular diagnostics, such as the identification of HMGA2 or PLAG1 alterations, can be helpful, their routine application is often limited by cost, technical availability, and the absence of specific molecular signatures in many salivary gland tumors.[8] This has led to a growing interest in identifying adjunctive histopathologic markers that are both practical and informative in routine diagnostics.

The Ki-67 index is one such marker, commonly used as an indicator of cellular proliferation, as it is a nuclear protein expressed during all active phases of the cell cycle. Its expression is most closely associated with the mitotic phase. Due to its short half-life, the Ki-67 index provides a more accurate representation of active proliferation, minimizing residual staining once cells exit the proliferative cycle.[9] In parallel, mitotic count, which quantifies mitotic figures per 10 high-power fields or 2 mm^2, remains a standard but underutilized method for assessing proliferative activity.[10]

Despite the widespread use of the Ki-67 index in other tumor systems, comparative studies evaluating the mitotic count and Ki-67 index across various salivary gland tumors remain limited. Moreover, a universally accepted Ki-67 cut-off value to differentiate between benign and malignant salivary gland neoplasms is lacking. This study aimed to address these limitations by evaluating and comparing the Ki-67 index and mitotic count across a spectrum of benign and MSGTs to determine their average values, assess their diagnostic utility, and explore potential cut-off points. The ultimate goal is to enhance diagnostic accuracy in small biopsy specimens and support clinical decision-making, particularly in cases where definitive molecular testing is unavailable.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of the Institute of Pathology under the ethical approval number IOP-KM-R66-005, and the requirement for informed consent was waived due to the retrospective nature of the analysis.

Cases of benign and MSGTs were retrieved from formalin-fixed, paraffin-embedded (FFPE) tissue blocks archived at the Institute of Pathology, Ministry of Public Health, Bangkok, Thailand. All specimens were fixed in 10.00% neutral buffered formalin, processed, and embedded in paraffin. These specimens, including punch biopsies, needle biopsies, excisions, and surgical resections, were collected between 2017 and 2023. Due to the rarity of MSGTs, all 32 available malignant cases were included, consisting of 4 cases of Ca ex PA, 4 cases of low-grade Mucoepidermoid carcinoma (MEC), 4 cases of MC, 1 case of BCAC, 7 cases of AdCC, 3 cases of EMC, and 9 cases of SDC. For the benign group, a sample size was calculated using the formula for estimating the Finite Population Proportion to ensure statistical reliability.[11] The benign group included 36 cases of PA and 20 cases of BCA, totaling 56 benign salivary neoplasm cases. Clinical variables such as patient age, gland of origin, and disease duration were not used as selection criteria. These clinical factors were considered not to influence the histopathological evaluation or the interpretation of immunohistochemical (IHC) findings.

All specimens were sectioned, 4 micrometers thick, and stained with hematoxylin and eosin (H&E) as a routine process. Two pathologists independently reviewed all tumor sections to confirm the diagnosis in accordance with the 2024 WHO Classification of Head and Neck Tumors under a light microscope (Olympus BX53, Japan, field diameter 0.55 mm).

Mitotic count was evaluated in the most cellular regions of each tumor section, typically at the invasive tumor front, over 10 high-power fields or 2 mm^2, where mitotic activity is generally most prominent and has been associated with prognostic relevance.[12-14] Mitotic figures were identified and counted based on the criteria proposed by Van Diest et al.,[15-17] which define mitotic figures as cells exhibiting condensed chromatin, absence of a nuclear membrane, and no visible nucleolus. Structures such as apoptotic bodies, pyknotic nuclei, and hyperchromatic but non-mitotic nuclei were excluded. Counts were performed independently by a resident in anatomical pathology and a consultant pathologist. Both were blinded to the clinical and diagnostic information. The data were recorded based on 10 consecutive high-power fields (HPFs, 400x magnification) under a light microscope (Olympus BX53, Japan, field diameter 0.55 mm), starting from the field with the highest tumor presence. Any discrepancies were resolved through joint review and consensus.

For the evaluation of the Ki-67 proliferative index, staining was performed using a mouse monoclonal antibody against Ki-67 (clone MIB-1; Dako, Agilent Technologies, USA) at a dilution of 1:300. IHC analysis was performed on 4-μm-thick FFPE tissue sections using the Leica Bond automated staining system with Bond Polymer Refine Detection. Heat-induced epitope retrieval was carried out using an ethylenediaminetetraacetic acid-based buffer for 25 minutes, followed by a peroxide block for 5 minutes. Sections were incubated with the primary antibody for 40 minutes, followed by treatment with a post-primary reagent (10 minutes) and polymer (10 minutes). Detection was completed using 3,3'-diaminobenzidine chromogen for 3 minutes, and all slides were counterstained with hematoxylin for 15 minutes to visualize nuclear morphology. Positive Ki-67 expression was indicated by a brown nuclear signal. The index was calculated as the percentage of positively stained tumor nuclei relative to the total number of tumor nuclei counted.[18] Representative areas demonstrating the highest tumor cellularity ("hotspot" regions) were selected under low-power magnification. Within these areas, 1,000 tumor cell nuclei were manually counted at high-power magnification (400×). The counts were performed independently by a resident in anatomical pathology and a consultant pathologist, blinded to diagnostic information. Any discrepancies between observers were resolved by consensus to ensure consistency and minimize observer bias.

Statistical analyses were conducted using IBM SPSS Statistics 26 software, with a significance threshold at p-value ≤ 0.05. The diagnostic utility of the Ki-67 index and mitotic count was evaluated using ROC curve analysis, a non-parametric statistical method used to assess discriminatory performance between benign and malignant neoplasms.

The diagnostic performance was quantified using the AUC, which is the summary metric derived from the ROC curve and represents the probability that the classifier will correctly rank a randomly chosen malignant case higher than a randomly chosen benign case. AUC results were interpreted as follows: AUC ≥ 0.90 (Excellent), 0.80 ≤ AUC < 0.90 (Good), 0.70 ≤ AUC < 0.8 (Fair), 0.60 ≤ AUC < 0.7 (Poor) and 0.50 ≤ AUC < 0.60 (Fail). AUC values greater than 0.50 were considered meaningful, with 0.80 or higher generally considered acceptable. Graphs were generated using Program R.

RESULTS

This study analyzed the average mitotic count and Ki-67 index across various salivary gland tumor types. The benign group included 36 cases of PA and 20 cases of BCA. The malignant group comprised 4 cases each of Ca ex PA, low-grade MEC, and MC, 1 case of BCAC, 7 cases of AdCC, 3 cases of EMC, and 9 cases of SDC. As shown in **Table 1**, benign neoplasms, including PA and BCA, showed consistently low Ki-67 indices (0.47% and 1.70%, respectively) and low mitotic counts (0.44 and 0.55, respectively). In contrast, malignant tumors demonstrated significantly higher proliferative activity. Among the malignant tumors, SDC had the highest average Ki-67 index (14.38%) and mitotic count (12.13), followed by Ca ex PA (Ki-67: 12.50%, mitotic count: 7.00). Notably, low-grade MEC showed a high average Ki-67 index (10.00%) but a low mitotic count (0.25). Representative photomicrographs illustrating the typical histomorphology and proliferative activity of a benign and a malignant tumor in this cohort are provided in **Figure 1**.

To evaluate the diagnostic utility of the Ki-67 index and mitotic count, a ROC curve was constructed. A mitotic count of ≥ 2 yielded a sensitivity of 50.00 % and a specificity of 91.10 % for distinguishing malignant from benign tumors. A Ki-67 index of ≥ 5.00% demonstrated a higher sensitivity of 68.80% and a

Table 1 Average Values of the Mitotic Count and Ki-67 Index Classified by Tumor Type

Tumor Types	Average Ki-67 Index (%)	Average of Mitotic Count (per 10 HPF)
Pleomorphic adenoma	0.47	0.44
Basal cell adenoma	1.70	0.55
Myoepithelial carcinoma	5.00	2.75
Basal cell adenocarcinoma	5.00	2.00
Adenoid cystic carcinoma	5.71	2.14
Epithelial-myoepithelial carcinoma	8.33	7.33
Mucoepidermoid carcinoma, low grade	10.00	0.25
Carcinoma ex pleomorphic adenoma	12.50	7.00
Salivary duct carcinoma	14.38	12.13

Abbreviation: HPF, high-power field

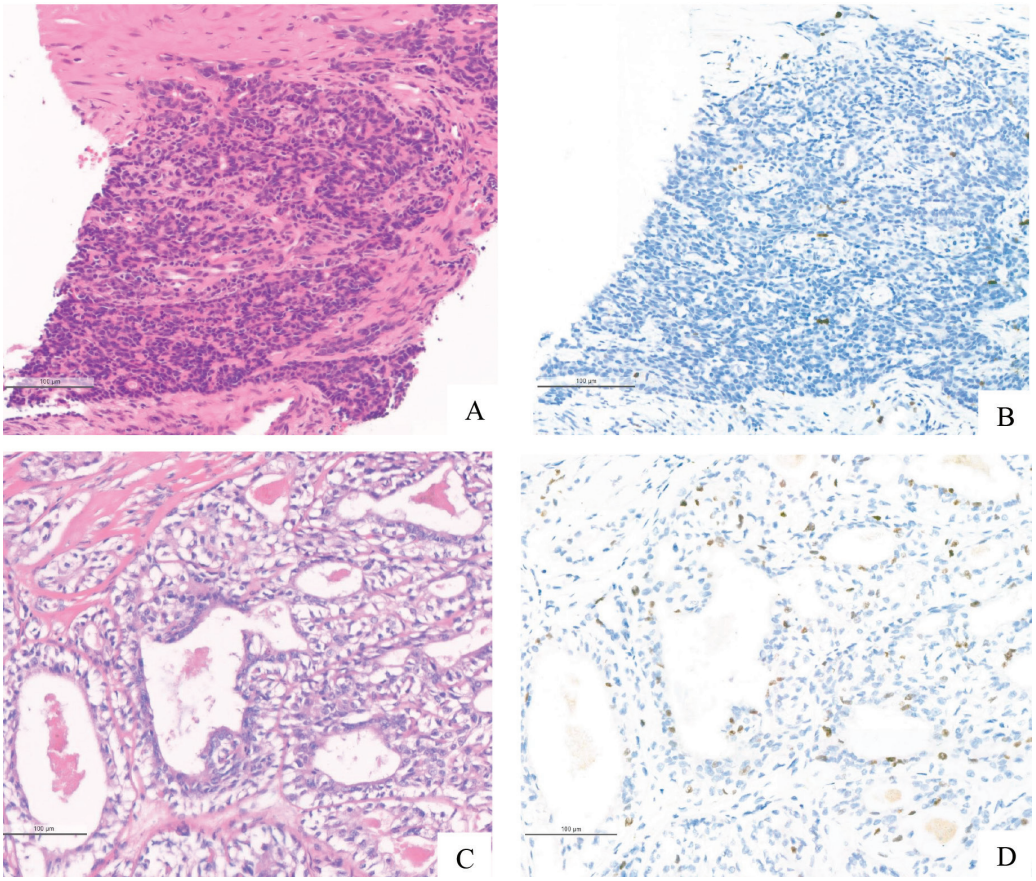

Figure 1 Histological features and the Ki-67 proliferative index, representative of the benign and malignant salivary gland tumors. (A, B) Basal cell adenoma (benign). (A) Hematoxylin and eosin stain shows a biphasic tumor morphology with no mitotic figures identified. (B) Ki-67 immunohistochemistry reveals a low proliferative index of approximately 1.00%. (C, D) Epithelial-myoepithelial carcinoma (malignant). (C) Hematoxylin and eosin stain shows a biphasic malignant tumor; no typical mitotic figures are present in this field. (D) Ki-67 immunohistochemistry demonstrates a significantly higher proliferative index of approximately 14.00%. All images were captured at 20x magnification. Scale bar represents 100 μm.

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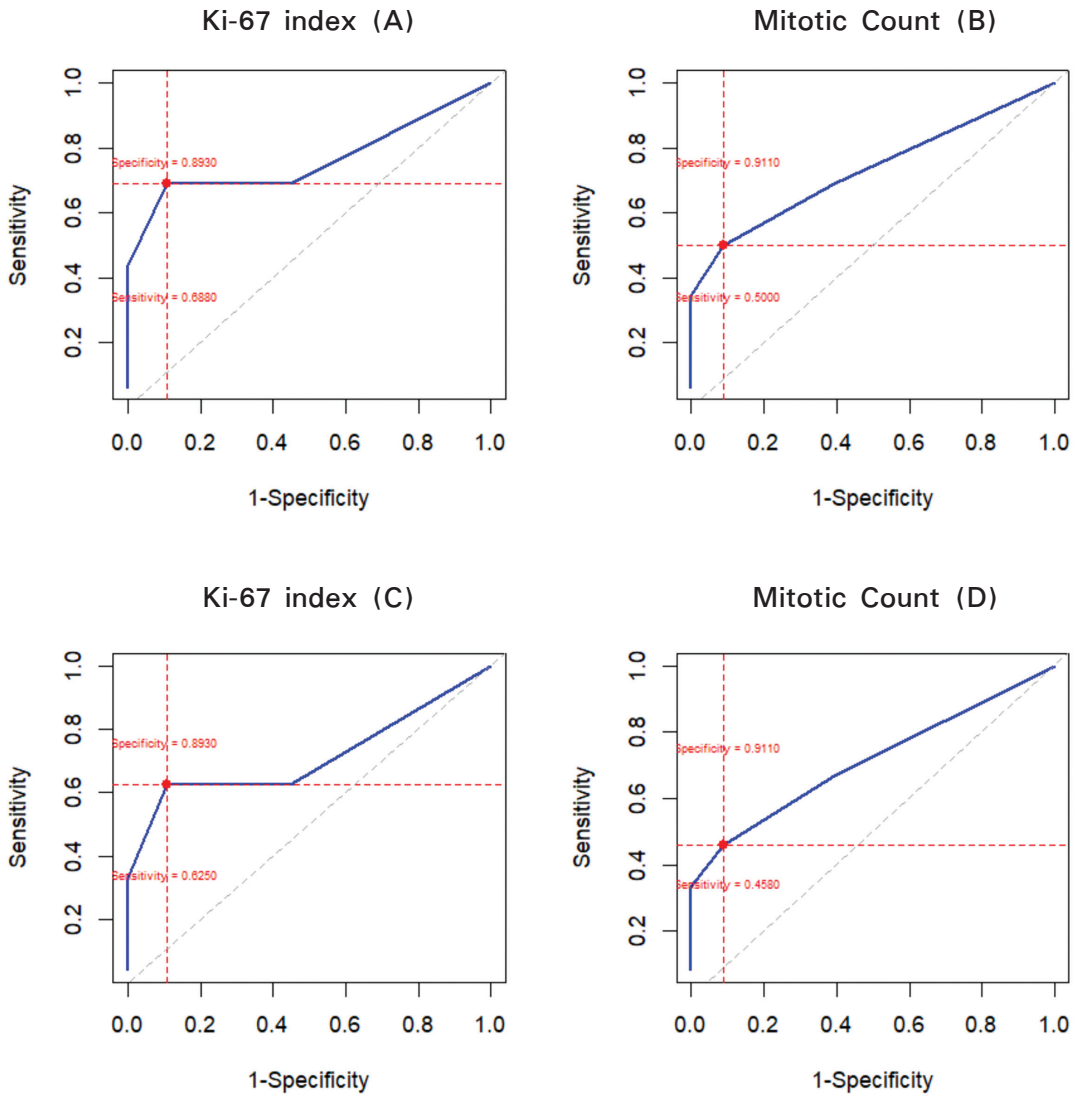

Figure 2 Receiver operating characteristic curves for the Ki-67 index (A, C) and mitotic count (B, D). Panels (A) and (B) represent analyses including salivary duct carcinoma, whereas panels (C) and (D) represent analyses excluding salivary duct carcinoma.

specificity of 89.30%. As presented in Table 2 and Figure 2, the Ki-67 index consistently maintained a higher sensitivity than the mitotic count at comparable false positive rates, suggesting it may offer greater utility in identifying malignant tumors.

For the Ki-67 index, the AUC was 0.76 (95% CI: 0.64-0.88), while the mitotic count showed a slightly lower AUC of 0.73 (95% CI: 0.61-0.85). When SDC cases were excluded, both markers demonstrated an AUC of 0.71. The AUC values for both markers were above 0.70, which is considered fair diagnostic performance, confirming their relevance in a broad spectrum of MSGTs.

DISCUSSION

This study aimed to evaluate the use of mitotic count and Ki-67 index as supplementary diagnostic tools for differentiating between benign and MSGTs, especially in cases where small biopsy specimens present a diagnostic challenge due to overlapping features. The results indicate that both markers have significant value in this regard. The findings showed a clear distinction in proliferation rates between benign and malignant tumors. Benign tumors like PA and BCA consistently showed low mitotic counts and Ki-67 indices. In contrast, malignant tumors such as SDC, Ca ex PA, and MEC exhibited much higher values for

Table 2 Sensitivity and Specificity for Mitotic Count and Ki-67 Index

Marker	Sensitivity (%)	Specificity (%)	AUC
Overall (including SDC)			
Mitotic count (≥ 2)	50.00	91.10	0.73
Ki-67 index (≥ 5.00%)	68.80	89.30	0.76
Overall (excluding SDC)			
Mitotic count (≥ 2)	45.80	91.10	0.71
Ki-67 index (≥ 5.00%)	62.50	89.30	0.71

Abbreviations: AUC, area under the curve; SDC, salivary duct carcinoma

these indices. These results are consistent with findings from a previous report in the literature[19-20].

A key finding was the establishment of optimal cut-off points: a mitotic count of ≥ 2 and a Ki-67 index of ≥ 5.00%. When a tumor's proliferation markers meet or exceed these thresholds, the likelihood of it being benign is significantly reduced. This is particularly important for differentiating benign tumors like myoepithelioma and BCA from their malignant counterparts, such as MC and BCAC. The study found the Ki-67 index to be a slightly more sensitive marker than the mitotic count. This was supported by ROC curve analysis, a non-parametric method that graphically illustrates a test's diagnostic ability by plotting sensitivity against the false positive rate. The Ki-67 index yielded a slightly better AUC—a summary measure of overall diagnostic performance where 1.0 is a perfect test—of 0.76 (95% CI: 0.64–0.88), compared to 0.73 (95% CI: 0.61–0.85) for the mitotic count. Since an AUC value greater than 0.70 is considered a fair diagnostic performance, this confirms that both markers are relevant for a wide range of MSGTs. The use of this non-parametric statistical method was appropriate for this study, as the data on mitotic counts and Ki-67 indices were not normally distributed.

While these markers are valuable, they should not be used as the sole basis for diagnosis. For example, some malignant tumors like MEC can have high Ki-67 indices but low mitotic counts. This highlights the need to interpret these findings in conjunction with other histomorphological features, as well as with clinical data and imaging studies. The study's results showed that both markers, when used together with morphological features, can significantly enhance diagnostic accuracy.

The study was also limited by its sample size, particularly the rarity of MSGTs, which led to a smaller number of malignant cases (32 cases). Despite this, the study provides valuable insights into the utility of these markers and supports their integration into routine diagnostic practice to improve patient care and prevent overtreatment.

CONCLUSION

Based on the study's results, a mitotic count of ≥ 2 and a Ki-67 index of ≥ 5.00% are strongly linked with MSGTs. When a tumor meets or exceeds these thresholds, the probability of it being benign decreases significantly. Therefore, these proliferation markers, especially when used with morphology, clinical findings, and imaging studies, can significantly improve diagnostic accuracy, particularly in small biopsy specimens where morphology alone can be misleading.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Data Availability Statement

The data analyzed in this study are stored at the Institute of Pathology, Ministry of Public Health, Thailand. Due to patient confidentiality and institutional regulations, the data are not publicly available. However, researchers may request access from the corresponding author, subject to approval from the Institute of Pathology's Ethics Committee.

REFERENCES

1. Bishop JA, Thompson LDR, Wakely PE, Weinreb I. Tumors of the salivary glands. Arlington: ARP Press; 2021.
2. Boukheris H, Curtis RE, Land CE, Dores GM. Incidence of carcinoma of the major salivary glands according to the WHO classification, 1992 to 2006: a population-based study in the United States. Cancer Epidemiol Biomarkers Prev 2009;18(11):2899-906. doi: 10.1158/1055-9965.EPI-09-0638.
3. Speight PM, Barrett AW. Salivary gland tumours. Oral Dis 2002;8(5):229-40. doi: 10.1034/j.1601-0825.2002.02870.x.
4. WHO classification of tumours. Head and neck tumours. 5th ed. Lyon: International Agency for Research on Cancer; 2024.
5. Mahomed Y, Meer S. Primary epithelial minor salivary gland tumors in South Africa: a 20-year review. Head Neck Pathol 2020;14(3):715-23. doi: 10.1007/s12105-019-01111-4.
6. Khuhaprema T, Srivatanakul P, Attasara P, Sriplung. H, Wiangnon S, Sumitsawan Y. Cancer in Thailand. Bangkok: National Cancer Institute; 2010.
7. Bell RB, Dierks EJ, Homer L, Potter BE. Management and outcome of patients with malignant salivary gland tumors. J Oral Maxillofac Surg 2005;63(7):917-28. doi: 10.1016/j.joms.2005.03.006.
8. Dulguerov P, Marchal F, Lehmann W. Postparotidectomy facial nerve paralysis: possible etiologic factors and results with routine facial nerve monitoring. Laryngoscope 1999;109(5):754-62. doi: 10.1097/00005537-199905000-00014.
9. Voz ML, Aström AK, Kas K, Mark J, Stenman G, Van de Ven WJ. The recurrent translocation t(5;8)(p13;q12) in pleomorphic adenomas results in upregulation of PLAG1 gene expression under control of the LIFR promoter. Oncogene 1998;16(11):1409-16. doi: 10.1038/sj.onc.1201660.
10. Gerdes J, Lemke H, Baisch H, Wacker HH, Schwab U, Stein H. Cell cycle analysis of a cell proliferation-associated human nuclear antigen defined by the monoclonal antibody Ki-67. J Immunol 1984;133(4):1710-5. doi: 10.4049/jimmunol.133.4.1710.
11. Yamane T. Statistics, An Introductory Analysis. 2nd ed. New York: Harper and Row; 1967.
12. Ellis PS, Whitehead R. Mitosis counting–a need for reappraisal. Hum Pathol 1981;12(1):3-4. doi: 10.1016/s0046-8177(81)80235-3.
13. Ibrahim A, Lashen A, Toss M, Mihai R, Rakha E. Assessment of mitotic activity in breast cancer: revisited in the digital pathology era. J Clin Pathol 2022;75(6):365-72. doi: 10.1136/jclinpath-2021-207742.
14. Meuten DJ, Moore FM, George JW. Mitotic count and the field of view area: time to standardize. Vet Pathol 2016;53(1):7-9. doi: 10.1177/0300985815593349.
15. Scolyer RA, Thompson JF. Mitotic rate in melanoma should be recorded as the number of mitoses per mm^2 (not per high power field): surgeons tell your pathologists! Am J Surg 2013;206(1):142-3. doi: 10.1016/j.amjsurg.2012.11.012.
16. van Diest PJ, van der Wall E, Baak JP. Prognostic value of proliferation in invasive breast cancer: a review. J Clin Pathol 2004;57(7):675-81. doi: 10.1136/jcp.2003.010777.
17. van Diest PJ, Baak JP, Matze-Cok P, Wisse-Brekelmans EC, van Galen CM, Kurver PH, et al. Reproducibility of mitosis counting in 2,469 breast cancer specimens: results from the Multicenter Morphometric Mammary Carcinoma Project. Hum Pathol 1992;23(6):603-7. doi: 10.1016/0046-8177(92)90313-r.
18. Biesterfeld S. Methodische Aspekte bei der standardisierten Beurteilung der mitotischen Aktivität von Tumorgeweben [Methodologic aspects of a standardized evaluation of mitotic activity in tumor tissues]. Pathologe 1997;18(6):439-44. doi: 10.1007/s002920050239.
19. Kazanceva A, Groma V, Smane L, Kornevs E, Teibe U. Proliferative potential in benign mixed salivary gland tumors and its value in primary and recurrent neoplasms. Stomatologija 2011;13(2):35-41.
20. Suzzi MV, Alessi A, Bertarelli C, Cancellieri A, Procaccio L, Dall'olio D, et al. Prognostic relevance of cell proliferation in major salivary gland carcinomas. Acta Otorhinolaryngol Ital 2005;25(3):161-8.

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ORIGINAL ARTICLE

Prevalence of Abnormal Health Check-Up Status in Bangkok Metropolitan Administration Officers

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ABSTRACT

Objective: Non-communicable diseases (NCDs) are a growing concern among urban workers. This study aimed to determine the prevalence and associated factors of abnormal health screening results among Bangkok Metropolitan Administration (BMA) employees.

Materials and Methods: A retrospective cross-sectional study was conducted among 3,652 BMA employees who underwent a health screening at Charoenkrung Pracharak Hospital in 2024. Data on laboratory results, chest X-rays, and behavioral risk factors were analyzed using multivariable logistic regression.

Results: The most common abnormalities were obesity (61.8%), hyperuricemia (32.9%), anemia (22.8%), and elevated liver enzymes (12.2%). Diabetes and hypertension were found in 8.0% and 11.3%, respectively. Chest X-ray findings included old pulmonary tuberculosis (4.9%) and active tuberculosis (1.5%). Male gender and obesity were significantly associated with hypertension (odds ratio (OR) = 2.08 and 4.75) and elevated liver enzymes (OR = 4.29 and 2.59).

Conclusion: A high burden of modifiable metabolic risk was observed among BMA employees, reflecting the health impact of urbanized lifestyles. These findings emphasize the importance of urban health strategies tailored to the metropolitan workforce, including routine screenings, early interventions, and city-based wellness initiatives that integrate lifestyle medicine into workplace settings to prevent the long-term burden of NCDs.

Keywords: health check-up, non-communicable diseases, prevalence, urban health

INTRODUCTION

The rising prevalence of non-communicable diseases (NCDs) poses a major challenge to health systems worldwide. These chronic conditions including diabetes, hypertension, dyslipidemia, and obesity account for a significant share of the global disease burden,[1] contribute to considerable losses in Disability-Adjusted Life Years (DALYs),[1] and impose increasing economic and societal costs. Routine health check-ups play a role in prevention by identifying and controlling risks, and detecting early stage chronic diseases.[2] These assessments are particularly important for urban government employees, who often face sedentary work, psychological stress, and irregular schedules that heighten health risks.[3] In Thailand, recent national surveys show high levels of NCD risk behaviors: unhealthy diets (56.9%), overweight/obesity (50.0%), physical inactivity (42.7%), alcohol consumption (29.7%), and smoking (16.6%).[4] Socioeconomic disparities also influence health behaviors, with

wealthier individuals consuming more alcohol and unhealthy foods, while smoking is more prevalent in lower-income groups.[4]

The Bangkok Metropolitan Administration (BMA) workforce plays a central role in maintaining the urban infrastructure and delivering public services, making their health status crucial for the efficiency of city governance.[5] As Thailand becomes an aging society, NCD-related disability and healthcare demands are expected to increase.[6] In response, BMA launched the "Healthy City for All" policy, including urban health zoning and citywide health screening initiatives. BMA staff, due to their urban lifestyle and work stress, face elevated risks for both non-communicable[7] and communicable diseases, such as tuberculosis.[8] Thailand mandates annual health checkups for high-risk employees, including civil servants, aligning with national labor regulations. According to national data, diabetes affects 8.9%, hypertension 24.7%, and obesity 37.5% of the population.[9] Poor dietary habits[4] and physical inactivity remain key contributors.[10] Charoenkrung Pracharak Hospital has taken the lead in annual health screenings for BMA workers across various departments to support early detection and public health resilience in Bangkok.

MATERIALS AND METHODS

This descriptive study aimed to assess the prevalence of abnormal health screening results among BMA civil servants and employees. Participants included those who underwent annual health checkups at Charoenkrung Pracharak Hospital between February 1 and May 31, 2024. Data were retrospectively collected from medical records and case report forms, with all personal identifiers anonymized for confidentiality. Independent variables included age, sex, body mass index (BMI), alcohol consumption, smoking, and job characteristics. Dependent variables were abnormal screening outcomes including NCDs (hypertension, diabetes, and dyslipidemia), obesity (classified as: normal BMI 18.5-22.99, overweight 23-24.99, obesity class I 25-29.99, class II 30-34.99, and morbid obesity ≥ 35), and chest X-ray abnormalities. Clinical assessments were conducted by licensed physicians. Laboratory tests were analyzed in certified labs, and chest X-rays interpreted by radiologists. Definitions followed national and World Health Organization diagnostic criteria: hypertension was defined as systolic Blood Pressure (BP) ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg; diabetes as fasting blood sugar (FBS) ≥ 126 mg/dL; hyperlipidemia as total cholesterol > 200 mg/dL or triglycerides > 150 mg/dL; anemia as hemoglobin <13.0 g/dL in males and < 12 g/dL in females;[11] hyperuricemia as a serum uric level ≥ 7 mg/dL in males and ≥ 6 mg/dL in female;[12] Elevated liver enzymes were defines as either aspartate aminotransferase or alanine transaminase levels exceeding the upper limit of normal set by the laboratory;[13] the estimated glomerular filtration rate (eGFR) was calculated using the THAI eGFR equation, which has been specifically validated for use in Thai population.[14] Descriptive statistics were used for quantitative variables and frequencies for categorical data. Associations between behavioral factors and outcomes were tested using multivariable logistic regression, with significance set at $p < 0.05$. Statistical analysis was performed using Statistical Package for the Social Sciences version 26. The study received ethics approval from the BMA's Ethics Review Committee (ethics certificate No. 99, Project ID: N003hn/68_EXP).

RESULTS

A total of 3,652 BMA employees were screened. The average age was 41.7 years, with 71.6% aged ≥ 35. Females made up 57.3%. Over 61% of employees had a BMI in the overweight or obese range. Among respondents, 48.9% reported alcohol use and 28.7% had a history of smoking **(Table 1)**.

Table 1 Demographics and Lifestyle Characteristics

Characteristics	Total (n = 3,652)
Age (years); mean ± SD	41.7 ± 10.5
Age > 35 years; n (%)	2,616 (71.6)
Gender; n (%)	
Male	1,559 (42.7)
Female	2,093 (57.3)
BMI (kg/m^2); mean ± SD (of 3,638 respondents)	25.1 ± 5.1
Overweight/obese; n (%) (of 3,638 respondents)	2,249 (61.8)
Alcohol use; n (%) (of 1,757 respondents)	860 (48.9)
Smoking history; n(%) (of 1,762 respondents)	506 (28.7)

Abbreviations: BMI, body mass index; kg/m^2, kilograms per square meter; n, number; SD, standard deviation

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Overall, 76.6% had at least 1 abnormal finding. Diabetes was found in 8.0%, hypertension in 11.3%, and chronic kidney disease (CKD) in 1.7%. Liver enzyme elevation occurred in 12.2%, while hyperuricemia affected 32.9%. Chest X-ray abnormalities included old tuberculosis (TB) (4.9%) and active TB (1.5%) **(Table 2)**.

Risk factor analysis showed a significant association between behavioral factors and NCDs **(Table 3)**. Diabetes: obesity (OR = 2.66, p = 0.004) was significantly associated. Male sex, alcohol, and smoking history were not statistically significant. Hypertension: significantly related to male sex (OR = 2.08, p < 0.001), age ≥ 35 years (OR = 2.81, p < 0.001), alcohol use (OR = 1.38, p = 0.037), and obesity (OR = 4.75, p < 0.001). Smoking was not significant. Liver enzyme elevation: significantly associated with male sex (OR = 4.29, p < 0.001) and obesity (OR = 4.29, p = 0.003). Alcohol and smoking were not significant. Abnormal chest X-ray: Age ≥ 35 (OR = 1.85, p = 0.009) was associated with lung abnormalities. Male sex, Alcohol, smoking, and obesity were not statistically significant predictors.

Table 2 Health Screening Results for BMA Employees

	Total (n)	Normal n (%)	Abnormal n (%)
Fasting blood sugar Diabetes (FBS ≥ 126 mg/dL)	2,604	1,676 (64.4)	928 (35.6) 209 (8)
Impaired fasting glucose (FBS = 100-125 mg/dL)			719 (27.6)
Hypercholesterolemia (≥ 200 mg/dL)	2,604	2,210 (84.9)	394 (15.1)
Hypertriglyceridemia (≥ 150 mg/dL)	2,605	2,376 (91.2)	229 (8.8)
Hypertension	3,611	3,204 (88.7)	407 (11.3)
Hyperuricemia	1,475	989 (67.1)	486 (32.9)
Elevated liver enzymes	2,604	2,287 (87.8)	318 (12.2)
Chronic kidney disease (eGFR) CKD stage 1	2,605	2,561 (98.3)	44 (1.7) 10 (0.4)
CKD stage 2			6 (0.2)
CKD stage 3a			22 (0.8)
CKD stage 3b			6 (0.2)
CKD stage 4			2 (0.1)
Pyuria + positive nitrite (suggestive of urinary tract infection)	1,733	1,729 (99.8)	4 (0.2)
Anemia (< 13.0 g/dL for males and < 12 g/dL for females)	3,639	2,811 (77.2)	828 (22.8)
Positive fecal occult blood			10 (0.3)
Chest X-ray Old TB	1,839	1,628 (88.5)	211 (11.5) 91 (4.9)
Active TB			28 (1.5)
Suspected lung mass			20 (1.2)
Cardiomegaly			10 (0.5)
Aortic calcification			9 (0.5)
Others (ventriculoperitoneal shunt, catheter devices)			3 (0.2)

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; g/dL, grams per deciliter; mg/dL, milligrams per deciliter; n, number; TB, tuberculosis

Table 3 Summary of the Factors Associated with Abnormal Health Outcomes

Factor	DM Adjusted OR (95%CI), P-value	HT Adjusted OR (95%CI), P-value	Elevated AST/ALT Adjusted OR (95%CI), P-value	Abnormal CXR Adjusted OR (95%CI), P-value
Male gender	1.42 (0.90, 2.24), p = 0.131	2.08 (1.48, 2.93), p = < 0.001*	4.29 (2.70, 6.09), p = < 0.001*	1.49 (0.98, 2.26), p = 0.063
Age ≥ 35 years	No data	2.81 (1.73, 4.59), p = < 0.001*	No data	1.85 (1.17, 2.92), p = 0.009*
Alcohol use	1.32 (0.87, 1.99), p = 0.190	1.38 (1.02, 1.86), p = 0.037*	1.18 (0.84, 1.65), p = 0.334	1.17 (0.79, 1.75), p = 0.426
Smoking	0.81 (0.53, 1.26), p = 0.350	0.79 (0.57, 1.08), p = 0.137	1.05 (0.75, 1.46), p = 0.782	0.73 (0.47, 1.13), p = 0.161
Obesity (BMI ≥ 23)	2.66 (1.37, 5.17), p = 0.004*	4.75 (2.91, 7.75), p = < 0.001*	2.59 (1.39, 4.82), p = 0.003*	No data

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; CI, confidence interval; CXR, chest X-ray; DM, diabetes mellitus; HT, hypertension; OR, odds ratio

Adjusted OR by male gender, Age ≥ 35 years, alcohol use, smoking and obesity (BMI ≥ 23)

* p < 0.05

Discussion

This study revealed a high prevalence of metabolic risk factors among BMA employees, with 76.6% exhibiting at least one abnormal health parameter. The most frequent findings included obesity, hyperuricemia, liver enzyme elevation, and anemia. These results are consistent with national trends, where nearly half of the adult population is overweight or obese, reflecting lifestyle and occupational patterns that promote physical inactivity[10] and poor dietary behaviors.[4]

Obesity, found in 61.8% of participants, is a well-established risk factor for diabetes and hypertension. In this cohort, obesity was significantly associated with diabetes (OR 2.66) and hypertension (OR 4.75), consistent with previous evidence linking central adiposity to insulin resistance[15] and hemodynamic dysregulation.[16] Male gender emerged as a significant predictor of hypertension, aligning with global and population-based studies demonstrating that men tend to develop NCD-related risk factors such as elevated blood pressure and obesity at younger age.[1,17] The prevalence of diabetes (8.0%) aligns with the national estimates(7.5-8.9%).[9,18] The prevalence of prediabetes (27.6%) was higher than national survey (10.6%).[18] However, the hypertension prevalence in this study (11.3%) was lower than the national data (25-30%),[19] likely reflecting a healthy-worker effect or the influence of single-occasion blood pressure measurements in less stressful screening environments. Nevertheless, multivariable logistic regression confirmed that hypertension was independently associated with male sex, age ≥ 35 years, alcohol consumption, and obesity. These associations are well explained by the underlying pathophysiology of sympathetic activation, renin–angiotensin–aldosterone system dysregulation, and vascular aging, mechanisms widely documented in prior epidemiologic and physiologic studies.[16,19] Interestingly, CKD prevalence was relatively low (1.7%) compared to previous Thai population studies, which reported rates up to 17.5%.[20] The lower detection may stem from one-time eGFR testing and the relatively healthy working population. The high prevalence of obesity and other NCDs raises concern for future renal burden, particularly as aging progresses.

Liver enzyme elevation (12.2%) was significantly associated with male gender and obesity, supporting the known role of metabolic and behavioral factors in liver dysfunction.[21-23] Notably, age was not a significant predictor, likely due to the narrow age distribution in this cohort. These findings mirror data from military[21] and diabetic populations,[22] where non-alcoholic fatty liver disease and alcohol-related liver damage are common.[21-23] Hyperuricemia affected 32.9% of participants, which is markedly higher than community-based reports in Thailand.[24] This may reflect urban

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dietary habits, male predominance, and coexisting metabolic risk factors, such as obesity and alcohol use, which alter uric acid metabolism.[25] Hyperuricemia is increasingly recognized as a contributor to metabolic syndrome, cardiovascular disease, and CKD progression.[26]

The prevalence of anemia in our cohort was 22.8%. This finding is consistent with recent reports in Thailand suggesting a significant health concern among the metropolitan workforce. This finding, combined with the fact that all cases were microcytic, emphasizes the need for screening inherited hemoglobin disorders and iron deficiency in the Thai population.[27] Iron deficiency anemia (IDA) must remain a primary consideration. This distinction is crucial, as IDA can be caused by chronic occult blood loss from colorectal cancer.[28] A finding supported by the 0.3% of our participants who tested positive for fecal occult blood, highlighting the clinical importance of differentiating these causes for appropriate management. The chest X-ray findings revealed old or active TB in 6.4% of screened individuals. While Bangkok remains endemic for TB, these findings emphasize the utility of routine imaging even in asymptomatic populations. Older age was significantly associated with radiologic abnormalities, aligning with TB epidemiology and cumulative exposure risk.[8] Incidental findings such as cardiomegaly and vascular calcification also hint at subclinical cardiovascular disease, further supporting the integration of imaging in comprehensive screening.

Collectively, this is the inaugural report describing screening outcomes among BMA workers. The findings reflect a high burden of modifiable NCD risk factors in an urban workforce. The associations observed support existing evidence and underscore the need for continued investment in health promotion, routine surveillance, and targeted lifestyle interventions. One limitation of this study is that the health screening was conducted under a government welfare program, with screening protocols determined primarily by age groups rather than occupational risk. Nonetheless, the scope of the screening remains broadly relevant, as it captures key health risks prevalent among urbanized populations.

CONCLUSION

This study identified a high prevalence of modifiable NCD risk factors among employees of the BMA. Obesity, elevated liver enzymes, hyperuricemia, and anemia were common, with male gender and obesity emerging as consistent predictors of multiple health abnormalities. Although the prevalence of some conditions, such as hypertension and CKD, appeared lower than national averages, the widespread presence of early metabolic disturbances signals a substantial future burden if unaddressed. These findings highlight the pressing need for urban-specific disease prevention strategies. In densely populated cities like Bangkok, civil servants often face unique health challenges related to sedentary work, limited green space, psychosocial stress, and dietary patterns shaped by the urban environment. Integrating routine health screenings with proactive lifestyle interventions, including nutrition education, workplace wellness programs, mental health support, and physical activity promotion, can play a pivotal role in reversing these trends. Preventive efforts tailored to urban contexts are essential for reducing the burden of NCDs and preserving the health, productivity, and resilience of the metropolitan workforce.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Author Contributions

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Formal analysis: N.C., W.N.
Funding acquisition: N.C., W.N.
Investigation: N.C.
Methodology: N.C., W.N.
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Validation: N.C.
Visualization: -
Writing – original draft preparation: N.C., W.N., P.C.
Writing – review & editing: N.C., W.N., P.C.

Data Availability Statement

Data supporting the findings of this study are available upon reasonable request from the corresponding author and subject to ethical approval.

REFERENCES

1. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020;396(10258):1223-49. doi: 10.1016/S0140-6736(20)307522.
2. Liss DT, Uchida T, Wilkes CL, Radakrishnan A, Linder JA. General health checks in adult primary care: a review. JAMA 2021;325(22):2294-306. doi: 10.1001/jama.2021.6524.
3. Janwantanakul P, Pensri P, Jiamjarasrangsri V, Sinsongsook T. Prevalence of self-reported musculoskeletal symptoms among office workers. Occup Med (Lond) 2008;58(6):436-8. doi: 10.1093/occmed/kqn072.
4. Vichitkunakorn P, Bunyanukul W, Apiwan K, Tanasanchonnakul D, Sittisombut M. Prevalence of non-communicable disease risk factors and their association with economic status: findings from the 2021 health behaviour of population survey in Thailand. Glob Health Action 2025;18(1):2485689. doi: 10.1080/16549716.2025.2485689.
5. Mesa-Vieira C, Gonzalez-Jaramillo N, Díaz-Ríos C, Pano O, Meyer S, Menassa M, et al. Urban governance, multisectoral action, and civic engagement for population health, wellbeing, and equity in urban settings: a systematic review. Int J Public Health 2023;68:1605772. doi: 10.3389/ijph.2023.1605772.
6. Potempa K, Rajataramya B, Singha-Dong N, Furspan P, Kahle E, Stephenson R. Thailand's challenges of achieving health equity in the era of non-communicable disease. Pac Rim Int J Nurs Res 2022;26(2):187-97.
7. World Health Organization. Urban health and NCDs in Thailand [internet]. 2021 [cited 2025 Nov 01]. Available from: https://www.who.int/thailand/our-work/NCDs
8. World Health Organization. Global tuberculosis report 2023 [internet]. 2023 [cited 2025 Nov 01]. Available from: https://www.who.int/teams/global-programme-on-tuberculosis-and-lung-health/tb-reports/global-tuberculosis-report-2023
9. Ministry of Public Health, Thailand. National NCD prevention and control plan 2017-2021. Nonthaburi: Ministry of Public Health; 2017. [cited 2025 Jun 8]. Available from: https://www.iccp-portal.org/sites/default/files/plans/Thailand%20National%20NCD%20plan%202017-2021.pdf
10. Topothai T, Tangcharoensathien V, Edney SM, Suphanchaimat R, Lekagul A, Waleewong O, et al. Patterns and correlates of physical activity and sedentary behavior among Bangkok residents: a cross-sectional study. PLoS One 2023;18(10):e0292222. doi: 10.1371/journal.pone.0292222.
11. Cappellini MD, Motta I. Anemia in clinical practice-definition and classification: does hemoglobin change with aging? Semin Hematol 2015;52(4):261-9. doi: 10.1053/j.seminhematol.2015.07.006.
12. The American College of Rheumatology (ACR). Gout Guideline [internet]. 2020 [cited 2025 Oct 5]. Available from: https://rheumatology.org/gout-guideline#2020-gout-guideline
13. Kwo PY, Cohen SM, Lim JK. ACG clinical guideline: evaluation of abnormal liver chemistries. Am J Gastroententerol 2017;112(1):18-35. doi: 10.1038/ajg.2016.517.
14. The Nephrology Society of Thailand. Clinical practice recommendation for the evaluation and management of chronic kidney disease in adults 2022 (revised edition) [internet]. 2022 [cited 2025 Oct 18]. Available from: https://www.nephrothai.org/wp-content/uploads/2023/03/CKD-guideline-2565-revised-edition.pdf
15. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 2006;444(7121):840-6. doi: 10.1038/nature05482.
16. Franklin SS, Gustin W 4th, Wong ND, Larson MG, Weber MA, Kannel WB, et al. Hemodynamic patterns of age-related changes in blood pressure: the Framingham Heart Study. Circulation 1997;96(1):308-15. doi: 10.1161/01.cir.96.1.308.
17. Roerecke M, Tobe SW, Kaczorowski J, Bacon SL, Vafaei A, Hasan OSM, et al. Sex-specific associations between alcohol consumption and incidence of hypertension: a systematic review and meta-analysis of cohort studies. J Am Heart Assoc 2018;7(13):e008202. doi: 10.1161/JAHA.117.008202.
18. Aekplakorn W, Chariyalertsak S, Kessomboon P, Sangthong R, Inthawong R, Putwattana P, et al. Prevalence and management of diabetes and metabolic risk factors in Thai adults: the Thai National Health Examination survey IV, 2009. Diabetes Care 2011;34(9):1980-5. doi: 10.2337/dc11-0099.
19. Sakboonyarat B, Poovieng J, Srisawat P, Hatthachote P, Mungthin M, Rangsin R, et al. Prevalence, awareness, and control of hypertension and associated factors among Royal Thai Army personnel in Thailand from 2017 to 2021. Sci Rep 2023;13(1): 6946. doi: 10.1038/s41598-023-34023-z.
20. Ingsathit A, Thakkinstian A, Chaiprasert A, Sangthawan P, Gojaseni P, Kiattisunthorn K, et al. Prevalence and risk factors of chronic kidney disease in the Thai adult population: Thai SEEK study. Nephrol Dial Transplant 2010;25(5):1567-75. doi: 10.1093/ndt/gfp669.
21. Sakboonyarat B, Poovieng J, Lertsakulbunlue S, Jongcherdchootrakul K, Srisawat P, Mungthin M. Association between raised blood pressure and elevated serum liver enzymes among active-duty Royal Thai Army personnel. BMC Cardiovasc Disord 2023;23(1):143. doi: 10.1186/s12872-023-03181-5.
22. Teshome G, Ambachew S, Fasil A, Abebe M. Prevalence of liver function test abnormality and associated factors in type 2 diabetes mellitus: a comparative cross-sectional study. EJIFCC 2019;30(3):303-16.
23. Lee DH, Ha MH, Christiani DC. Body weight, alcohol consumption and liver enzyme activity--a 4-year follow-up study. Int J Epidemiol 2001;30(4):766-70. doi: 10.1093/ije/30.4.766.
24. Lohsoonthorn V, Dhanamun B, Williams MA. Prevalence of hyperuricemia and its relationship with metabolic syndrome

in Thai adults receiving annual health exams. Arch Med Res 2006;37(7):883-9. doi: 10.1016/j.arcmed.2006.03.008.
25. Aihemaitijiang S, Zhang Y, Zhang L, Yang J, Ye C, Halimulati M, et al. The association between purine-rich food intake and hyperuricemia: a cross-sectional study in Chinese adult residents. Nutrients 2020;12(12):3835. doi: 10.3390/nu12123835.
26. Kuwabara M. Hyperuricemia, cardiovascular disease, and hypertension. Pulse (Basel) 2016;3(3-4):242-52. doi: 10.1159/000443769.
27. Pyae TW, Sanchaisuriya K, Athikamanon S, Sanchaisuriya P, Srivorakun H, Chaibunruang A, et al. Anemia in an ethnic minority group in lower northern Thailand: a community-based study investigating the prevalence in relation to inherited hemoglobin disorders and iron deficiency. PLoS One 2023;18(6):e0287527. doi: 10.1371/journal.pone.0287527.
28. Pham J, Laven-Law G, Winter JM, Wassie MM, Cock C, Symonds EL. The diagnostic accuracy of a fecal immunochemical test in detecting colorectal cancer and advanced precancerous colorectal neoplasia in patients with iron deficiency: a protocol for systematic review and meta-analysis. Gastroenterol Res Pract 2023;2023:5982580. doi: 10.1155/2023/5982580.

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ORIGINAL ARTICLE

Impact of COVID-19 Pandemic on Open Fracture Management at Vajira Hospital

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ABSTRACT

Objectives: Patients with open fractures were often treated later than usual during the COVID-19 pandemic, which could impact their outcomes, particularly regarding infection risks. However, some studies suggest that the timing of surgery does not directly influence infection rates. We aimed to examine how the COVID-19 pandemic affected the way open fractures were managed, focusing on any changes in treatment timing and patient outcomes before and during the pandemic.

Materials and Methods: Retrospective data at Vajira Hospital were collected and divided into two groups: one group received treatment before the COVID-19 pandemic (pre-COVID group), and the other group during the COVID-19 pandemic (COVID group). Key factors such as injury time, time to first surgery, and time to first dose of antibiotics were considered. The primary outcome was the difference in waiting times for surgery. Secondary outcomes included infection rate, nonunion rate, and reoperation rate.

Results: The researchers collected data from a total of 76 patients for each of the pre-COVID and COVID groups. No significant differences were found in waiting times for surgery or in the time to the first dose of antibiotics between the two groups. The mean waiting time for surgery was shorter in the COVID group (587.2 min) compared to the pre-COVID group (683.4 min), but this difference was not statistically significant. The mean time to the first dose of antibiotics in the COVID group (183.8 min) was shorter than in the pre-COVID group (212.2 min), but did not meet the statistically significant threshold. There were no significant differences in complication rate (infection rates, nonunion rates, and reoperation rates) between groups.

Conclusion: COVID-19 did not affect the waiting time for the treatment of open fractures and did not impact the outcomes or complications of open fracture treatment at Vajira Hospital. This may be attributed to the hospital's strict criteria for emergency surgeries, prioritizing critically needed cases, ensuring timely and standard treatment.

Keywords: complication, COVID-19, open fracture

INTRODUCTION

The COVID-19 pandemic began in early 2020. As the virus spreads through droplets, strict hygiene and respiratory protection measures were implemented nationwide, significantly impacting hospital management, leading to shortages in medical resources. Routine practice guidelines were adjusted to accommodate the situation, which resulted in longer waiting times due to additional procedural steps. For example, patients requiring urgent surgery might undergo the GeneXpert test. A rapid molecular test that provides quicker results than the reverse transcription-polymerase chain reaction, but still delays the surgical preparation. Additionally, treatment delays occurred due to a shortage of medical staff, blood supplies, and equipment.

Open fractures are an urgent orthopedic condition, requiring prompt management for irrigation and debridement upon arrival at the emergency room. It was traditionally believed that surgical intervention for open fractures should occur within 6 h[1] (the "6-h rule") to reduce the risk of infection. However, recent studies suggest that the timing of surgery may not directly affect infection rates. A study by Weber et al.[2] found no significant difference in the time from injury to surgery for open long bone fractures between patients who developed infections and those who did not, though the infection rate was influenced by the severity of the fracture as classified by the Gustilo-Anderson system. In another study Higgin et al.[3] found a higher infection rate in patients who underwent surgery within 12 h compared to those after 12 h. Additionally, Charalambous et al.[4] found no difference in outcomes between surgeries performed within 6 h and those performed later. Many studies have explored risk factors for postoperative infections in open fractures, with the time from injury to surgery not identified as a significant factor. Current guidelines in England state that there is no evidence-based support for the 6-h rule.[5] However, there are still no definitive studies outlining the optimal time frame for surgery in open fracture treatment.

It is assumed that delays in treatment, compared to pre-pandemic times, may affect the treatment outcomes. Several studies have examined the impact of the COVID-19 pandemic on the treatment of open fractures, all finding longer times from injury to surgery than before the pandemic. However, the infection rate did not differ. Additionally, some studies noted that definitive treatment also took longer.

No studies have been conducted in Thailand regarding the effects of the COVID-19 pandemic on open fracture treatment. Treatment approaches vary systematically between countries, including differences in patient demographics. Analyzing these variations can provide valuable insights and help guide future open fracture treatments in Thailand.

MATERIALS AND METHODS

This study was approved by the Vajira Institutional Review Board (COA 019/2566). Retrospective data were collected using the EPHIS database, divided into two groups: those who visited before the COVID-19 pandemic (pre-COVID group) and those who visited the emergency department at Vajira Hospital, a level I trauma center, during the pandemic (COVID group). Key factors that may affect treatment outcomes, such as injury time, time to first surgery, and time to the first dose of antibiotics, were considered. The primary outcome was the time to first surgery. The secondary outcomes included the infection rate, nonunion rate, and reoperation rate. This retrospective review included patients diagnosed with open long bone fractures between January 1, 2018, and December 31, 2021, at Vajira Hospital. The pre-COVID group included data from January 1, 2018 to December 31, 2019 and the COVID group included data from January 1, 2020 to December 31, 2021. Full medical records were available, containing information on injury time, surgery time, diagnosis, and waiting time for the first antibiotic dose. Some missing demographic data were collected from telephone interviews. All patients had a follow-up period of at least 3 months after definitive treatment. Patients with pathological fractures, such as those caused by infection or cancer, were excluded. This study calculated the sample size by setting a Type I error of 0.05 and a power of 80%. The variances were referenced from the study by Gupta et al.,[6] resulting in 76 patients per group. For the result, the T-test and the Chi-square were used for statistical analysis.

RESULTS

A total of 152 patients who received the treatment for open long bone fractures were included (76 in the pre-COVID and 76 in the COVID group). The demographic data for each group are shown in **Table 1**. The results indicated similar gender and age distributions

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Table 1 Demographic Characteristics

Group	COVID	Pre-COVID
Total, number	76	76
Sex (%)		
Male	62 (81)	57 (75)
Female	14 (19)	19 (25)
Age, mean (SD)	39.87 (10.8)	35.2 (12.4)
Smoking, number (%)	22 (29)	13 (17)
Underlying disease (%)		
Hypertension	7 (9)	6 (7.8)
Diabetes mellitus	2 (2.6)	3 (3.9)
Dyslipidemia	6 (7.8)	2 (2.6)
Stroke	1 (1.3)	1 (1.3)
Heart disease	1 (1.3)	1 (1.3)
Other	3 (3.9)	4 (5.2)
Operation (%)		
Fixation	56 (73.7)	60 (78.9)
No implant	20 (26.3)	16 (21.1)

Abbreviation: SD, standard deviation

between the two groups. However, the COVID group had a higher number of smokers than the pre-COVID group. Regarding underlying conditions, the COVID group had a higher prevalence of dyslipidemia compared to the pre-COVID group, while the incidence of other conditions was similar in both groups. As for surgical procedures, both groups underwent fixation and debridement without fixation, with similar distributions between the groups.

The time to surgery was shorter for patients who visited during the COVID group compared to those who visited before the pandemic, but this difference was not statistically significant (587.2 min vs 683.4 min, P = 0.09). Similarly, the time to the first dose of antibiotics was shorter in the COVID group, but no significant difference (183.8 min vs 212.2 min, P = 0.27). (Table 2)

Regarding the secondary surgical outcomes. For infection rates, both groups had a rate of 9.2%. Additionally, the nonunion rate was higher in the pre-COVID group but not statistically significant (1.3% vs 3.9%, P = 0.23). The reoperation rate was found to be higher in the COVID group but did not reach statistical significance (10.5% vs 7.9%, P = 0.39) (Table 3). The operation rate was collected from all types of operations, including second-third look debridement and revision surgery.

DISCUSSION

During the COVID-19 pandemic, hospitals had to implement additional procedures in the patient care process to prevent viral spread. These included wearing personal protective equipment, cleaning protocols, COVID-19 screening tests, and limitations on the number of staff and available facilities. As a result, the care provided to each patient took longer than usual, leading to the hypothesis of this study that the

Table 2 Time to Surgery and Time to the First Dose of Antibiotics

		Group		P-value
		COVID (n = 76)	Pre-COVID (n = 76)	
Time to surgery	Mean(min)	587.2	684.4	0.09
	Standard deviation	394.4	302.3	
	Standard error mean	45.2	34.6	
Time to the first dose of antibiotics	Mean (min)	183.8	212.2	0.27
	Standard deviation	182.6	134.0	
	Standard error mean	20.9	15.3	

Abbreviation: n, number

Table 3 Surgical Outcomes between Groups

Outcomes	Group		P-value
	COVID (n = 76)	Pre-COVID (n = 76)	
Infection, number (%)	7 (9.2)	7 (9.2)	1.00
Nonunion, number (%)	1 (1.3)	3 (3.9)	0.23
Re-operation, number (%)	8 (10.5)	6 (7.8)	0.39

Abbreviation: n, number

treatment of patients with open fractures might be delayed and could potentially increase the risk of postoperative complications.

A multicenter cohort study from the United States and Canada found an increase in the number of cases that did not meet the 24-h waiting time for open fracture surgery during the COVID-19 period (2.7% vs 3.9%).[7] A cohort study from the United Kingdom reported a significant decrease in cases meeting the 12-h surgical benchmark during the pandemic, from 57.1% to 31.8% (P = 0.004), with no significant change in infection rates.[8] A study from India found longer times for the first dose of antibiotics and a higher infection rate during the COVID-19 period, although this difference was not statistically significant.[8] The findings from our institute showed that the waiting times for antibiotic administration and surgery were not significantly different from the pre-pandemic period. Several factors can explain this. Due to the government's lockdown policy, the number of accident patients decreased. Stricter criteria for defining urgent cases in the emergency room led to a reduced patient volume, along with more stringent emergency surgery indications, resulting in fewer surgical cases overall. Additionally, effective management policies under resource constraints, including limited equipment, tools, operating rooms, and staff, helped maintain treatment standards similar to pre-pandemic conditions. In our institute, a policy has been implemented to cancel elective surgeries and to operate the surgical rooms only for urgent cases that require immediate surgical intervention. This has significantly reduced the number of operating room sessions compared to the pre-COVID period, making the waiting list for receiving the treatment shorter, and the number of personnel is sufficient to handle the workload, even under conditions with limited staffing. Campbell et al.[9] reported a 64% decrease in emergency department visits during the lockdown at the Royal London Hospital, with an 18% decrease in open lower extremity fracture cases. Choudhary et al.[10] found that open fracture admissions were 21% lower than usual, and the waiting time for surgery was significantly reduced, with no difference in infection rates. The results of this study indicate that, despite the challenges posed by the pandemic, which hindered urgent care delivery, effective management following strict standard treatment guidelines and proper operating room management can maintain treatment outcomes at the expected level and reduce the incidence of complications.

Traditionally, the "6-h rule" recommended early surgical management for open fractures within 6 h to reduce the risk of infection.[1] However, recent studies have challenged this rule (9.7 h vs 11.4 h, P = 0.09), suggesting that the timing of surgery, "6-h rule", does not directly correlate with infection rates.[3,5,11-13] Different guidelines are used in various institutes based on current evidence and surgeon preferences. The BOAST Guideline[5] (British Orthopedic Association Standards for Trauma and Orthopedics) recommends surgery within 12 h for high-energy injuries and 24 h for low-energy injuries. In Thailand, open fractures are still considered urgent, and the time for surgery outside regular operating room hours varies between hospitals, depending on the situation and available resources. Our findings align with this view, as we observed no significant difference in infection rates based on the timing of surgery, the mean time to surgery was more than 6 hours in both groups (9.8h for COVID vs 11h for pre-COVID), resulting in the rate of infection at 9%, not higher compared to the overall infection rate from other recent literature (13-18% in long bone fracture).[14,15] The operation can be considered an urgency rather than an emergency condition. Moreover, a systematic review and meta-analysis by Kortram et al.[12] highlighted that factor, like fracture severity, rather than the surgery timing, may have a more significant effect on infection rates. However, there is still a lack of high-quality studies to establish a consensus on the optimal timing for surgery in open fractures.[16]

There were some limitations in our study, such as its retrospective design and the potential for

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selection bias. Additionally, since the study was conducted in a single institution, findings may not be fully applicable to other settings. Some missing information, which is not recorded in the medical data, such as smoking status, was obtained by the researcher through telephone interviews with the patients, which may have been related to issues of recall bias. Some incomplete data, which could affect the surgical outcomes, such as the level of contamination and soft tissue injury, may cause the research findings to be distorted from reality. Therefore, future research should include these details to provide more accurate and reliable conclusions. Furthermore, our study was underpowered to detect small differences in infection, nonunion, and reoperation rates, as indicated by the post hoc power analysis (5%, 18%, and 9%, respectively). Thus, the absence of significant differences does not necessarily exclude a clinically meaningful effect.

CONCLUSION

While the COVID-19 pandemic posed significant challenges in managing open fractures, our study indicates that, despite these challenges, the quality of care for open fracture patients remained consistent. No significant differences were found in the time to receive the surgery or, time to the first dose of antibiotics. The clinical outcomes, such as infection, nonunion, and reoperation, did not show a statistically significant difference. Further research is needed to understand the long-term impact of the pandemic on fracture management and to identify strategies for optimizing care during similar crises. In summary, hospitals should maintain strict standards for prioritizing urgent necessary treatments first, especially in situations with limited resources and risks of infectious outbreaks, to ensure satisfactory treatment outcomes and reduce complications from the care provided.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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Writing – review & editing: P.N.

Data Availability Statement

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

REFERENCES

1. Kindsfater K, Jonassen EA. Osteomyelitis in grade II and III open tibia fractures with late debridement. J Orthop Trauma 1995;9(2):121-7. doi: 10.1097/00005131-199504000-00006.
2. Weber D, Dulai SK, Bergman J, Buckley R, Beaupre LA. Time to initial operative treatment following open fracture does not impact development of deep infection: a prospective cohort study of 736 subjects. J Orthop Trauma 2014;28(11):613-9. doi: 10.1097/bot.0000000000000197.
3. Higgin R, Dean M, Qureshi A, Hancock N. Outcomes following the delayed management of open tibial fractures. Injury 2021;52(8):2434-8. doi: 10.1016/j.injury.2021.05.042.
4. Charalambous CP, Siddique I, Zenios M, Roberts S, Samarji R, Paul A, et al. Early versus delayed surgical treatment of open tibial fractures: effect on the rates of infection and need of secondary surgical procedures to promote bone union. Injury 2005;36(5):656-61. doi: 10.1016/j.injury.2004.10.007.
5. Al-Hourani K, Pearce O, Kelly M. Standards of open lower limb fracture care in the United Kingdom. Injury 2021;52(3):378-83. doi: 10.1016/j.injury.2021.01.021.
6. Gupta R, Singhal A, Kapoor A, Dhillon M, Masih GD. Effect of COVID-19 on surgical management of open fractures and infection rates: a tertiary care experience in Indian set-up. J Clin Orthop Trauma 2021;12(1):16-21. doi: 10.1016/j.jcot.2020.10.050.
7. Gitajn IL, Werth PM, Sprague S, O'Hara N, Della Rocca G, Zura R, et al. Association of COVID-19 with achieving time-to-surgery benchmarks in patients with musculoskeletal trauma. JAMA Health Forum 2021;2(10):e213460. doi: 10.1001/jamahealthforum.2021.3460.
8. O'Hagan P, Drummond I, Lin D, Khor KS, Vris A, Jeyaseelan L. Impact of the COVID-19 pandemic on the management of open fractures in a major trauma centre. J Clin Orthop Trauma 2021;21:101509. doi: 10.1016/j.jcot.2021.101509.
9. Campbell E, Zahoor U, Payne A, Popova D, Welman T, Pahal GS, et al. The COVID-19 pandemic: the effect on open lower limb fractures in a London major trauma centre - a

plastic surgery perspective. Injury 2021;52(3):402-6. doi: 10.1016/j.injury.2020.11.047.

10. Choudhary R, Gupta M, Huq S, Maamoun W. Management of open fractures of the lower limb during the COVID-19 pandemic: are the standards of treatment being maintained? A study from a major trauma centre in England. Int J Res Orthop 2021;7(5):894-900. doi: 10.18203/issn.2455-4510.
11. Prodromidis AD, Charalambous CP. The 6-hour rule for surgical debridement of open tibial fractures: a systematic review and meta-analysis of infection and nonunion rates. J Orthop Trauma 2016;30(7):397-402. doi: 10.1097/BOT.0000000000000573.
12. Kortram K, Bezstarosti H, Metsemakers WJ, Raschke MJ, Van Lieshout EMM, Verhofstad MHJ. Risk factors for infectious complications after open fractures; a systematic review and meta-analysis. Int Orthop 2017;41(10):1965-82. doi: 10.1007/s00264-017-3556-5.
13. Schenker ML, Yannascoli S, Baldwin KD, Ahn J, Mehta S. Does timing to operative debridement affect infectious complications in open long-bone fractures? A systematic review. J Bone Joint Surg Am 2012;94(12):1057-64. doi: 10.2106/JBJS.K.00582.
14. Haile AM, Dagnaw B, Gebeyehu M, Mengesha S, Yoseph T, Nigussie H, et al. Fracture-related infection in open long-bone fractures: a bicenter case-control study in a limited resource country. JB JS Open Access 2025;10(2):e25.00043. doi: 10.2106/JBJS.OA.25.00043.
15. Chebli D, Dhaif F, Ridha A, Schade A, Khatri C. A meta-analysis of the incidence of infections following open tibia fractures and the microorganisms that cause them in high-, middle- and low-income countries. Trop Doct 2024;54(3):272-81. doi: 10.1177/00494755241232171.
16. Foote CJ, Tornetta P 3rd, Reito A, Al-Hourani K, Schenker M, Bosse M, et al. A reevaluation of the risk of infection based on time to debridement in open fractures: results of the GOLIATH meta-analysis of observational studies and limited trial data. J Bone Joint Surg Am 2021;103(3):265-73. doi: 10.2106/JBJS.20.01103. Erratum in: J Bone Joint Surg Am 2021;103(6):e25. doi: 10.2106/JBJS.ER.20.01103.

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REVIEW ARTICLE

Systemic Medications and Their Effects on the Retina and Choroid: An Updated Review

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ABSTRACT

This review provides a comprehensive analysis of systemic medications and illicit substances that can lead to various forms of retinal and choroidal toxicity. Accurate diagnosis requires a detailed medication history and the identification of characteristic retinal changes using multimodal imaging techniques. The discussion includes drugs associated with retinal pigment epithelial disruption, vascular alterations, cystoid macular edema, crystalline deposits, drug-induced retinal folds, and uveitis. The ocular effects of emerging chemotherapeutic and immunotherapeutic agents are also examined. Key mechanisms of action, preventive strategies, and available treatment options are explored in detail. The focus is on medications frequently encountered in ophthalmic practice and important considerations for eye care professionals. Many drug-induced retinal toxicities are reversible with discontinuation of the medication, especially when detected early before causing significant visual impairment. However, certain agents may lead to permanent and progressive retinal damage. Close monitoring and timely intervention by ophthalmologists are essential. This review highlights the importance of early detection and proper management of medication-induced retinal and choroidal toxicity to reduce the risk of vision loss and related complications.

Keywords: crystalline maculopathy, cystoid macular edema, diffuse retinal pigment epithelium changes, retinal and choroidal toxicity, vascular damage

INTRODUCTION

Although posterior segment toxicity is uncommon, it remains a serious complication associated with certain systemic medications. This review examines commonly encountered medications in clinical practice and outlines key considerations for ophthalmologists.

We undertook a thorough PubMed search for English-language articles dating back to January 1960, targeting publications from January 1990 to April 2025. The search employed keywords including “retinal toxicity,” “choroidal toxicity,” “drug-induced retinopathy,” and the names of specific systemic medications known or suspected to affect the retina. Retinal and choroidal toxicities are classified into several main categories, including retinal pigment epithelial (RPE) disruption, maculopathy, vascular damage, crystalline deposits, uveitis, and the toxicity related to illicit substances. A clear understanding of these categories is crucial for clinicians to effectively identify, manage, and reduce the risk of medication-related ocular toxicity. A summary of common systemic medication–induced retinal and choroidal toxicities is provided in Table 1.

Table 1 Summary of Retinal and Choroidal Toxicities Associated with Systemic Medications

Toxicity Categories	Drugs	Findings & Diagnostics	Management / Recommendations
RPE Disruption	HCQ, Chloroquine	Cornea verticillata, parafoveal or pericentral EZ loss, RPE atrophy, pigment mottling, optic atrophy, RP-like changes bull's-eye maculopathy SD-OCT, FAF, HVF 10-2/30-2, mfERG (optional). Asian patients may benefit from wide-field imaging.	Risk increases with > 5.0 mg/kg/day (HCQ), renal impairment, and tamoxifen used. Discontinue if toxicity is suspected. Damage may progress post-cessation.
	Pentosan Polysulfate Sodium	Speckled hypo/hyperautofluorescence around fovea, RPE nodules, outer retinal atrophy, thinning of ONL and choroid. OCT, FAF, NIR imaging.	Baseline and annual screening recommended after 500 g cumulative dose. Discontinue if toxicity is suspected. Damage may progress post-cessation.
	Phenothiazines: Thioridazine, Chlorpromazine	Non-specific macular pigment changes. RPE/choriocapillaris atrophy, vascular narrowing, optic atrophy, pigment plaques. ERG/EOG abnormalities in late stages.	Monitor daily and cumulative dose. Discontinue early if toxicity suspected. Some cases may stabilize or partially improve.
	Deferoxamine	Nyctalopia, visual field loss. Pigmentary retinopathy (minimal, focal, patchy, or speckled patterns), outer retinal deposits, EZ disruption. Rare: CSCR-like changes.	Maximum dose ≤ 50 mg/kg/day. Baseline and regular monitoring. Reduce dose if toxicity occurs.
	MEK inhibitors	Bilateral multifocal serous detachments, often fovea-involving. May mimic CSC but lacks leakage or choroidal thickening. Uveitis, CME, and optic neuropathy, have been reported.	Risk factors include age, impaired renal function, and preexisting eye diseases. Usually self-limited. Conservative management unless persistent. Consider stopping drug if severe.
	FGFR inhibitors	Serous subretinal fluid, pseudovitelliform lesions, EZ disruption. Often asymptomatic. Findings resemble MEK retinopathy.	Monitor with OCT. Often resolves after drug cessation. Long-term effects unknown.
Maculopathy	Nicotinic acid	CME FA typically shows no leakage. Prolonged use may lead to macular atrophy.	Discontinuation or dose reduction usually leads to resolution.
	Antimicrotubule agents	CME FA typically shows no leakage.	Discontinuation or dose reduction usually leads to resolution. Topical or systemic CAI
	Fingolimod	CME FA typically shows no leakage.	Topical anti-inflammatory agents, corticosteroids, CAI, and anti-VEGF

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Table 1 Summary of Retinal and Choroidal Toxicities Associated with Systemic Medications (cont.)

Toxicity Categories	Drugs	Findings & Diagnostics	Management / Recommendations
Vascular damage	Talc	Capillary nonperfusion, microaneurysms, cotton-wool spots, and retinal neovascularization.	Discontinue intravenous drug use, Manage ischemia or neovascularization (e.g., anti-VEGF, PRP if needed)
	OCP	May induce a hypercoagulable state, potentially leading to retinal vein/artery occlusion or ischemic optic neuropathy.	Discontinue OCP if event occurs Consider alternative contraception
	Interferon	Cotton-wool spots, hemorrhages, CME, and vascular occlusions	Retinal findings typically improve after discontinuation of the drug.
	Ergot Alkaloids	Particularly at high doses, can cause retinal vasospasm and ischemia.	Stop medication Consider vasodilator therapy if needed
Crystalline deposits	Tamoxifen	May cause dyschromatopsia, visual loss crystalline deposits, CME (dose-dependent), disruption of EZ, OCTA: right-angled vessels, deep capillary plexus changes (MacTel2-like)	Eye exam every 6 months if on > 20 mg/day > 2 yrs Consider stopping drug if symptomatic Manage CME with anti-VEGF, steroids, or oral CAIs
	Canthaxanthin	Crystalline maculopathy Often asymptomatic	Deposits resolve slowly after discontinuation
	Methoxyflurane	Crystalline retinopathy, cotton-wool spots possible	Avoid in renal impairment Discontinue if toxicity evident
Uveitis	Checkpoint inhibitors	Uveitis (anterior, posterior, panuveitis) VKH-like, Behçet-like features	Topical/local/systemic steroids as needed Continue therapy if responsive
	BRAF inhibitors	Anterior uveitis most common VKH-like posterior uveitis and panuveitis also reported	Topical/local/systemic steroids as needed Continue therapy if responsive

Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine kinase; CAI, carbonic anhydrase inhibitors; CME, cystoid macular edema; CSC or CSCR, central serous chorioretinopathy; EOG, electrooculography; ERG, electroretinography; EZ, ellipsoid zone; FA, fluorescein angiography; FAF, fundus autofluorescence; FGFR, fibroblast growth factor receptor; HCQ, hydroxychloroquine; HVF 10-2/30-2, Humphrey visual field 10-2 or 30-2 testing pattern; HVF, Humphrey visual field; MacTel2, macular telangiectasia type 2; MEK, mitogen-activated protein kinase/extracellular signal–regulated kinase pathway; mfERG, multifocal electroretinography; NIR, near-infrared reflectance; OCP, oral contraceptives; OCT, optical coherence tomography; OCTA, optical coherence tomography angiography; ONL, outer nuclear layer; PRP, panretinal photocoagulation; RP, retinitis pigmentosa; RPE, retinal pigment epithelium; SD-OCT, spectral-domain optical coherence tomography; VEGF, vascular endothelial growth factor; VKH, Vogt–Koyanagi–Harada syndrome

Toxicity Related to Retinal Pigment Epithelial Disruption

Chloroquine Derivatives: Chloroquine, Hydroxychloroquine

Chloroquine, a 4-aminoquinoline drug, is primarily used for malaria treatment and prevention, as well as certain inflammatory conditions.[1] Hydroxychloroquine, a related compound with better safety, is Food and Drug Administration-approved for systemic lupus erythematosus, rheumatoid arthritis, and malaria prophylaxis, and has largely replaced chloroquine. Both drugs accumulate in melanin-rich tissues, particularly the RPE and uveal tissues.[2] The mechanism of toxicity is unclear but may involve RPE lysosomal dysfunction leading to photoreceptor loss, inhibition of retinol recycling, and direct retinal toxicity.[3-5] Hydroxychloroquine toxicity is dose- and duration-dependent, with early signs including cornea verticillata and subtle macular changes that can progress to bull's-eye maculopathy, marked by a ring of depigmentation surrounding the fovea.[6] Advanced toxicity may mimic retinitis pigmentosa, with pigment mottling, vascular attenuation, optic atrophy, and bone spicule formation.[7] Hydroxychloroquine toxicity has an estimated prevalence of 7.5%, with variations influenced by daily dosage and duration of use.[8] Current recommendations limit hydroxychloroquine to ≤ 5.0 mg/kg/day and chloroquine to ≤ 2.3 mg/kg/day, based on actual body weight[7]. In individuals of shorter stature, particularly those 5 feet 2 inches (157 cm) or below, careful dosage calculation based on ideal body weight is essential to prevent excessive drug exposure. For chloroquine, toxicity is more likely above 2.3 mg/kg/day, with risk rising after cumulative doses of 100–300 g. Patients of shorter stature require careful dosing to avoid overdosing.

Spectral-domain optical coherence tomography (SD-OCT) is a key imaging modality for detecting retinal toxicity, revealing structural changes such as outer nuclear layer thinning, outer segment hyperreflectivity, and ellipsoid zone (EZ) disruption. Fundus autofluorescence (FAF) is particularly sensitive for early detection, often showing a paracentral hyperautofluorescent ring that progresses to pericentral mottled hypoautofluorescence with hyper-autofluorescent borders, and eventually to complete pericentral signal loss in advanced cases.[9] Patterns of retinal toxicity vary across ethnic groups. Asian patients may develop peripheral retinal damage **(Figure 1)**, making ultrawide-field FAF a crucial diagnostic tool. In contrast, African American, Hispanic, and European patients predominantly exhibit a parafoveal damage pattern, though African American and Hispanic individuals may have a higher likelihood of extramacular involvement.

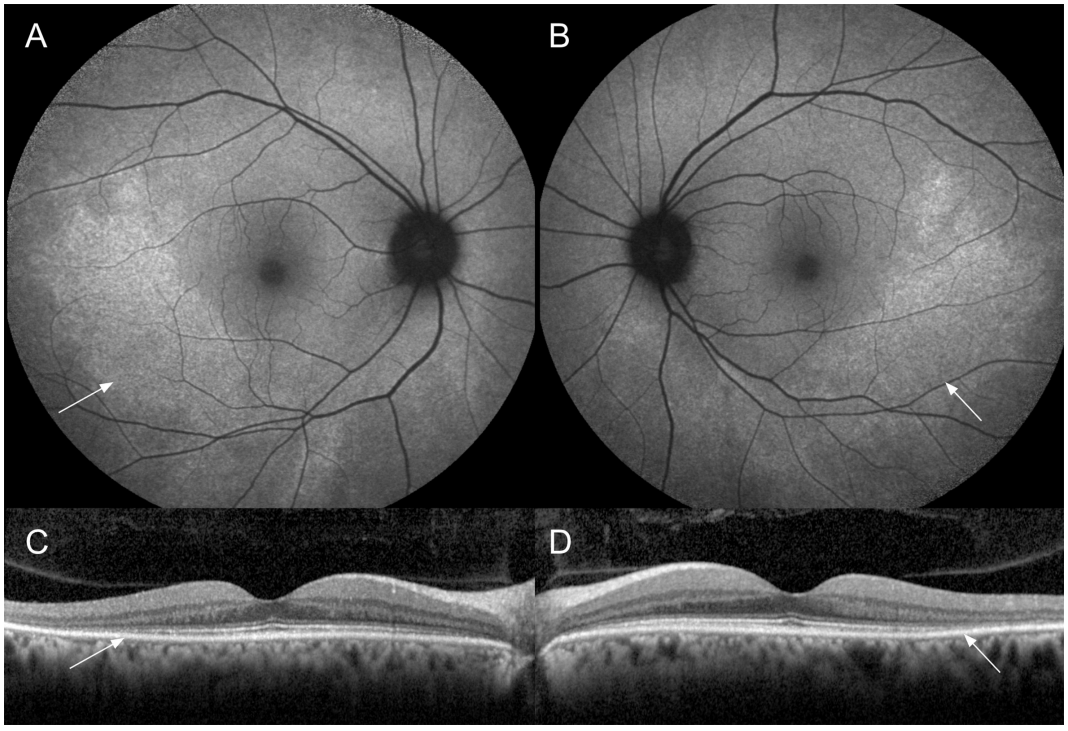

Figure 1 (A-B) Fundus autofluorescence shows perifoveal hyperautofluorescence of both eyes indicative of hydroxychloroquine toxicity in an Asian patient. (C-D) Spectral-domain optical coherence tomography reveals outer retinal thinning corresponding to the FAF abnormalities, consistent with chronic hydroxychloroquine-induced retinal damage.

The multifocal electroretinogram (mfERG) is the most sensitive test for hydroxychloroquine toxicity, detecting functional abnormalities even when fields, SD-OCT, and full-field ERG are normal.[7, 9] Abnormalities may appear as foveal, paracentral, peripheral, or generalized dysfunction. While not used for routine screening, mfERG supports multimodal imaging for reliable detection and monitoring.[9, 10]

The estimated risk of hydroxychloroquine toxicity is 1% after 5-7 years or a cumulative dose of 1000 g, rising to 20% after 20 years.[11,12] Chloroquine, due to its slow excretion, can remain in the body for years and has been linked to delayed-onset retinopathy even seven years post-cessation. In addition to dose and duration, risk factors include renal impairment, which prolongs drug clearance; concurrent tamoxifen use, which increases toxicity risk; and pre-existing retinal disease. Age, liver dysfunction, and genetic predisposition may also contribute.[7] Routine screening is vital for early detection. The 2016 American Academy of Ophthalmology (AAO) guidelines advise a baseline exam within the first year of therapy and annual screening after five years, or sooner in high-risk patients. Standard tests include SD-OCT and Humphrey Visual Field (HVF) 10-2, with HVF 24-2 or 30-2 preferred in Asian populations due to peripheral involvement. FAF and mfERG can detect subtle changes not seen with other modalities. If toxicity is suspected, prompt drug discontinuation is recommended; mild to moderate cases may stabilize, but severe disease can progress despite cessation. mfERG changes may show partial recovery. Ophthalmologists play a central role in counseling, risk assessment, and long-term monitoring. Updated AAO screening guidelines are expected in late 2025.

Pentosan Polysulfate Sodium

Pentosan Polysulfate Sodium (PPS) is commonly prescribed for the management of interstitial cystitis, a condition predominantly affecting women.[7] Early manifestations of PPS-related toxicity appear to originate in the RPE, leading to RPE thickening followed by progressive photoreceptor degeneration and RPE atrophy. This pathological progression differs from hydroxychloroquine-induced toxicity, which initially presents as pericentral EZ disruption or loss, followed by subsequent RPE damage and atrophy in later stages.[13]

The pathophysiology of PPS-associated maculopathy remains unclear, particularly whether RPE damage is primary or secondary to choroidal involvement. Recent studies suggest a potential choroidal role, with observed reductions in stromal choroidal area and increased choroidal vascular index in affected eyes.[14] Multimodal imaging is essential for detecting characteristic features of PPS toxicity. OCT findings range from early hyper-reflective RPE nodules to advanced RPE and outer retinal atrophy. FAF often shows a speckled pattern of hypo- and hyperautofluorescence radiating around the fovea **(Figure 2)**. Near-infrared reflectance (NIR) imaging can highlight punctate RPE changes and may be more sensitive than FAF in early disease.

Patients with cumulative doses exceeding 1500 g are at an increased risk of developing toxicity, though cases have been documented with doses as low as 435 g.[15] A baseline ophthalmic evaluation with OCT, FAF, and NIR is recommended at therapy initiation, with annual imaging starting at 500 g cumulative dose.[16] If toxicity is identified, PPS should be discontinued immediately, as retinal damage may be irreversible and progressive even after cessation. A prospective study of 26 eyes with PPS-associated maculopathy showed continued progression over 13 to 30 months, with a median lesion enlargement rate of 0.42 mm/year and significant thinning of the central macula, nuclear layers, and subfoveal choroid. New areas of RPE atrophy developed, and existing lesions expanded, highlighting the need for long-term follow-up after drug cessation.[17]

Phenothiazines

Phenothiazines are commonly used to treat psychotic disorders. Thioridazine, though effective, has been withdrawn in some regions due to its association with cardiac arrhythmias but remains available in certain countries.[7] Chlorpromazine, lacking the piperidyl side chain of thioridazine, has much lower retinal toxicity. Both drugs bind strongly to melanin, causing pigmentation of the skin, conjunctiva, cornea, lens, and retina, but not all phenothiazines are retinotoxic.[18] Early manifestations of thioridazine toxicity often present as non-specific pigmentary changes in the macula, which may advance to extensive nummular atrophy of the RPE and choriocapillaris[19] **(Figure 3)**. Early findings include mild field constriction or paracentral/ring scotomas, with ERG and EOG abnormalities in advanced disease.[20] Late stages show vascular narrowing, optic atrophy, and patchy depigmentation with hyperpigmented plaques.[21]

Chlorpromazine toxicity is rare but has been reported with prolonged high-dose use (e.g., 2400 mg/day for one year), presenting as pigmentary retinopathy, vessel attenuation, and optic pallor.[22] Thioridazine toxicity is dose-dependent, sometimes occurring within two weeks

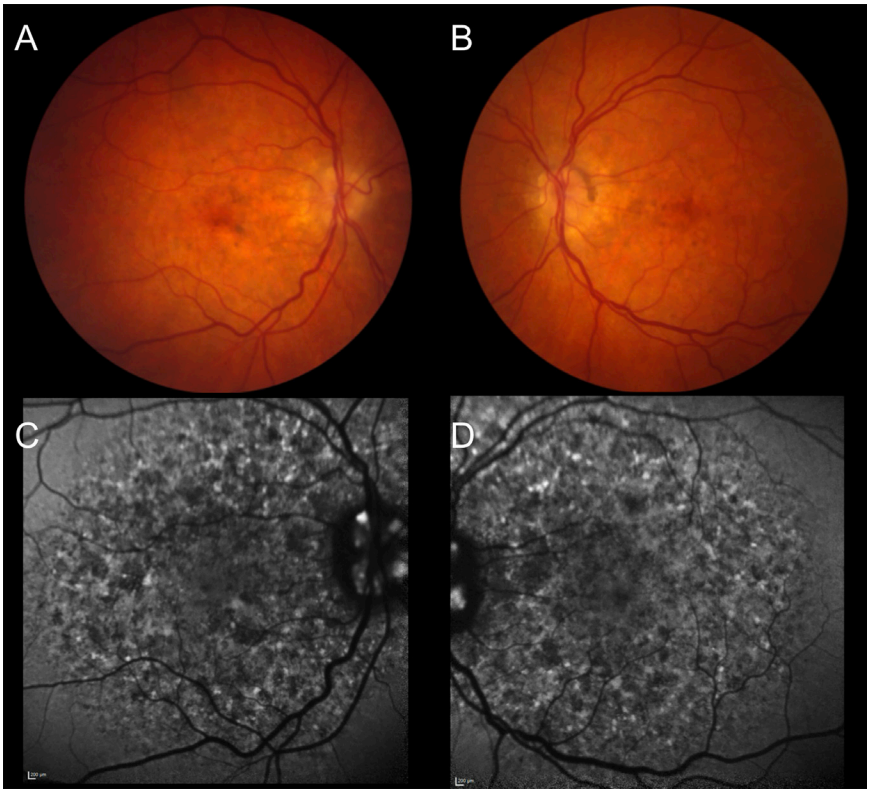

Figure 2 (A-B) Color fundus photographs and (C-D) fundus autofluorescence of both eyes show a speckled pattern of hypoautofluorescence and hyperautofluorescence corresponding to these RPE changes associated with pentosan polysulfate sodium (PPS)–related maculopathy.

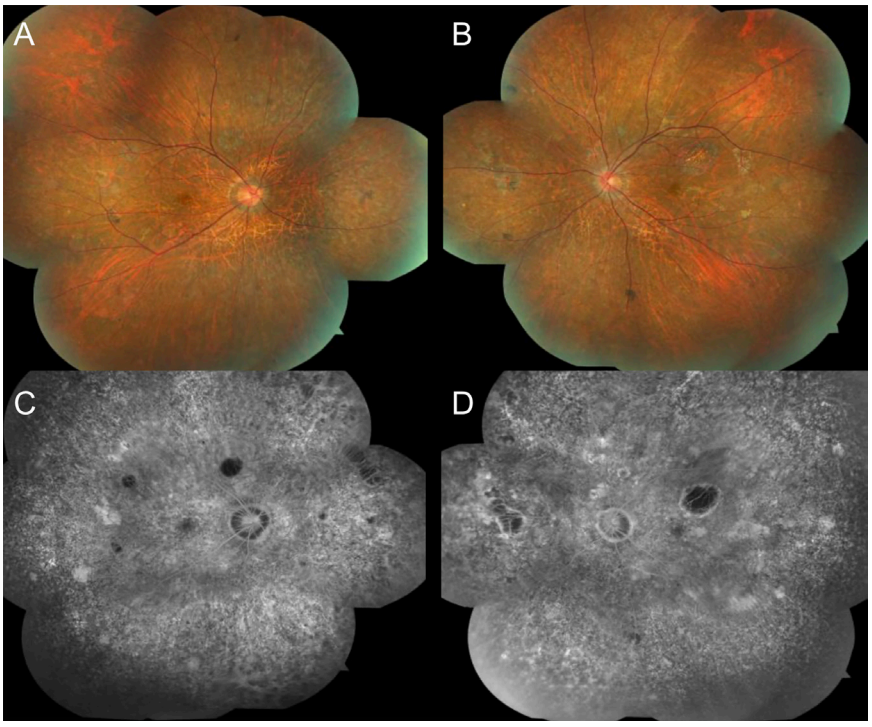

Figure 3 (A-B) Wide-angle color fundus photographs and (C-D) fluorescein angiography of both eyes showing diffuse granular pigment stippling and nummular pigment loss and choriocapillaris disruption as a thioridazine toxicity.

at high doses; risk is lower below 800 mg/day, but cumulative exposure remains important. Early drug cessation may stabilize or partly improve vision, though progression can still occur due to prior retinal injury.

Deferoxamine

Deferoxamine, an iron- and aluminum-chelating agent used in thalassemia and aplastic anemia, can rarely cause retinal toxicity, possibly via copper depletion in the RPE. Clinical signs include progressive vision loss, nyctalopia, and visual field defects, with pigmentary retinopathy as the hallmark. Early findings may show grayish macular discoloration, later progressing to diffuse pigmentary change. OCT typically reveals hyperreflective outer retinal deposits or Bruch's–RPE interface changes, leading to EZ disruption and photoreceptor thinning.[23] FAF patterns have been classified as minimal, focal, patchy, or speckled.[24] Rarely, bilateral central serous chorioretinopathy (CSC) has also been reported.[25] To reduce risk, adult dosing should not exceed 50 mg/kg/day.[26] While no formal guidelines exist, baseline and regular ophthalmic screening is recommended. If discontinuation is not feasible, dose reduction may help limit retinal damage.

Mitogen-Activated Protein Kinase Inhibitors

Mitogen-activated protein kinase (MEK) inhibitors (trametinib, cobimetinib, binimetinib) treat metastatic melanoma with BRAF mutations by blocking the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway. Retinal toxicity is dose-dependent and often reversible, even without stopping treatment. Risk factors include age, impaired renal function, and preexisting eye disease.[27] RPE dysfunction may lead to subretinal fluid via outer blood-retinal barrier disruption.[28] MEK inhibitors are most frequently associated with bilateral multifocal serous retinal detachments, with at least one detachment involving the fovea[7] **(Figure 4)**. Despite clinical evidence of retinal toxicity, some patients on MEK inhibitors remain asymptomatic.[6] Additional ocular manifestations, including uveitis, cystoid macular edema (CME), and optic neuropathy,

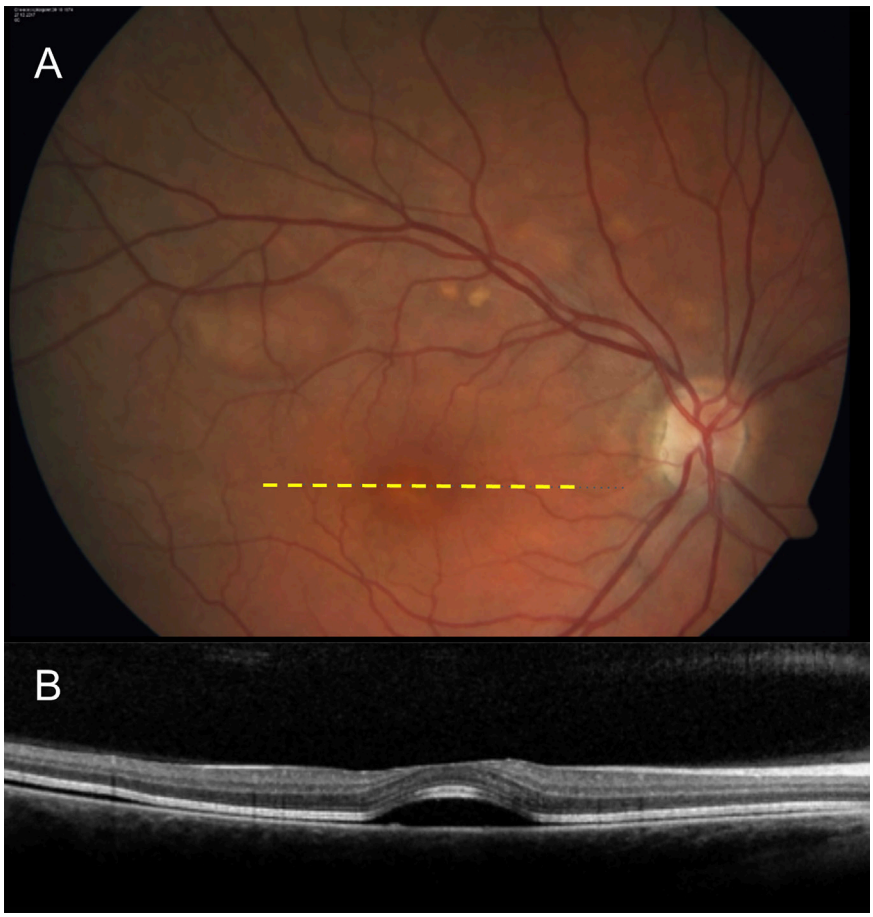

Figure 4 (A) Color fundus photographs of right eye reveal localized serous retinal detachments following initiation of MEK inhibitor therapy for metastatic melanoma. (B) Spectral-domain optical coherence tomography demonstrates shallow, loculated subretinal fluid predominantly in the subfoveal region.

have been reported. MEK inhibitor–associated serous retinal detachments may mimic CSC, but lack hallmark CSC features such as RPE defects, choroidal thickening, or leakage on FAF, fundus fluoresceine (FA), and SD-OCT. SD-OCT is the most informative modality, with four described fluid patterns: dome-shaped (most common), caterpillar-like, wavy, and splitting.[29] Management is usually conservative, as subretinal fluid often resolves spontaneously. Symptoms are typically mild and appear within days of treatment. Persistent cases may require drug discontinuation. Corticosteroids or NSAIDs can be used for associated uveitis or macular edema.[30]

Fibroblast Growth Factor Receptor Inhibitors

Fibroblast growth factor receptor (FGFR) inhibitors, approved for cholangiocarcinoma and urothelial carcinoma, include erdafitinib, pemigatinib, and infigratinib. Acting upstream of MEK, they can cause serous retinal detachments resembling MEK inhibitor–associated retinopathy. Though rare, FGFR-related retinopathy is documented: in an AZD4547 trial, subretinal fluid occurred in 22% of eyes. Reported cases with erdafitinib showed pseudovitelliform lesions, OCT changes, and bilateral serous detachments, often asymptomatic and sometimes resolving spontaneously without stopping therapy.[31] Pemigatinib has similarly been linked to multifocal serous detachments, resolving within days of drug cessation.[32] The long-term retinal effects of FGFR inhibitors remain uncertain, highlighting the need for further studies and clear monitoring guidelines.

Toxicity Related to Maculopathy

Nicotinic Acid

Niacin (nicotinic acid), used to lower lipids, can rarely cause retinal toxicity. Patients may present with blurred vision, metamorphopsia, or paracentral scotomas.[33] OCT typically shows cystoid spaces in the inner nuclear and outer plexiform layers, while FA reveals no leakage. The mechanism may involve direct Müller cell toxicity and selective blood-retinal barrier disruption. Most cases resolve after discontinuation or dose reduction,[34] but prolonged use with persistent edema can lead to macular atrophy.

Antimicrotubule Agents

Paclitaxel and docetaxel are widely used in the treatment of various malignancies, including breast, lung, and prostate cancer. Both agents have been linked to the development of CME, which typically lacks leakage on FA.[35] The proposed mechanism involves Müller cell dysfunction and subclinical extracellular fluid accumulation, like niacin-induced toxicity. Macular edema often resolves following drug discontinuation, and treatment with topical or systemic carbonic anhydrase inhibitors may also be beneficial[36, 37] **(Figure 5)**.

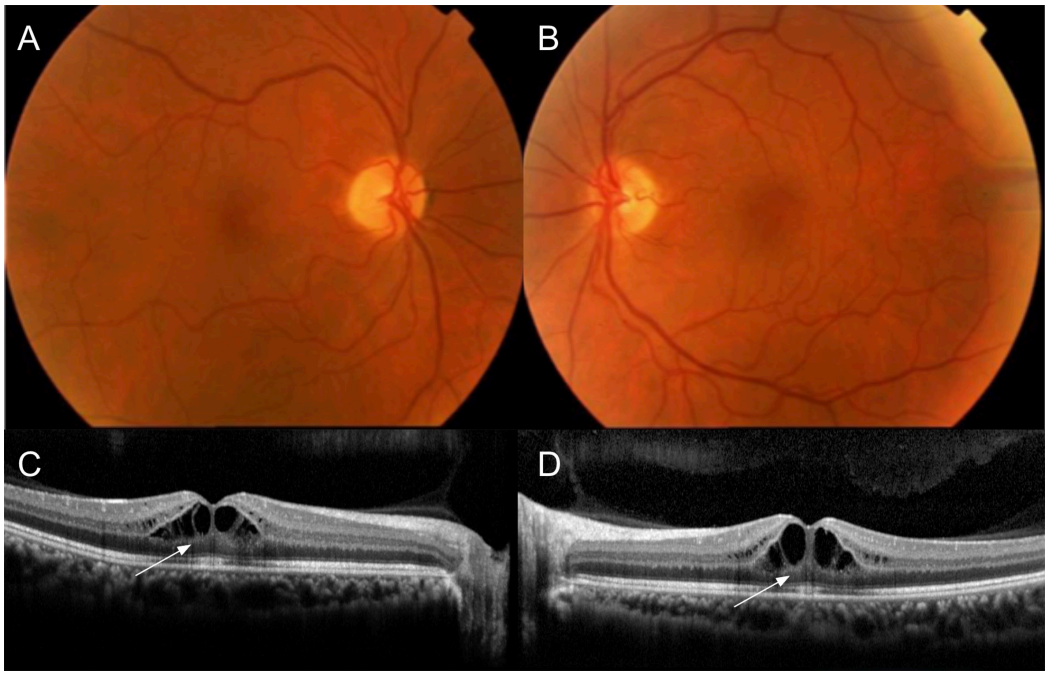

Figure 5 (A-B) Color fundus photographs and (C-D) Spectral-domain optical coherence tomography of both eyes revealing bilateral cystoid macular edema associated with paclitaxel therapy.

Fingolimod

Fingolimod, a disease-modifying agent for relapsing-remitting multiple sclerosis, acts via modulation of the sphingosine-1-phosphate receptor. A notable ocular adverse effect is fingolimod-associated macular edema (FAME), caused by blood-retinal barrier disruption, leading to protein leakage and osmotic fluid accumulation within the retina. FAME is a dose-dependent adverse effect, most reported at the standard dose of 0.5 mg daily, and generally resolves after drug discontinuation.[38] However, there is no established consensus on the optimal management approach beyond stopping the medication. Treatments that have shown potential efficacy in promoting FAME resolution include topical anti-inflammatory agents, corticosteroids, carbonic anhydrase inhibitors, and anti-vascular endothelial growth factor (VEGF) therapy.[39-42]

Toxicity Related to Vascular Damage

Talc

Talc, an inactive component of medications such as methylphenidate and methadone, can cause retinal toxicity in intravenous drug users who inject crushed tablets. Repeated injections allow talc particles to enter systemic circulation and embolize to the retina. Emboli lodge in small arterioles, producing ischemic retinopathy with capillary nonperfusion, microaneurysms, cotton-wool spots, and, in advanced stages, retinal neovascularization.[43] Management centers on patient counseling and cessation of intravenous drug use to stabilize findings and prevent progression.[44,45]

Oral Contraceptives

Contraceptive pills containing estrogen (typically ethinylestradiol at 20-40 μg per day) or progestin may induce a hypercoagulable state, with estrogen posing a higher risk. Retinal vascular occlusions have been reported in young women using these agents, particularly those on higher-dose formulations (≥ 30-40 μg).[46] Documented complications include central retinal vein occlusion, retinal and cilioretinal artery occlusion, superior ophthalmic vein thrombosis, and anterior ischemic optic neuropathy.[47-49] Although the evidence remains inconclusive, large-scale studies suggest an increased prevalence of retinal vascular abnormalities among contraceptive pill users.[50]

Interferon

Interferon alpha-2a is an antiviral and immunomodulatory agent used to treat melanoma, renal cell carcinoma, lymphoma, leukemia, and chronic hepatitis C. While generally well tolerated,[51] it has been associated with retinal vascular toxicity, often presenting as cotton-wool spots and intraretinal hemorrhages with preserved visual acuity **(Figure 6)**. In some cases, more severe complications such as vascular occlusion, CME or non-arteritic anterior ischemic optic neuropathy can occur.[52-54] The proposed mechanism involves impaired retinal microcirculation due to leukocyte adhesion and entrapment in the vasculature.[55] Patients with diabetes or hypertension are at higher risk. Retinal findings typically improve after discontinuation of the drug.[56]

Ergot Alkaloids

Ergot alkaloids, particularly ergotamine, have been associated with retinal toxicity, presenting as retinal vasculopathy, ischemia, and potential vision loss. These effects are primarily attributed to vasospasm and reduced retinal blood flow, especially when used at higher-than-recommended doses, which can lead to retinal vasoconstriction.[57]

Toxicity Related to Crystalline Deposits

Tamoxifen

Tamoxifen, a selective estrogen receptor modulator, is widely used for estrogen receptor–positive breast cancer and has been studied in other malignancies such as glioblastoma. Retinal toxicity occurs in 0.9-12% of patients on standard doses (10-20 mg/day), usually after 2-3 years, but higher daily (60-100 mg) or cumulative doses (> 100 g) may cause earlier onset.[58] Tamoxifen retinopathy is often asymptomatic but may result in vision loss or dyschromatopsia.[59] Typical findings include crystalline retinopathy with intraretinal crystals, CME, and pigmentary changes **(Figure 7)**. FAF may be normal or show mixed autofluorescence, while OCT reveals hyperreflective inner retinal deposits and disruption of the ELM, ellipsoid, and interdigitation zones. CME is dose-dependent, with lower doses more often linked to cysts than frank edema. Early OCT/ Optical Coherence Tomography Angiography features may mimic macular telangiectasia type 2 (MacTel type 2), including deep plexus alterations, right-angled vessels, and Müller cell dysfunction.

Regular ophthalmic evaluation is recommended for patients on tamoxifen, particularly those who remain asymptomatic but require continued treatment for systemic malignancies. Follow-up exams every six months are advised, particularly for patients receiving 20 mg/day of tamoxifen for two years or longer.[60] In symptomatic cases, consultation with an oncologist is necessary to assess the risk-

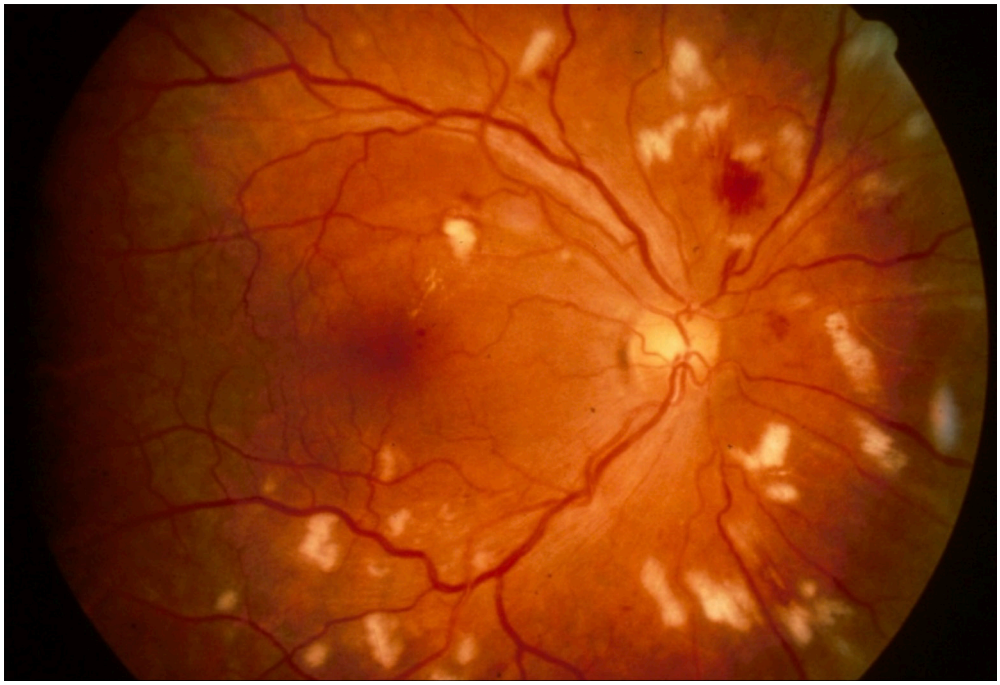

Figure 6 Color fundus photograph of right eye demonstrating cotton-wool spots and intraretinal hemorrhages associated with interferon alpha-2a toxicity.

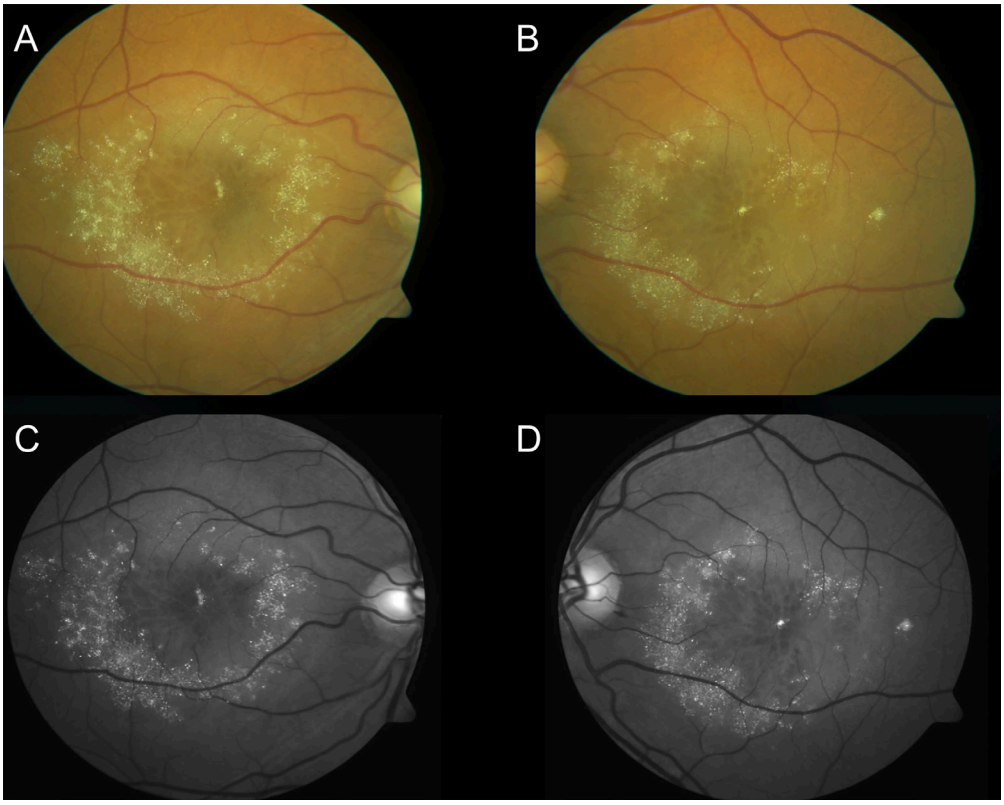

Figure 7 (A-B) Color fundus photographs of of both eyes reveal crystalline deposits at the macula. (C-D) Blue light reflectance imaging highlights punctate hyperreflective foci surrounding the macula, consistent with crystalline retinopathy secondary to tamoxifen toxicity.

benefit ratio of discontinuing the drug, as cessation often leads to improvement in visual function and resolution of edema. Management strategies for CME include intravitreal anti-VEGF therapy, intravitreal corticosteroids, and oral carbonic anhydrase inhibitors.[61, 62]

Canthaxanthine

Canthaxanthin, a carotenoid used for treating photo-sensitivity disorders and as an oral tanning agent or food additive, has been primarily associated with retinal toxicity in the context of sun-tanning use. Crystalline retinal deposits are thought to result from Müller cell atrophy and inner retinal spongy degeneration.[63] While many cases remain asymptomatic, prolonged high-dose use (total dose > 19 g generally over a 2-year timeframe) can lead to yellow-orange crystals forming a macular ring.[6] These deposits resolve slowly after discontinuation, with clearance potentially taking up to two decades. Electrophysiologic studies suggest gradual functional retinal recovery following cessation.[64]

Methoxyflurane

Methoxyflurane, a volatile anesthetic, can cause renal failure from calcium oxalate deposition, particularly in kidney impairment. Retinal involvement manifests as crystalline retinopathy with yellow-white macular or arteriolar deposits, sometimes with cotton-wool spots. Histology shows crystal accumulation in the RPE and inner retina.[65]

Toxicity Related to Uveitis

Checkpoint Inhibitors

Checkpoint inhibitors—including Programmed Cell Death protein 1 (pembrolizumab, nivolumab), Programmed Cell Death Ligand 1 (atezolizumab, avelumab, durvalumab), and Cytotoxic T-Lymphocyte Associated protein-4 (ipilimumab)—enhance antitumor immunity by blocking inhibitory pathways. Initially approved for metastatic melanoma, they are now used in multiple cancers. Their immune-modulating effects may trigger ocular autoimmunity,[66] typically within weeks to months of therapy. Reported complications include dry eye, myasthenia-like ophthalmopathy, uveitis, and syndromes resembling Vogt-Koyanagi-Harada (VKH) **(Figure 8)**, Behçet's disease, and uveal effusion.[67] Management requires coordination between oncologists and ophthalmologists. Most uveitis cases respond to topical steroids, while severe inflammation may require intraocular implants, periocular injections, or systemic therapy. Immunotherapy discontinuation is rarely necessary and reserved for severe or refractory cases.

BRAF Inhibitors

BRAF inhibitors, including vemurafenib and dabrafenib, are approved for metastatic cutaneous melanoma and are often combined with MEK inhibitors. Anterior uveitis is the most common ocular adverse effect, though VKH-like uveitis and panuveitis have also been reported.[68,69] The mechanism may involve immune responses against melanocyte-associated antigens shared by melanoma and choroidal tissue. Most cases respond well to topical, local, or systemic corticosteroids without requiring discontinuation of therapy. However, in rare cases with persistent vision loss, stopping the drug may be necessary.

Miscellaneous

Sulfa Drugs

Sulfa-containing drugs such as sulfonamides, acetazolamide, hydrochlorothiazide, and topiramate can cause ocular effects involving the ciliary body and choroid, including edema, choroidal effusion, and lens swelling. These changes may lead to transient myopia, retinal folds, shallow anterior chamber, or angle-closure glaucoma. FA typically shows no vascular leakage, suggesting that retinal folds are due to vitreous traction from axial changes rather than vascular pathology. These effects are usually reversible upon drug discontinuation.[70]

Phosphodiesterase-5 Inhibitors

Phosphodiesterase-5 (PDE-5) inhibitors, such as sildenafil, are used for pulmonary hypertension and erectile dysfunction by enhancing cyclic guanosine monophosphate-mediated smooth muscle relaxation. They also inhibit retinal PDE-6, disrupting phototransduction and sodium channel regulation in photoreceptors. Reported ocular effects include anterior ischemic optic neuropathy, subretinal hemorrhage, CSC, and extraocular muscle palsy. A common dose-dependent effect is bluish dyschromatopsia, typically appearing 1-2 hours post-dose. OCT in long-term or high-dose use may reveal EZ hyperreflectivity or disruption.[71] While most visual symptoms resolve within 24 hours, rare cases of persistent photoreceptor damage lasting up to a year have been described.

Alkyl Nitrites

Alkyl nitrites ("poppers") are volatile recreational drugs linked to retinal toxicity, particularly after the 2006 UK switch from isobutyl to isopropyl nitrite, though amyl

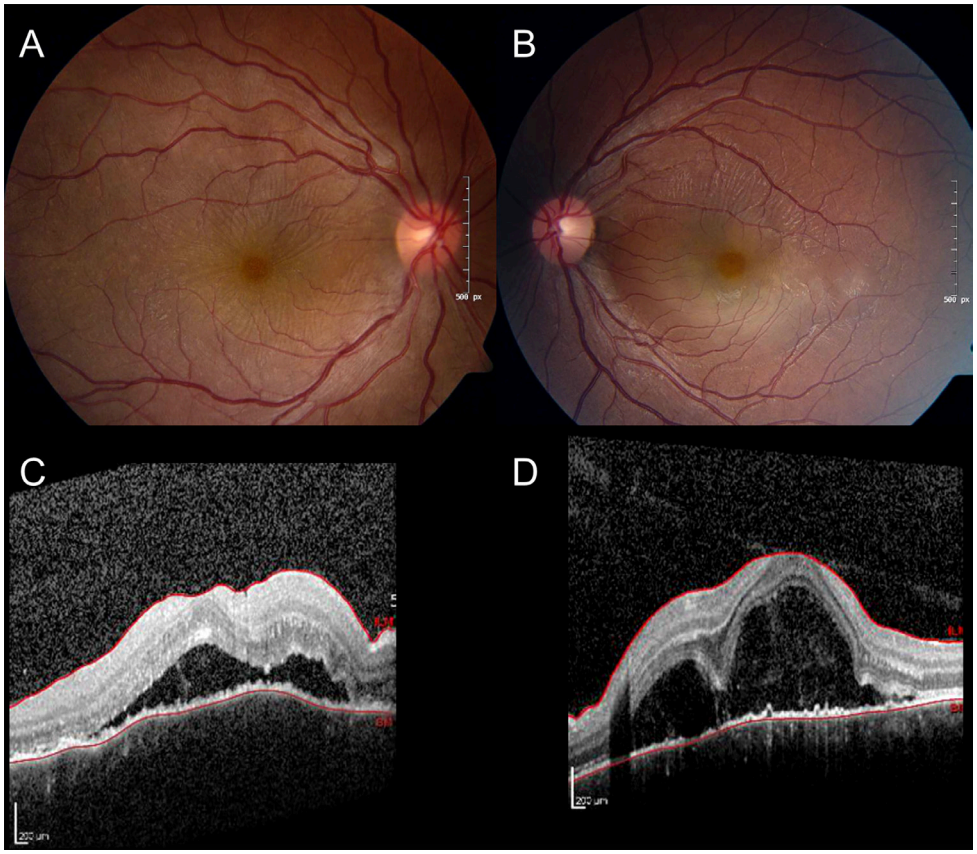

Figure 8 (A-B) Color fundus photographs of both eyes showing central macular striae and subretinal fluid. (C-D) Optical coherence tomography from another patient receiving checkpoint inhibitor therapy demonstrates subretinal fluid consistent with a Vogt-Koyanagi-Harada (VKH)-like presentation.

isobutyl nitrite has also been implicated. The proposed mechanism involves nitric oxide–mediated photoreceptor dysfunction.[72] Patients typically present with central visual disturbances (blurred vision, scotomas, metamorphopsia, phosphenes). Fundus findings range from normal to yellow foveal lesions, but OCT is most sensitive, revealing photoreceptor disruption, vitelliform-like deposits, or outer retinal microholes. As the condition may mimic photic injury, a detailed history of exposures is essential. Symptoms often improve with drug cessation, but structural retinal changes usually persist, and complete recovery is uncommon.[69]

Anaplastic Lymphoma Kinase Inhibitors

Anaplastic lymphoma kinase (ALK) inhibitors, including crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, and entrectinib, are targeted therapies for non-small cell lung carcinoma. The most common ocular side effect is impaired light-dark adaptation, often presenting as light trails following moving objects.[73] Other symptoms include blurred vision, photopsia, photophobia, floaters, diplopia, accommodation difficulty, and visual field defects. Structural changes such as macular edema, cataracts, and vitreous detachment have also been reported. These visual disturbances typically improve over time without requiring dose adjustment.

Illicit and Controlled Substances

Cocaine

Cocaine, derived from the Erythroxylon coca plant, exerts potent vasoconstrictive effects through benzoylmethylecgonine, a vasoactive metabolite that enhances sympathetic activity by blocking sodium channels. These physiological effects can lead to ocular complications, including retinal hemorrhages, alterations in vessel caliber, microvascular changes, and vascular occlusions **(Figure 9)**. Cocaine use has also been associated with acute macular neuroretinopathy, retinal vasculitis, posterior uveitis, and frosted branch angiitis.[74] However, differentiating these manifestations from those

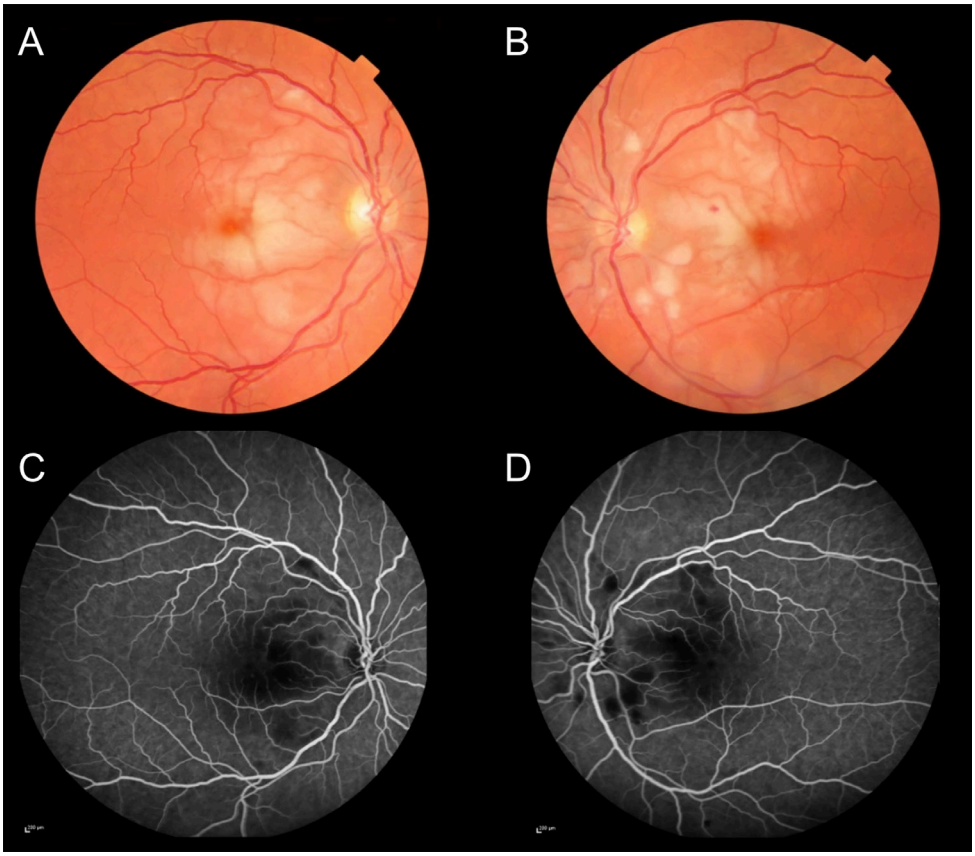

Figure 9 (A-B) Color fundus photographs and fluorescein angiography of both eyes eyes reveal multiple cotton wool spots and corresponding areas of blockage on angiography (C-D), consistent with Purtscher-like retinopathy in a patient with a history of cocaine use.

caused by other systemic conditions such as inflammation, trauma, hypotension, or eclampsia is often difficult. A detailed clinical history, including inquiry into substance use, is essential for accurate diagnosis and appropriate management.

Methamphetamine

Methamphetamine, a potent psychostimulant related to amphetamine, produces sympathomimetic effects and systemic cardiovascular and neurological complications. Ocular toxicity, reported in both humans and animal models, includes anophthalmia, microphthalmia, retinal folding, optic disc hypoplasia, scleritis, crystalline retinopathy, vascular occlusions, hemorrhages, and vasculitis.[72] These effects likely stem from oxidative stress and vascular spasm, causing vasoconstriction, ischemia, and retinal vascular injury.[75]

Cannabis and Cannabinoids

Cannabis is widely used and linked to ocular effects including eyelid tremors, ptosis, corneal opacification, reduced corneal healing, and retinal vascular changes. Mediated via CB1/CB2 receptors, it has been associated with branch retinal artery occlusion, central retinal vein occlusion, and hemorrhagic macular infarction.[73] Once considered for glaucoma therapy, it is no longer recommended due to only transient IOP reduction.[76]

CONCLUSION

A wide range of systemic medications, both prescribed and illicit, can cause retinal and choroidal toxicity. Diagnosis often depends on recognizing characteristic retinal patterns, making a thorough drug and substance use history essential. Toxicity may occur at any dose level. Illicit substances like methamphetamine, cocaine, and synthetic cannabinoids are increasingly implicated. As new agents emerge, clinicians must stay vigilant. Prompt identification and withdrawal of the offending drug are key to preserving vision. However, in some cases—such as with hydroxychloroquine and PPS—retinal toxicity may persist or even progress despite discontinuation, underscoring the need for early detection and long-term monitoring.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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Project administration: TK
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Writing – review & editing: TK

REFERENCES

1. Stokkermans TJ, Falkowitz DM, Trichonas G. Chloroquine and hydroxychloroquine toxicity. In: StatPearls, editor. StatPearls Publishing; 2024.
2. Bernstein H, Zvaifler N, Rubin M, Mansour AM. The ocular deposition of chloroquine. Invest Ophthalmol 1963;2(4):384-92.
3. Ivanina TA, Zueva MV, Lebedeva MN, Bogoslovsky AI, Bunin AJ. Ultrastructural alterations in rat and cat retina and pigment epithelium induced by chloroquine. Graefes Arch Clin Exp Ophthalmol 1983;220(1):32-8. doi: 10.1007/BF02307013.
4. Pasadhika S, Fishman GA, Choi D, Shahidi M. Selective thinning of the perifoveal inner retina as an early sign of hydroxychloroquine retinal toxicity. Eye (Lond) 2010;24(5):756-62. doi: 10.1038/eye.2010.21.
5. Xu C, Zhu L, Chan T, Lu X, Shen W, Madigan MC, et al. Chloroquine and hydroxychloroquine are novel inhibitors of human organic anion transporting polypeptide 1A2. J Pharm Sci 2016;105(2):884-90. doi: 10.1002/jps.24663.
6. Somisetty S, Santina A, Sarraf D, Mieler WF. The impact of systemic medications on retinal function. Asia Pac J Ophthalmol (Phila) 2023;12(2):115-57. doi: 10.1097/APO.0000000000000605.
7. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 Revision). Ophthalmology 2016;123(6):1386-94. doi: 10.1016/j.ophtha.2016.01.058.
8. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. JAMA Ophthalmol 2014;132(12):1453-60. doi: 10.1001/jamaophthalmol.2014.3459.
9. Kellner U, Renner AB, Tillack H. Fundus autofluorescence and mfERG for early detection of retinal alterations in patients using chloroquine/hydroxychloroquine. Invest Ophthalmol Vis Sci 2006;47(8):3531-8. doi: 10.1167/iovs.05-1290.
10. Maturi RK, Yu M, Weleber RG. Multifocal electroretinographic evaluation of long-term hydroxychloroquine users. Arch Ophthalmol 2004;122(7):973-81. doi: 10.1001/archopht.122.7.973.
11. Lyons JS, Severns ML. Detection of early hydroxychloroquine retinal toxicity enhanced by ring ratio analysis of multifocal electroretinography. Am J Ophthalmol 2007;143(5):801-9. doi: 10.1016/j.ajo.2006.12.042.
12. Wolfe F, Marmor MF. Rates and predictors of hydroxychloroquine retinal toxicity in patients with rheumatoid arthritis and systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2010;62(6):775-84. doi: 10.1002/acr.20133.
13. Garrity ST, Jung JY, Zambrowski O, Pichi F, Su D, Arya M, et al. Early hydroxychloroquine retinopathy: optical coherence tomography abnormalities preceding Humphrey visual field defects. Br J Ophthalmol 2019;103(11):1600-4. doi: 10.1136/bjophthalmol-2018-313350.
14. Santina A, Fogel-Levin M, Abraham N, Sarraf D. Nine-year progression of pentosan maculopathy with multimodal retinal imaging. Retin Cases Brief Rep 2023;17(6):664-7. doi: 10.1097/ICB.0000000000001276.
15. Barnett JM, Jain N. Potential new-onset clinically detectable pentosan polysulfate maculopathy years after drug cessation. Retin Cases Brief Rep 2022;16(6):724-6. doi: 10.1097/ICB.0000000000001090.
16. Somisetty S, Santina A, Abraham N, Lu A, Morales VR, Sarraf D. Rapid pentosan polysulfate sodium maculopathy progression. Retin Cases Brief Rep 2023;17(6):660-3. doi: 10.1097/ICB.0000000000001273.
17. Somisetty S, Santina A, Au A, Romero-Morales V, Bousquet E, Sarraf D. Progression of pentosan polysulfate sodium maculopathy in a prospective cohort. Am J Ophthalmol 2023;255:57-67. doi: 10.1016/j.ajo.2023.05.021.
18. Kinross-Wright V. Clinical trial of a new phenothiazine compound: NP-207. Psychiat Res Rep 1956(4):89-94.
19. Meredith TA, Aaberg TM, Willerson WD. Progressive chorioretinopathy after receiving thioridazine. Arch Ophthalmol 1978;96(7):1172-6. doi: 10.1001/archopht.1978.03910060006002.
20. Miyata M, Imai H, Ishikawa S, Nakajima S. Change in human electroretinography associated with thioridazine administration. Ophthalmologica 1980;181(3-4):175-80. doi: 10.1159/000309049.
21. Miller FS 3rd, Bunt-Milam AH, Kalina RE. Clinical-ultrastructural study of thioridazine retinopathy. Ophthalmology 1982;89(12):1478-88. doi: 10.1016/s0161-6420(82)34613-8.
22. Siddall JR. The ocular toxic findings with prolonged and high dosage chlorpromazine intake. Arch Ophthalmol 1965;74(4):460-4. doi: 10.1001/archopht.1965.00970040462005.
23. Wu CH, Yang CP, Lai CC, Wu WC, Chen YH. Deferoxamine retinopathy: spectral domain-optical coherence tomography findings. BMC ophthalmol 2014;14:1-3. doi: 10.1186/1471-2415-14-88.
24. Viola F, Barteselli G, Dell'arti L, Vezzola D, Villani E, Mapelli

C, et al. Abnormal fundus autofluorescence results of patients in long-term treatment with deferoxamine. Ophthalmology 2012;119(8):1693-700. doi: 10.1016/j.ophtha.2012.01.039.
25. Vahdani K, Makrygiannis G, Kaneshyogan H, Sian IS, Giasin O. Bilateral central serous retinopathy in a patient with paroxysmal nocturnal hemoglobinuria treated with deferoxamine. Eur J Ophthalmol 2016;26(6):e152-4. doi: 10.5301/ejo.5000840.
26. Brittenham GM. Iron-chelating therapy for transfusional iron overload. N Engl J Med 2011;364(2):146-56. doi: 10.1056/NEJMct1004810.
27. Booth AEC, Hopkins AM, Rowland A, Kichenadasse G, Smith JR, Sorich MJ. Risk factors for MEK-associated retinopathy in patients with advanced melanoma treated with combination BRAF and MEK inhibitor therapy. Ther Adv Med Oncol 2020;12:1758835920944359. doi: 10.1177/1758835920944359.
28. Nti AA, Serrano LW, Sandhu HS, Uyhazi KE, Edelstein ID, Zhou EJ, et al. Frequent subclinical macular changes in combined BRAF/MEK inhibition with high-dose hydroxychloroquine as treatment for advanced metastatic BRAF mutant melanoma: preliminary results from a phase I/II clinical treatment trial. Retina 2019;39(3):502-13. doi: 10.1097/IAE.0000000000002027.
29. Francis JH, Habib LA, Abramson DH, Yannuzzi LA, Heinemann M, Gounder MM, et al. Clinical and morphologic characteristics of MEK inhibitor–associated retinopathy: differences from central serous chorioretinopathy. Ophthalmology 2017;124(12):1788-98. doi: 10.1016/j.ophtha.2017.05.038.
30. Mozo Cuadrado M, Tabuenca Del Barrio L, Compains Silva E. Bilateral drug-induced uveitis and epiretinal membrane during the treatment of a metastatic cutaneous melanoma. Ocul Immunol Inflamm 2021;29(3):543-5. doi: 10.1080/09273948.2019.1685111.
31. Ramtohul P, Denis D, Comet A. Pseudovitelliform maculopathy associated with FGFR inhibitor therapy. Ophthalmol Retina 2021;5(2):140. doi: 10.1016/j.oret.2020.10.005.
32. Alekseev O, Ojuok E, Cousins S. Multifocal serous retinopathy with pemigatinib therapy for metastatic colon adenocarcinoma. Int J Retina Vitreous 2021;7(1):34. doi: 10.1186/s40942-021-00305-9.
33. Fraunfelder FW, Fraunfelder FT, Illingworth DR. Adverse ocular effects associated with niacin therapy. Br J Ophthalmol 1995;79(1):54-6. doi: 10.1136/bjo.79.1.54.
34. Freisberg L, Rolle TJ, Ip MS. Diffuse macular edema in niacin-induced maculopathy may resolve with dosage decrease. Retin Cases Brief Rep 2011;5(3):227-8. doi: 10.1097/ICB.0b013e3181e180c0.
35. Joshi MM, Garretson BR. Paclitaxel maculopathy. Arch Ophthalmol 2007 May;125(5):709-10. doi: 10.1001/archopht.125.5.709.
36. Telander DG, Sarraf D. Cystoid macular edema with docetaxel chemotherapy and the fluid retention syndrome. Semin Ophthalmol 2007;22(3):151-3. doi: 10.1080/08820530701457373.
37. Dwivedi R, Tiroumal S. Possible efficacy of topical dorzolamide in the treatment of paclitaxel-related cystoid macular edema. Retin Cases Brief Rep 2018;12(1):75-79. doi: 10.1097/ICB.0000000000000433.
38. Pul R, Osmanovic A, Schmalstieg H, Pielen A, Pars K, Schwenkenbecher P, et al. Fingolimod associated bilateral cystoid macular edema-wait and see? Int J Mol Sci 2016;17(12):2106. doi: 10.3390/ijms17122106.
39. Afshar AR, Fernandes JK, Patel RD, Ksiazek SM, Sheth VS, Reder AT, et al. Cystoid macular edema associated with fingolimod use for multiple sclerosis. JAMA Ophthalmol 2013;131(1):103-7. doi: 10.1001/jamaophthalmol.2013.570.
40. Chui J, Herkes GK, Chang A. Management of fingolimod-associated macular edema. JAMA Ophthalmol 2013;131(5):694-6. doi: 10.1001/jamaophthalmol.2013.47.
41. Schröder K, Finis D, Harmel J, Ringelstein M, Hartung HP, Geerling G, et al. Acetazolamide therapy in a case of fingolimod-associated macular edema: early benefits and long-term limitations. Mult Scler Relat Disord 2015;4(5):406-8. doi: 10.1016/j.msard.2015.06.015.
42. Thoo S, Cugati S, Lee A, Chen C. Successful treatment of fingolimod-associated macular edema with intravitreal triamcinolone with continued fingolimod use. Mult Scler 2015;21(2):249-51. doi: 10.1177/1352458514528759.
43. Friberg TR, Gragoudas ES, Regan CD. Talc emboli and macular ischemia in intravenous drug abuse. Arch Ophthalmol 1979;97(6):1089-91. doi: 10.1001/archopht.1979.01020010543006.
44. Ruys J, de Smet MD, Van de Sompel W. Bilateral talc maculopathy and fibrovascular proliferation in a drug abuser. Retin Cases Brief Rep 2010;4(2):123-4. doi: 10.1097/ICB.0b013e31819bfa57.
45. Martidis A, Yung CW, Ciulla TA. Talc embolism: a static retinopathy. Am J Ophthalmol 1997;124(6):841-3. doi: 10.1016/s0002-9394(14)71704-0.
46. Niazi S, Gnesin F, Jawad BN, Niazi Z, Løkkegaard E, Mørch L, et al. Hormonal contraception and retinal vascular occlusion risk. Am J Ophthalmol 2025;277:286-94. doi: 10.1016/j.ajo.2025.05.027.
47. Gombos GM, Moreno DH, Bedrossian PB. Retinal vascular occlussion induced by oral contraceptives. Ann Ophthalmol 1975;7(2):215-7.
48. Perry HD, Mallen FJ. Cilioretinal artery occlusion associated with oral contraceptives. Am J Ophthalmol 1977;84(1):56-8. doi: 10.1016/0002-9394(77)90323-3.
49. Varga M. Recent experiences on the ophthalmologic complications of oral contraceptives. Ann Ophthalmol 1976;8(8):925-34.
50. Vessey MP, Hannaford P, Mant J, Painter R, Frith P, Chappel D. Oral contraception and eye disease: findings in two large cohort studies. Br J Ophthalmol 1998;82(5):538-42. doi: 10.1136/bjo.82.5.538.
51. Schulman JA, Liang C, Kooragayala LM, King J. Posterior segment complications in patients with hepatitis C treated with interferon and ribavirin. Ophthalmology 2003;110(2):437-42. doi: 10.1016/S0161-6420(02)01741-4.
52. Tokai R, Ikeda T, Miyaura T, Sato K. Interferon-associated retinopathy and cystoid macular edema. Arch Ophthalmol 2001;119(7):1077-9. doi: 10.1001/archopht.119.7.1077.
53. Hejny C, Sternberg P, Lawson DH, Greiner K, Aaberg TM Jr. Retinopathy associated with high-dose interferon alfa-2b therapy. Am J Ophthalmol 2001;131(6):782-7. doi: 10.1016/s0002-9394(01)00836-4.

54. Fraunfelder FW, Fraunfelder FT. Interferon alfa-associated anterior ischemic optic neuropathy. Ophthalmology 2011;118(2):408-11.e1-2. doi: 10.1016/j.ophtha.2010.03.063.
55. Nishiwaki H, Ogura Y, Miyamoto K, Matsuda N, Honda Y. Interferon alfa induces leukocyte capillary trapping in rat retinal microcirculation. Arch Ophthalmol 1996;114(6):726-30. doi: 10.1001/archopht.1996.01100130718014.
56. Willson RL, Ross RD, Willson LM, Cohen G, Redfield TL, Gitter KA. Interferon-associated retinopathy in a young, insulin-dependent diabetic patient. Retina 2000;20(4):413-5. doi: 10.1097/00006982-200004000-00023.
57. Mindel JS, Rubenstein AE, Franklin B. Ocular ergotamine tartrate toxicity during treatment of Vacor-induced orthostatic hypotension. Am J Ophthalmol 1981;92(4):492-6. doi: 10.1016/0002-9394(81)90641-3.
58. Kaiser-Kupfer MI, Kupfer C, Rodrigues MM. Tamoxifen retinopathy. A clinicopathologic report. Ophthalmology 1981;88(1):89-93. doi: 10.1016/s0161-6420(81)35071-4.
59. Heier JS, Dragoo RA, Enzenauer RW, Waterhouse WJ. Screening for ocular toxicity in asymptomatic patients treated with tamoxifen. Am J Ophthalmol 1994;117(6):772-5. doi: 10.1016/s0002-9394(14)70321-6.
60. Bazvand F, Mahdizad Z, Mohammadi N, Shahi F, Mirghorbani M, Riazi-Esfahani H, et al. Tamoxifen retinopathy. Surv Ophthalmol 2023;68(4):628-40. doi: 10.1016/j.survophthal.2023.02.003.
61. Rahimy E, Sarraf D. Bevacizumab therapy for tamoxifen-induced crystalline retinopathy and severe cystoid macular edema. Arch Ophthalmol 2012;130(7):931-2. doi: 10.1001/archophthalmol.2011.2741.
62. Jeng KW, Wheatley HM. Intravitreal triamcinolone acetonide treatment of tamoxifen maculopathy with associated cystoid macular edema. Retin Cases Brief Rep 2015;9(1):64-6. doi: 10.1097/ICB.0000000000000093.
63. Chan A, Ko TH, Duker JS. Ultrahigh-resolution optical coherence tomography of canthaxanthine retinal crystals. Ophthalmic Surg Lasers Imaging 2006;37(2):138-9. doi: 10.3928/1542-8877-20060301-09.
64. Weber U, Goerz G, Baseler H, Michaelis L. Canthaxanthin-retinopathie. Follow-up of over 6 years. Klin Monbl Augenheilkd 1992;201(3):174-7. doi: 10.1055/s-2008-1045888.
65. Novak MA, Roth AS, Levine MR. Calcium oxalate retinopathy associated with methoxyflurane abuse. Retina 1988;8(4):230-6. doi: 10.1097/00006982-198808040-00002.
66. Dalvin LA, Shields CL, Orloff M, Sato T, Shields JA. Checkpoint inhibitor immune therapy: systemic indications and ophthalmic side effects. Retina 2018;38(6):1063-78. doi: 10.1097/IAE.0000000000002181.
67. Thomas S, Bae C, Joy-Ann T, Traverse W. Behcet's-like syndrome following pembrolizumab: an immune-related adverse event associated with programmed death receptor-1 inhibitor therapy. J Oncol Pharm Pract 2020;26(4):995-9. doi: 10.1177/1078155219877219.
68. Fusumae T, Kamiya K, Maekawa T, Komine M, Murata S, Inoda S, et al. Vogt-Koyanagi-Harada disease-like uveitis induced by vemurafenib for metastatic cutaneous malignant melanoma. J Dermatol 2018;45(6):e159-60. doi: 10.1111/1346-8138.14200.
69. Agemy SA, Mehta AN, Pachydaki SI, Tewari A. Bilateral panuveitis in a patient on vemurafenib BRAF inhibitor therapy for stage IV melanoma. Eur J Ophthalmol 2014;24(4):629-32. doi: 10.5301/ejo.5000423.
70. Fraunfelder FW, Fraunfelder FT, Keates EU. Topiramate-associated acute, bilateral, secondary angle-closure glaucoma. Ophthalmology 2004;111(1):109-11. doi: 10.1016/j.ophtha.2003.04.004.
71. Yan H, Yu W. Retinal toxicity of long term overdose of sildenafil citrate: a case report. Am J Ophthalmol Case Rep 2022;29:101761. doi: 10.1016/j.ajoc.2022.101761.
72. Vignal-Clermont C, Audo I, Sahel JA, Paques M. Poppers-associated retinal toxicity. N Engl J Med 2010;363(16):1583-5. doi: 10.1056/NEJMc1005118.
73. Ali A, Shah AA, Jeang LJ, Fallgatter KS, George TJ, DeRemer DL. Emergence of ocular toxicities associated with novel anticancer therapeutics: what the oncologist needs to know. Cancer Treat Rev 2022;105:102376. doi: 10.1016/j.ctrv.2022.102376.
74. Bhavsar KV, Lin S, Rahimy E, Joseph A, Freund KB, Sarraf D, Cunningham ET Jr. Acute macular neuroretinopathy: a comprehensive review of the literature. Surv Ophthalmol 2016;61(5):538-65. doi: 10.1016/j.survophthal.2016.03.003.
75. Guo J, Tang W, Liu W, Zhang Y, Wang L, Wang W. Bilateral methamphetamine-induced ischemic retinopathy. Am J Ophthalmol Case Rep 2019;15:100473. doi: 10.1016/j.ajoc.2019.100473.
76. Aktaş S, Tetikoğlu M, İnan S, Aktaş H, Özcura F. Unilateral hemorrhagic macular infarction associated with m arijuana, alcohol and antiepileptic drug intake. Cutan Ocul Toxicol 2017;36(1):88-95. doi: 10.3109/15569527.2016.1141420.

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CASE REPORT

Fungal Ball of the Sphenoid Lateral Recess with Infraorbital Nerve Hypoesthesia: A Case Report and Literature Review

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ABSTRACT

A fungal ball in the lateral recess of the sphenoid sinus (LRSS) is a rare entity, particularly when it presents atypically as facial hypoesthesia. Due to its deep location and proximity to critical neurovascular structures, it can present with atypical symptoms and radiological features that can mimic skull base malignancy, complicating diagnosis. Only one similar case has been previously reported in the literature. We report a case of a 59-year-old male who presented with a one-month history of progressive headache and left facial numbness. Neurological examination revealed diminished pinprick sensation in the infraorbital nerve distribution. A computed tomography showed a hypodense mass with rim calcification and pterygoid bone erosion adjacent to the left sphenoid sinus, raising suspicion of an invasive skull base lesion. The patient underwent endoscopic transpterygoid sphenoidotomy, which revealed fungal concretions encased within a bony partition in the LRSS. Histopathological analysis confirmed *Aspergillus* spp. without mucosal invasion or malignancy. Postoperatively, the patient recovered from facial numbness and had an uneventful one-year follow-up.

Keywords: fungus, fungal ball, lateral recess, endoscopic sinus surgery, transpterygoid approach

INTRODUCTION

Fungal rhinosinusitis (FRS) is a spectrum of conditions classified into non-invasive and invasive forms, each with distinct clinical features, management strategies, and prognoses. Non-invasive FRS includes saprophytic fungal infestation, fungal ball, and allergic fungal rhinosinusitis (AFRS); these forms are typically confined to the sinus cavity without mucosal or bony invasion and often present with mild or nonspecific symptoms such as nasal congestion, purulent rhinorrhea, or facial pain.[1] AFRS frequently occurs in atopic individuals and is characterized by nasal polyposis and eosinophilic mucin containing fungal hyphae.[1,2]

In contrast, invasive fungal rhinosinusitis (IFRS) is categorized into acute and chronic forms, with the acute type rapidly affecting immunocompromised patients and often resulting in severe complications such as orbital or intracranial involvement, while the chronic form progresses more slowly and can affect immunocompetent hosts.[1,3] Invasive types are associated with a significantly worse prognosis and require immediate surgical intervention, antifungal therapy, and correction of immune status, unlike non-invasive forms, which rarely threaten life. This distinction is important to prevent potentially catastrophic outcomes.[1,3,4]

The fungal ball is a non-invasive form of FRS that causes mucosal inflammation and bone reaction without soft tissue or vessel invasion on histopathological examination.[1,4,5] It is commonly found in the maxillary sinus of immunocompetent, middle-aged women.[1,5] Meanwhile, sphenoid sinus fungal ball (SSFB) is the second most commonly involved sinus (approximately 10%) after the maxillary sinus, often occurring in elderly patients and in the smaller side of the sphenoid sinus.[1,5-9]

The sphenoid sinus is located deeply within the skull, adjacent to the middle cranial fossa and cavernous sinus. In a very well-pneumatized sphenoid, the lateral recess can be found in the adjacent pterygoid bone, lateral to the foramen rotundum and vidian canal. Although fungal ball in the sphenoid is not uncommon, a fungal ball confined exclusively to the lateral recess of the sphenoid sinus (LRSS), with almost complete ossified bone septation between the sinus and recess, has never been reported in the literature to our knowledge. The location of isolated LRSS is also challenging, as it cannot be readily accessed via conventional sphenoidotomy.

The fungal ball of the sphenoid sinus commonly presents with headache, retro-orbital pain, postnasal drip, or visual loss.[5,10] However, this report describes a fungal ball located in the LRSS, atypically presenting with numbness of cranial nerve V2 (CNV2), demonstrating calcified septation between the sphenoid sinus and the LRSS on computed tomography (CT), and requiring an endoscopic transpterygoid approach for removal of the fungus.

CASE REPORT

A 59-year-old Thai male presented with a progressive left-sided headache for one month. He also reported left-sided facial numbness but denied sinonasal symptoms, facial pain, facial palsy, ocular symptoms, or loss of smell. He had no significant past medical history, including absence of underlying disease, use of immunosuppressive therapy, recent antibiotics, or herbal medicines.

On physical examination, bilateral inferior turbinate hypertrophy was noted, with no evidence of discharge from the osteomeatal complex or sphenoethmoidal recess. No nasal polyps or mass were detected. Neurological examination revealed decreased pinprick sensation in the distribution of the CNV2. Ophthalmologic assessment showed bilateral visual acuity of 20/40 with full extraocular muscle movement, negative relative afferent pupillary defect, and normal light reflex.

A contrast-enhanced CT scan of the paranasal sinuses demonstrated almost complete opacification of the left sphenoid sinus with a hypodense mass surrounded by ring enhancement. Bony erosion was identified at the inferomedial plate of the pterygoid process. Based on these findings, the provisional diagnosis included a sphenoid sinus tumor with bony erosion and cranial nerve involvement **(Figure 1)**.

The operation started with left uncinectomy, maxillary antrostomy, complete anterior and posterior ethmoidectomy, and wide sphenoidotomy. After the sphenoid sinus was opened via the transethmoidal approach, the mucosa within the sinus was markedly swollen, making visualization and access to the LRSS difficult despite the application of topical decongestant. In routine sphenoidotomy, if the LRSS is not readily visible after lateral widening of the ostium, surgeons would avoid drilling or removing the lateral wall because of the risk of internal carotid artery (ICA) injury. Consequently, the left transpterygoid approach was performed by removing the pterygoid base that forms the anterior wall of the LRSS to directly access the pathology.

The lateral nasal wall mucosa over the palatine bone at the posterior wall of the maxillary sinus was elevated, and the sphenopalatine artery (SPA) was identified. The crista ethmoidalis of the palatine bone was removed using a Kerrison Rongeur, and SPA ligation was performed with bipolar cautery and subsequently cut. The periosteum and contents of medial pterygopalatine fossa were tracked laterally, until reaching the pterygoid base of the sphenoid bone, where the vidian nerve from the vidian canal and CNV2 from the foramen rotundum could be identified. However, the vidian nerve was inevitably sacrificed to achieve maximum exposure of the LRSS. Finally, the base of the pterygoid bone was drilled to provide access to the lateral recess and to fully delineate all walls of the LRSS.

Intraoperative findings revealed a fungal concretion encased within a bony partition separating the lateral recess from the sphenoid sinus cavity. Localized bony erosion was noted at the base of the pterygoid bone. The mucosa appeared mildly pale and polypoid without ischemic or necrotic changes. The fungal concretion and adjacent mucosa were sent for

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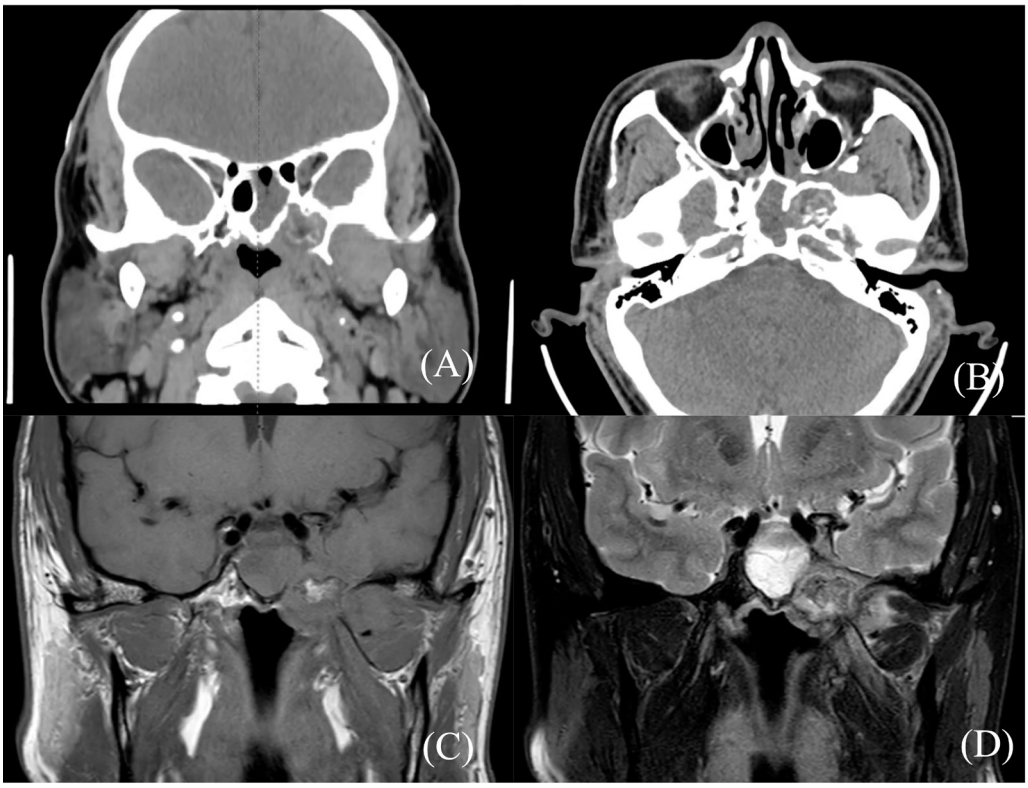

Figure 1 Computed Tomography scan showing opacification of the left sphenoid sinus with sclerotic bone change, a hypodense lesion with peripheral hyperdensity within the lateral recess of the sphenoid sinus (LRSS), and erosion of the greater wing of the sphenoid bone: coronal (A) and axial (B) views. Magnetic Resonance Imaging reveals a hypointense lesion within the left sphenoid sinus and lateral recess on a T1-weighted image (C), and a hyperintense lesion within the left sphenoid sinus together with a hypointense lesion within the left LRSS (D).

pathological examination, including Gomori Methenamine Silver (GMS) and Periodic Acid-Schiff (PAS) staining for fungal identification. The sclerotic septation bone between the lateral recess and the main sphenoid sinus was drilled to reconnect the sphenoid sinus cavity and the lateral recess **(Figure 2)**.

Postoperatively, the patient was advised to use budesonide 1 mg mixed with 250 mL normal saline for nasal irrigation once daily in the morning, and saline irrigation alone in the evening. Oral amoxicillin-clavulanic acid 1000 mg was also prescribed twice daily for 7 days.

The pathological report confirmed the presence of fungal hyphae consistent with *Aspergillus* spp. without evidence of mucosal invasion or malignancy. At the four-week follow-up, the patient developed dry eye, which was evaluated by an ophthalmologist and managed with artificial tear drops. At the three-month follow-up, the facial numbness had significantly improved, and the dry eye had completely resolved. There was no recurrence of the fungal ball, after one-year follow-up.

The study was approved by the Ethics Committee of Rajavithi Hospital (Trial No. 67015) on March 20th, 2024.

DISCUSSION

Fungal ball is classified as a secondary localized chronic rhinosinusitis according to the European Position Paper of Rhinosinusitis and Nasal Polyps 2020.[2] Fadda et al. outlined clinicopathological diagnostic criteria for fungal ball, which include sinus opacification with or without flocculent calcification, presence of cheesy or clay-like material within the sinus, matted and dense conglomeration of hyphae separate from sinus mucosa, chronic inflammatory response without eosinophil predominance, granulomatous response, or allergic mucin, and no histologic evidence of fungal invasion of mucosa, blood vessels, or underlying bone.[10] In clinical practice, the diagnosis of a fungal ball is primarily based on the presence of fungal concretions within the paranasal

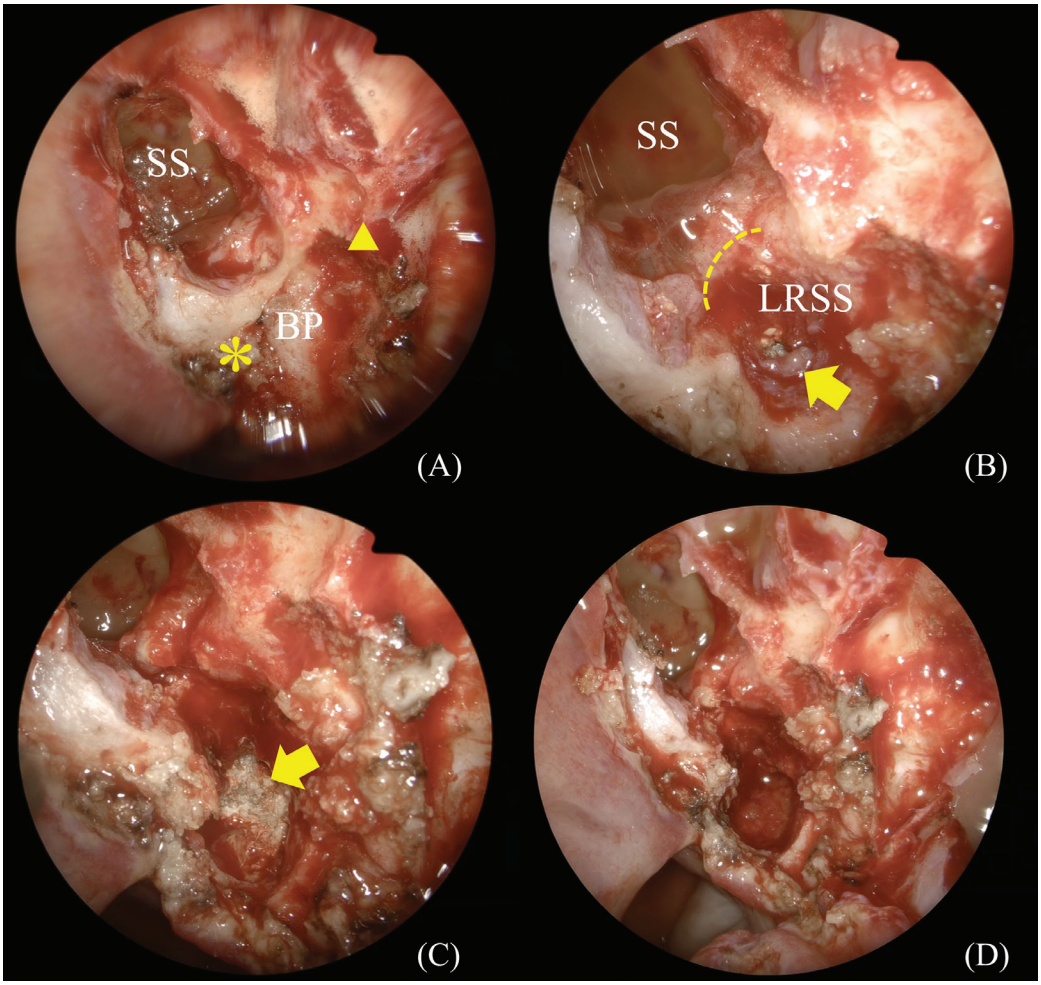

Figure 2 (A) Intraoperative findings of the transpterygoid approach showing the sphenoid sinus, base of the pterygoid process, vidian canal (asterisk), and foramen rotundum (triangle). (B) After drilling the base of the pterygoid process, the lateral recess of the sphenoid sinus (LRSS) was exposed, and the bony partition (dashed line) was visualized; the fungal ball was partially visible (arrow). (C) Surrounding soft tissue and bone were drilled, and the fungal ball was fully exposed (arrow). (D) The fungal ball was removed through irrigation and suction.

sinus, without the features of AFRS or IFRS. Despite our patient presenting with cranial nerve involvement and bony destructive lesion of the pterygoid bone, the diagnosis remains consistent with fungal ball based on the pathological criteria.

The sphenoid sinus represents the second most frequent site of fungal ball involvement following maxillary sinus, with reported prevalence rates ranging from 10% to 25% across studies.[5,7,8,11] Current demographic data indicate a predilection for immunocompetent elderly female patients, though the precise pathophysiological mechanisms underlying this epidemiological pattern remain under investigation.[7-9,12] While definitive risk factors remain unestablished, clinical observations suggest potential associations with prior sinonasal surgical interventions and diabetes mellitus in select case series.[5,6,12] Furthermore, Meerwein et al. found that the smaller sphenoid side may be more frequently affected (78%).[9]

Clinical presentations of SSFB include headache, retro-orbital pain, postnasal drip, or visual loss.[5,10] Furthermore, atypical presentations such as facial numbness, hyposmia, or hypogeusia have also been reported.[7] Some SSFB patients who visit the clinic without any symptoms may have incidental findings on CT or magnetic resonance imaging (MRI) performed

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for other reasons. Facial numbness in the distribution of CNV2 is a distinctive clinical presentation in this case.

Jiang et al. reported the symptoms of 77 patients with SSFB including: headache (79.2%), rhinological symptoms (29.9%), eye symptoms (7.8%), and asymptomatic (9.1%).[6] Likewise, Leroux et al. observed in 24 patients that 62% had headache, 21% had rhinological symptoms, and 16% were asymptomatic. Notably, only one patient in their study presented with CNV2 hypoesthesia.[7] Hence, this rare presentation of CNV2 hypoesthesia in our patient with SSFB underscores the importance of considering a wide range of symptoms when evaluating patients with SSFB.

The bony walls of the paranasal sinuses can be affected by pathology within the sinus cavity. Chronic rhinosinusitis with or without nasal polyps produces persistent inflammation of the sinus wall, which consequently leads to proliferation of the periosteum, bone remodeling, and neo-osteogenesis, manifesting as osteitic or sclerotic bone changes on radiographic study.[13,14] Furthermore, benign sinonasal tumors such as inverted papilloma, mucocele, AFRS and fungal balls progressively increase intrasinus pressure against the sinus walls and similarly enhance neo-osteogenesis.[1,15,16] Conversely, in cases of sinonasal malignancy or IFRS, these diseases invade the sinus walls and compromise the vascular supply, resulting in bone resorption and erosion.[1,17] Considering this case, the pattern of bone erosion raises concern for aggressive disease, as it lacks the bony strut typically seen in inverted papilloma, the localized sclerotic bone found in a typical fungal ball, the diffuse osteoneogenesis characteristic of AFRS, or the sinus wall ballooning expansion observed in mucocele.

Specifically, osteolytic lesions in fungal ball cases are less common than sclerotic lesions. The prevalence of osteolysis compared to sclerosis in SSFB has been reported in several studies: Jiang et al. observed 41.6% vs. 93.5%, Leroux et al. found a prevalence of 25% vs. 44%, and Kim et al. reported 40% vs. 64%[6-8] The underlying pathophysiology of osteolytic bone lesions is not fully understood, but it is hypothesized to result from mechanical pressure, chronic inflammation, and/or fungal metabolites and enzymes.[11,15,18] In our case, the bone erosion may have resulted from a combination of the hypothesized mechanisms, whereby the fungal concretion was confined within a small partition of the sphenoid sinus characterized by marked mucosal inflammation and bony septation. This anatomical configuration limited effective drainage into the sphenoid antrum, thereby increasing pressure within the LRSS, while fungal enzymes further disrupted normal bone healing and resorption processes. Thus, fungal ball should remain a consideration in the differential diagnosis for sphenoid sinus wall erosion on CT or MRI, even though sinonasal malignancy and IFRS should be of greater concern.

Endoscopic sphenoidotomy is the preferred treatment for removing fungal balls in the sphenoid sinus.[7,8,12] Meier et al. reviewed forty-three patients with SSFB who underwent sphenoidotomy using different approaches, including transethmoidal sphenoidotomy (76.7%) and transnasal sphenoidotomy (23.3%), to provide sufficient access.[12] However, the transpterygoid approach may be necessary in cases where the tumors or tumor-like lesions are located in the LRSS.[19,20] This approach involves partial or total removal of the pterygoid bone, enabling access to deeper anatomical regions, including the pterygopalatine fossa, LRSS, petrous apex, Meckel's cave, infratemporal fossa, and the middle or posterior skull base.[21]

In this case, anterior removal of the pterygoid base was required to access the LRSS. This was achieved by first identifying the vidian nerve and CNV2, followed by drilling the anterior face of the LRSS between both important landmarks. Through this approach, the fungal ball was adequately removed without limitation from the bony septum between the sphenoid antrum and LRSS. This necessity justified selecting the transpterygoid approach over the transnasal or transethmoidal approaches, which are more commonly used for fungal balls of the sphenoid sinus but may not provide sufficient access in scenarios where the fungal concretion is not connected to the main part of the sphenoid sinus.

The major concern with the transpterygoid approach is the risk of intraoperative and postoperative complications. Injury to critical structures such as the ICA and orbit may occur, particularly in cases of limited surgical experience or poor visualization.[20,21] Good anatomical knowledge, surgical skills, and the use of navigation systems can help minimize these risks. Li et al. classified pterygoid process pneumatization into three types: 1.) no identifiable LRSS, 2.)

superolateral pneumatization toward the greater wing of the sphenoid without extension below the vidian canal, and 3.) pneumatization of both the greater wing and the caudal pterygoid process.[22] In some cases, the vidian nerve can be preserved; however, lesions involving the superior or lateral wall of the LRSS may necessitate vidian neurectomy to achieve full exposure and surgical freedom. In the present case, the vidian nerve was sacrificed to maximize exposure of the LRSS and to allow evaluation of its mucosa and bony walls. The study of Lyu et al. show 16.7% develop dry eye at 1-2 month after vidian neurectomy, but the symptoms spontaneously resolved by 3-4 months with only conservative management such as artificial tears.[23] Preoperative counseling and postoperative ophthalmologic monitoring for dry eye are therefore essential.

Histopathology is essential for diagnosing and differentiating FRS, particularly distinguishing non-invasive fungal balls from IFRS. Routine fungal staining, such as GMS and PAS, confirms fungal elements and identifies pathogens. Biopsy of surrounding mucosa and bone helps rule out malignancy or secondary infections, especially in cases with bony erosion. Early histopathological confirmation facilitates appropriate next surgical intervention, if needed, reducing the risk of disease progression and recurrence.[24] Fungal culture is less important in cases of fungal balls, as only 30% yield growth, and *Aspergillus fumigatus* is typically identified.[25] A fungal ball was finally confirmed in our case, even though the preoperative findings suggested IFRS or sinonasal malignancy.

The transpterygoid approach was successfully employed for the fungal ball in the LRSS in our case. At the three-month follow-up, the CNV2 hypesthesia had spontaneously resolved, and there was no disease progression or recurrence at one year. Consequently, the temporary CNV2 numbness was more likely attributable to nerve compression or fungal toxin effects than to direct invasion or permanent neural injury.

Our case presentation demonstrates a rare finding of unilateral SSFB confined to the LRSS. The lesion is localized with sclerotic septation between the lateral recess and the sinus, mimicking a tumor within the pterygoid bone. The case also involved facial numbness in the CNV2 area, which completely resolved after surgery.

CONCLUSION

SSFB can mimic invasive fungal sinusitis or malignancy due to bony erosion and cranial nerve involvement, but it remains a non-invasive entity. CNV2 hypesthesia can occur without foramen rotundum erosion, likely due to local inflammation, bone reaction, or toxin release. An endoscopic transpterygoid approach is recommended for direct access to the LRSS. The SSFB should be included in the differential diagnoses of skull base lesions with cranial nerve involvement and bony erosion.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Author Contributions

Conceptualization: W.C.
Data curation: V.P.
Formal analysis: V.P., W.C.
Funding acquisition: W.C.
Investigation: V.P., W.C.
Methodology: P.S., Wo.C.
Project administration: P.T., Pa.T.
Resources: N.A., I.R.
Software: N.S., T.D.
Supervision: W.C.
Validation: V.P., W.C.
Visualization: V.P.
Writing – original draft preparation: V.P.
Writing – review & editing: W.C.

REFERENCES

1. Deutsch PG, Whittaker J, Prasad S. Invasive and non-invasive fungal rhinosinusitis-a review and update of the evidence. Medicina (Kaunas) 2019;55(7):319. doi: 10.3390/medicina55070319.
2. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. European position paper on rhinosinusitis and nasal polyps 2020. Rhinology 2020;58(Suppl S29):1-464. doi: 10.4193/Rhin20.600.
3. Roland LT, Humphreys IM, Le CH, Babik JM, Bailey CE, Ediriwickrema LS, et al. Diagnosis, prognosticators, and management of acute invasive fungal rhinosinusitis:

multidisciplinary consensus statement and evidence-based review with recommendations. Int Forum Allergy Rhinol 2023;13(9):1615-714. doi: 10.1002/alr.23132.
4. Montone KT. Pathology of fungal rhinosinusitis: A Review. Head Neck Pathol 2016;10(1):40-6. doi: 10.1007/s12105-016-0690-0.
5. Dufour X, Kauffmann-Lacroix C, Ferrie JC, Goujon JM, Rodier MH, Karkas A, et al. Paranasal sinus fungus ball and surgery: a review of 175 cases. Rhinology 2005;43(1):34-9. doi: 10.4193/Rhin.
6. Jiang T, Zhang Q, Li C, Li T, Sun S, Chen A, et al. Clinical characteristics of sphenoid sinus fungus ball: a nine-year retrospective study of 77 cases. Laryngoscope 2023; 133(12):3292-8. doi: 10.1002/lary.30683.
7. Leroux E, Valade D, Guichard JP, Herman P. Sphenoid fungus balls: clinical presentation and long-term follow-up in 24 patients. Cephalalgia 2009;29(11):1218-23. doi: 10.1111/j.1468-2982.2009.01850.x.
8. Kim JS, Kim BK, Hong SD, Kim HJ, Kim HY. Clinical characteristics of sphenoid sinus fungal ball patients with visual disturbance. Clin Exp Otorhinolaryngol 2016;9(4): 326-31. doi: 10.21053/ceo.2015.01571.
9. Meerwein CM, Seresirikachorn K, Lindsay B, Sacks PL, Kalish L, Campbell RG, et al. Sphenoid sinus fungal ball and reestablishing sinus function. Laryngoscope 2024;134(12):4888-92. doi: 10.1002/lary.31635.
10. Fadda G-L, Succo G, Moretto P, Veltri A, Castelnuovo P, Bignami M, et al. Endoscopic endonasal surgery for sinus fungus balls: clinical, radiological, histopathological, and microbiological analysis of 40 cases and review of the literature. Iran J Otorhinolaryngol 2019;31(102):35-44.
11. Jiang RS, Huang WC, Liang KL. Characteristics of sinus fungus ball: a unique form of rhinosinusitis. Clin Med Insights Ear Nose Throat 2018;11:1179550618792254. doi: 10.1177/1179550618792254.
12. Meier JC, Scangas GA, Remenschneider AK, Sadow P, Chambers K, Dedmon M, et al. Skull base erosion and associated complications in sphenoid sinus fungal balls. Allergy Rhinol (Providence) 2016;7(4):227-32. doi: 10.2500/ar.2016.7.0182.
13. Jun YJ, Shin JM, Lee JY, Baek BJ. Bony changes in a unilateral maxillary sinus fungal ball. J Craniofac Surg 2018;29(1):e44-e47. doi: 10.1097/SCS.0000000000004010.
14. Snidvongs K, McLachlan R, Sacks R, Earls P, Harvey RJ. Correlation of the Kennedy Osteitis score to clinico-histologic features of chronic rhinosinusitis. Int Forum Allergy Rhinol 2013;3(5):369-75. doi: 10.1002/alr.21113.
15. Inci MF, Ozkan F, Aksoy A, Kelleş M. Radiological aspect of fungus ball within a mucocele of the sphenoid sinus. JBR-BTR 2013;96(6):372-4. doi: 10.5334/jbr-btr.465.
16. Illing EA, Dunlap Q, Woodworth BA. Outcomes of pressure-induced cranial neuropathies from allergic fungal rhinosinusitis. Otolaryngol Head Neck Surg 2015;152(3):541-5. doi: 10.1177/0194599814567302.
17. Knisely A, Holmes T, Barham H, Sacks R, Harvey R. Isolated sphenoid sinus opacification: a systematic review. Am J Otolaryngol 2017;38(2):237-43. doi: 10.1016/j.amjoto.2017.01.014.
18. Zhang X, Zhang N, Huang Q, Cui S, Liu L, Zhou B. Analysis of metabolites of fungal balls in the paranasal sinuses. BMC Infect Dis 2022;22(1):733. doi: 10.1186/s12879-022-07710-x.
19. Vazquez A, Liu JK, Eloy JA. Endoscopic endonasal surgery of the sphenoid sinus: extended approaches. Oper Tech Otolayngol Head Neck Surg 2014;25(2):174-9. doi: 10.1016/j.otot.2014.02.007.
20. Bolger WE. Endoscopic transpterygoid approach to the lateral sphenoid recess: surgical approach and clinical experience. Otolaryngol Head Neck Surg 2005;133(1):20-6. doi: 10.1016/j.otohns.2005.03.063.
21. Kasemsiri P, Solares CA, Carrau RL, Prosser JD, Prevedello DM, Otto BA, et al. Endoscopic endonasal transpterygoid approaches: anatomical landmarks for planning the surgical corridor. Laryngoscope 2013;123(4):811-5. doi: 10.1002/lary.23697.
22. Li L, London NR, Prevedello DM, Carrau RL. Endonasal exposure of lateral recess of the sphenoid sinus: significance of pterygoid process pneumatization. Am J Rhinol Allergy 2023;37(3):291-7.
23. Wan X, Lin T, Luo Y, Hong J, Cheng J, Zhao K. The effect of vidian neurectomy on the ocular surface - the primary results from a six-month pilot study. Ther Clin Risk Manag 2024;20:335-40. doi: 10.2147/TCRM.S455608.
24. Guarner J, Brandt ME. Histopathologic diagnosis of fungal infections in the 21st century. Clin Microbiol Rev 2011;24(2): 247-80. doi: 10.1128/CMR.00053-10.
25. Klossek JM, Serrano E, Péloquin L, Percodani J, Fontanel JP, Pessey JJ. Functional endoscopic sinus surgery and 109 mycetomas of paranasal sinuses. Laryngoscope 1997;107(1): 112-7. doi: 10.1097/00005537-199701000-00021.

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