

Serum Leptin, Body Mass Index, and Ocular Tumours: A Case–Control Study

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Abstract

AIM: To determine whether serum leptin concentration and body mass index (BMI) differ between patients with ocular or ocular adnexal tumours and tumour-free controls, and to quantify the precision of any null finding.

METHODS: A case–control study was conducted at the reconstruction and oncology clinic of a tertiary university hospital in Medan, Indonesia, from December 2025. Thirty consecutive patients with an ocular or adnexal tumour and 25 controls attending the same clinic for refractive error were enrolled. Fasting serum leptin was measured by enzyme-linked immunosorbent assay, sampled after excision in the malignant group, and BMI was interpreted using Asia-Pacific thresholds. Cases were analysed both as a single group and divided into malignant and benign lesions. Every comparison was accompanied by an effect size with a 95% confidence interval (CI), and logistic regression was adjusted for age and sex. The smallest detectable difference was calculated at the achieved sample size.

RESULTS: Median serum leptin was 17.7 ng/mL (interquartile range 14.8–31.5) in cases and 24.0 ng/mL (12.7–61.0) in controls, a difference in the opposite direction to that predicted and not statistically significant (Hodges-Lehmann -6.39 ng/mL, 95% CI -19.0 to $+4.7$; $P=0.208$). Discrimination was absent, with an area under the receiver operating characteristic curve of 0.40 (95% CI 0.25–0.56). Separating the 10 malignant from the 20 benign lesions did not change the result (Kruskal-Wallis $P=0.437$; malignant versus control $P=0.281$). After adjustment for age and sex, leptin was not associated with malignancy (odds ratio 0.886 per 10 ng/mL, 95% CI 0.654–1.201), whereas age was (odds ratio 1.162 per year, 95% CI 1.018–1.326, $P=0.026$). BMI showed the same pattern. Leptin correlated with BMI in every subset examined (all participants $\rho=0.634$, cases $\rho=0.672$, controls $\rho=0.663$; all $P<0.001$), matching published population estimates. At this sample size the smallest detectable difference was a 2.48-fold ratio of geometric means.

CONCLUSION: In this cohort, serum leptin and BMI do not distinguish patients with ocular tumours from controls. The expected leptin–BMI relationship is preserved, indicating that the null result reflects the biology sampled rather than assay failure. Because sampling in the malignant group followed excision, these data address leptin after treatment rather than as a preoperative marker, and they provide no basis for adding serum leptin to the assessment of ocular masses. Detecting a 1.5-fold difference would require 138 participants per group sampled before intervention.

INTRODUCTION

Cancer remains among the largest contributors to premature death worldwide. Estimates from the International Agency for Research on Cancer put the global burden for 2022 at close to 20 million new cases and 9.7 million deaths, with about one in five people developing cancer during their lifetime¹. Those estimates draw on population-based registries and national vital statistics across 185 countries², and they represent a continued rise from the 19.3 million cases recorded two years earlier³.

Obesity has become one of the few modifiable exposures implicated across many of these cancers. More than two billion adults now live with overweight or obesity⁵, and forecasts project 3.8 billion by 2050⁴. Between 4% and 8% of all cancers are attributed to excess adiposity⁶. In a cohort of 2.6 million Catalan adults, longer duration and earlier onset of overweight were positively associated with 18 cancers⁷, and a pooled Swedish cohort of 4.1 million individuals found hazard ratios of 1.17 in men and 1.13 in women per 5 kg/m² increment for cancers not previously classified as obesity-related⁸.

Leptin offers a plausible mechanism connecting the two. It is secreted by adipose tissue in proportion to fat mass and acts well beyond energy homeostasis⁹. In malignancy it has been linked to invasion and metastasis¹⁰, to angiogenesis and vasculogenic mimicry through JAK-STAT3, MAPK/ERK, and PI3K-Akt signalling¹¹, and to inflammatory pathways in colorectal carcinogenesis¹². Reviews of leptin alongside adiponectin describe effects spanning tumour initiation, epithelial-mesenchymal transition, and metastatic progression¹³, and the same three signalling cascades act cooperatively in non-malignant proliferation as well¹⁴.

The evidence is not uniform. A synthesis of transcriptomic and clinical data concluded that leptin's role differs substantially between tumour types rather than acting as a general driver¹⁵, and a recent systematic review described the overall picture as controversial¹⁶. A meta-analysis of 30 studies in colorectal cancer, one of the malignancies where the obesity link is best established, found no association between circulating leptin and cancer risk (odds ratio 1.12, 95% CI 0.96–1.31), although leptin was associated with adenoma¹⁷. Any expectation of a straightforward leptin–tumour gradient therefore needs qualification.

Whether this biology extends to the eye is largely unknown. Leptin receptors are functionally active in ocular adnexal tissue: receptor deficiency disrupts lacrimal gland circadian rhythms and contributes to dry eye¹⁸, which establishes that the target tissue can respond. Ocular and adnexal tumours themselves are not rare in clinical practice. A series of 5146 eyelid lesions from South China found 85.1% to be benign, with basal cell carcinoma the commonest malignancy¹⁹, and a Hong Kong registry recorded rising incidence of eyelid cancer and ophthalmic lymphoma over 14 years²⁰. The distribution of eyelid malignancy also differs between Asian and Western populations²¹. Yet the dominant risk factor for the keratinocyte cancers that make up most eyelid malignancy is ultraviolet exposure rather than metabolic status²², while for ocular adnexal lymphoma an adiposity link is at least biologically arguable through leptin²³. The two compartments of ocular oncology may therefore behave differently.

To our knowledge, no study has measured circulating leptin in patients with ocular tumours. The question matters practically as well as mechanistically: if leptin discriminated, it would be an inexpensive serum test available in most district laboratories. It also matters that such a study be reported carefully, since claims about adiposity and cancer are particularly vulnerable to detection bias, collider bias, and reverse causation²⁴. This study measured serum leptin and BMI in patients with ocular

and adnexal tumours and in tumour-free controls from the same clinic, and asked not only whether an association exists but how large a difference the design could have detected.

SUBJECTS AND METHODS

Ethical Approval

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Health Research Ethics Committee of Universitas Sumatera Utara (approval 1458/KEPK/USU/2025, valid 22 December 2025 to 22 December 2026). Written informed consent was obtained from every participant after the purpose of the study, the venepuncture procedure, and the handling of personal data had been explained. Participation was voluntary, and refusal carried no consequence for clinical care.

Study Design and Setting

An observational analytic study with a case–control design was conducted at the Reconstruction and Oncology Division of the Department of Ophthalmology, Prof. dr. Chairuddin Panusunan Lubis Universitas Sumatera Utara Hospital, Medan, Indonesia. Recruitment began in December 2025 and continued until the target sample was reached.

Participants

Cases were consecutive patients attending the oncology clinic with an ocular or ocular adnexal tumour. Controls were patients attending the same clinic during the same period for refractive error, without any ocular or adnexal mass. Drawing both groups from one clinic limits referral bias, but the controls are not a general-population sample, and the consequences are addressed below.

Inclusion required age 18 years or older and written informed consent. Patients were excluded if they had a known systemic malignancy at another site, were pregnant or lactating, had chronic kidney disease or a chronic inflammatory disorder, or were taking corticosteroids or weight-modifying medication, since each independently alters circulating leptin.

In patients with malignant lesions, blood was drawn after surgical excision of the tumour rather than before it. Serum leptin in this group therefore reflects the postoperative state, with the lesion already removed, and the study measures circulating leptin in patients who have had an ocular malignancy rather than in patients presenting with an undiagnosed mass. This has direct consequences for interpretation, which are set out in the Discussion.

Grouping and Classification

The comparison specified in advance was tumour versus control. Because the biological rationale for leptin derives from malignant rather than benign proliferation, a second analysis divided cases into malignant and benign groups using the histopathological or clinical diagnosis in the medical record.

Lymphoid neoplasms were classified by the fifth edition of the World Health Organization classification of haematolymphoid tumours²⁵, and keratinocyte carcinomas by standard histopathological criteria²⁶. Both analyses are reported, and neither replaces the other.

Anthropometric Assessment

Body weight and height were measured, and BMI was calculated as weight in kilograms divided by height in metres squared. BMI was interpreted using World Health Organization Asia-Pacific thresholds, with 18.5 to 22.9 kg/m² as normal, 23.0 to 27.4 as overweight, and 27.5 or above as obese²⁷. These thresholds are more appropriate than the standard cut-offs for Southeast Asian populations²⁸, although the optimal Indonesian cut-off remains debated and definitions vary between Indonesian investigators²⁹.

Participants were measured in light clothing without shoes. Weight and height were each recorded twice and the mean of the two readings was used.

Blood Sampling and Leptin Assay

Venous blood was drawn in the fasting state from the antecubital vein, allowed to clot, and centrifuged. Serum was aliquoted into labelled tubes and stored frozen until batch analysis. Serum leptin was measured in duplicate by enzyme-linked immunosorbent assay following the manufacturer's protocol, and concentrations were read from a standard curve constructed with the supplied calibrators.

Statistical Analysis

Analyses were performed in SPSS and independently reproduced in Python 3 (pandas, SciPy 1.17, statsmodels 0.14) directly from the raw data file; the two sets of results agreed to the third decimal place.

Distributional assumptions were assessed with the Shapiro-Wilk test. Serum leptin departed markedly from normality ($P < 0.001$; skewness 3.71, kurtosis 15.98) and is therefore summarised as median with interquartile range and compared with the Mann-Whitney U test. BMI and age are summarised as mean $\pm$ standard deviation and as median with range. Categorical variables were compared with Fisher's exact test.

A null result is uninformative without a statement of what magnitude of difference would have been detectable, so every non-significant comparison is reported with an effect size and its confidence interval rather than a P value alone. The Hodges-Lehmann estimator gives the median difference between groups, with a 95% CI from 20 000 bootstrap resamples. Cliff's delta gives a non-parametric standardised effect. Discrimination of leptin for tumour status was quantified by the area under the receiver operating characteristic curve with a bootstrap confidence interval.

Associations were examined further with binary logistic regression adjusted for age and sex, the two variables most strongly associated with circulating leptin in reference populations^{31,32}. Odds ratios are

reported per 10 ng/mL for leptin and per 5 kg/m² for BMI. The correlation between BMI and leptin was assessed with Spearman's rank coefficient, computed separately in cases, in controls, and in the pooled sample, with confidence intervals from the Fisher transformation.

Three sensitivity analyses were specified: repeating the primary comparison after excluding leptin values above published upper reference limits; repeating the BMI–leptin correlation after retaining only one subject per unique weight-and-height combination; and comparing the malignant subgroup separately against controls.

The smallest detectable difference was calculated on the logarithmic scale from the pooled within-group standard deviation, for a two-sided alpha of 0.05 and 80% power at the achieved sample size. No adjustment for multiple comparisons was applied, and all P values other than that for the primary comparison are exploratory. Significance was set at P<0.05, two-sided.

RESULTS

Characteristics of the Study Population

Fifty-five participants were enrolled, 30 with an ocular or adnexal tumour and 25 controls. Their characteristics appear in Table 1.

Table 1 Demographic, anthropometric, and biochemical characteristics of the study population

Characteristic	Tumour (n=30)	Control (n=25)	P
Age (a), mean±SD	37.5±11.0	31.8±4.6	0.067 [⊠]
Age (a), median (range)	34.0 (23–69)	32.0 (22–40)	
Male, n (%)	8 (26.7)	6 (24.0)	1.000 [⊠]
Female, n (%)	22 (73.3)	19 (76.0)	
BMI (kg/m ²), mean±SD	22.1±3.9	21.4±4.4	
BMI (kg/m ²), median (range)	24.4 (16.2–27.0)	19.0 (16.2–32.3)	
Serum leptin (ng/mL), median (IQR)	17.7 (14.8–31.5)	24.0 (12.7–61.0)	0.208 [⊠]

[⊠]Mann-Whitney U test; [⊠]Fisher's exact test. BMI: Body mass index; IQR: Interquartile range; SD: Standard deviation.

Cases were on average 5.7 years older than controls, a difference that did not reach significance (Hodges-Lehmann +3.0a, 95% CI –1.0 to +7.0, P=0.067). The age range was much wider among cases (23–69a) than controls (22–40a), because the control group consisted of younger patients attending for refractive correction. The sex distribution was almost identical, with women making up roughly three quarters of both groups.

Among the 30 tumours, 20 (66.7%) were benign and 10 (33.3%) malignant. Benign lesions comprised 12 epidermal or epidermoid cysts, three non-neoplastic naevi, two conjunctival cysts, one pleomorphic adenoma, one squamous papilloma, and one unspecified eyelid tumour. Malignant lesions comprised four squamous cell carcinomas, two basal cell carcinomas, one orbital lymphoma, one orbital adenocarcinoma, one adnexal tumour, and one retro-orbital tumour. The predominance of benign lesions matches the 85.1% reported in a series of 5146 eyelid lesions¹⁹.

Serum Leptin Did Not Distinguish Patients With Ocular Tumours From Controls

Median serum leptin was lower in the tumour group than in controls, 17.7 against 24.0 ng/mL. The direction is opposite to that predicted by the leptin–carcinogenesis hypothesis, and the difference was not significant (U=300, z=−1.268, P=0.208). The Hodges-Lehmann estimate was −6.39 ng/mL (95% CI −19.0 to +4.7), and Cliff’s delta was −0.20, a small effect whose confidence interval includes zero in both directions.

Discrimination was absent. The area under the receiver operating characteristic curve for serum leptin as a marker of tumour status was 0.40 (95% CI 0.25 to 0.56), which does not exceed the 0.50 expected of an uninformative test (Figure 1B).

In crude logistic regression, each 10 ng/mL increment carried an odds ratio for tumour status of 0.769 (95% CI 0.585 to 1.011, P=0.060). After adjustment for age and sex the estimate was essentially unchanged at 0.786 (95% CI 0.597 to 1.034, P=0.085).

The distribution shown in Figure 1A explains the wide confidence intervals. Values spanned 1.01 to 269.81 ng/mL, and two control participants had concentrations of 199.2 and 269.8 ng/mL, far above the published upper reference limits of 19.85 ng/mL in men and 54.86 ng/mL in women from a Chinese population-based sample³¹. These two observations alone lifted the control mean to 47.8 ng/mL against a median of 24.0 ng/mL.

The pre-specified sensitivity analysis excluding them moved the comparison further from significance rather than towards it. The control median fell to 20.6 ng/mL and P rose from 0.208 to 0.425. The finding of no detectable difference is therefore not an artefact of the two extreme observations.

Separating Malignant From Benign Lesions Did Not Reveal an Association

Grouping epidermal cysts with orbital lymphoma may obscure a genuine effect, so the cases were re-analysed as three classes. The result did not change (Table 2).

Table 2 Serum leptin and body mass index across malignant, benign, and control groups

Variable	Malignant (n=10)	Benign (n=20)	Control (n=25)	P
Serum leptin (ng/mL), median (IQR)	15.6 (3.3–40.2)	18.0 (16.1–24.5)	24.0 (12.7–61.0)	0.437
Serum leptin (ng/mL), mean±SD	21.1±19.2	19.9±9.5	47.8±63.4	
BMI (kg/m ²), median (IQR)	20.5 (16.4–24.4)	24.4 (19.0–26.2)	19.0 (19.0–24.4)	0.178
BMI (kg/m ²), mean±SD	20.4±3.9	22.9±3.8	21.4±4.4	

⌘Kruskal-Wallis test across the three groups. BMI: Body mass index; IQR: Interquartile range; SD: Standard deviation.

No pairwise comparison approached significance. Malignant cases versus controls gave P=0.281 (Hodges-Lehmann –9.91 ng/mL, 95% CI –30.7 to +22.8; Cliff's delta –0.24), malignant versus benign cases gave P=0.878, and benign cases versus controls gave P=0.309.

In logistic regression restricted to malignant cases and controls and adjusted for age and sex, leptin remained unassociated with malignancy (odds ratio 0.886 per 10 ng/mL, 95% CI 0.654 to 1.201, P=0.437). In the same model age was associated with malignancy (odds ratio 1.162 per year, 95% CI 1.018 to 1.326, P=0.026). This is the expected relationship for malignant ocular tumours and shows that the model could detect an association when one was present.

BMI behaved similarly. It did not differ across the three groups (P=0.178), and after adjustment for age and sex it was not associated with tumour status (odds ratio 1.433 per 5 kg/m², 95% CI 0.698 to 2.943, P=0.328); age remained associated in the same model (odds ratio 1.112 per year, 95% CI 1.008 to 1.226, P=0.033).

Serum Leptin Correlated With Body Mass Index in Every Subset

The relationship between BMI and serum leptin was positive, moderate to strong, and consistent across all three subsets (Table 3, Figure 2).

Table 3 Spearman rank correlation between body mass index and serum leptin

Subset	n	ρ	95% CI	P
All participants	55	0.634	0.431 to 0.777	<0.001
Tumour group	30	0.672	0.393 to 0.838	<0.001
Control group	25	0.663	0.341 to 0.846	<0.001
One subject per unique weight-and-height combination	20	0.623	—	0.003

CI: Confidence interval.

The magnitude closely matches population-based estimates. In 1242 Chinese adults, BMI correlated with the natural logarithm of leptin at $r=0.698$ in men and $r=0.626$ in women³¹. The correlation persisted in the final row of Table 3, which retains only one subject per distinct weight-and-height pair, and it was of similar strength in cases and controls separately.

Precision of the Null Findings

With 30 cases and 25 controls and a pooled within-group standard deviation of 1.199 on the logarithmic scale, the smallest difference detectable with 80% power at a two-sided alpha of 0.05 was a 2.48-fold ratio of geometric means. Detecting a 1.5-fold difference would require 138 participants per group. All negative findings above should be read as differences not detected at this sample size rather than as evidence that no difference exists.

DISCUSSION

Serum leptin did not separate patients with ocular tumours from controls, and the point estimate ran opposite to the hypothesis. Three features of the data argue that this is a genuine null rather than a failed measurement. Discrimination was at chance, with an area under the curve of 0.40. The result survived removal of the two extreme control values and in fact weakened further. And the effect estimate was accompanied by a confidence interval that excludes any large effect in the predicted direction.

One competing explanation must be set against that reading. In the malignant group, blood was drawn after the tumour had been excised. If circulating leptin were elevated by the presence of an ocular malignancy, whether through tumour-derived secretion or through a systemic inflammatory response to it, removal of the lesion would be expected to abolish that elevation before the sample was taken. The design therefore cannot exclude a preoperative difference that had resolved by the time of measurement, and it cannot evaluate leptin as a preoperative diagnostic test, which is the use to which such a marker would be put. What the study does establish is that circulating leptin after excision does not differ from that of tumour-free patients, and that leptin measured at this point carries no information about which patients have had an ocular malignancy. A study designed to answer the diagnostic question would need to sample before any intervention.

This finding has precedent. In colorectal cancer, where the obesity association is among the best characterised, a meta-analysis of 30 studies found no relationship between circulating leptin and cancer risk¹⁷. Two recent syntheses concluded that leptin's oncological role is tumour-type dependent rather than general¹⁵ and that the overall evidence remains contested¹⁶. Much of the mechanistic work supporting a pro-tumour role comes from cell lines and animal models: leptin drives vasculogenic mimicry in breast cancer cells through the Ob-R/STAT3 axis³³, promotes proliferation in non-small-cell

lung cancer via PI3K/AKT³⁴, and confers chemoresistance in acute myeloid leukaemia through JAK2/STAT3³⁵. Demonstrating that a pathway can operate in vitro is not the same as showing that circulating concentrations vary detectably between patients and controls. Our data are consistent with the receptor being present and functional in ocular adnexal tissue¹⁸ while systemic leptin concentration carries no diagnostic signal.

The composition of the case group offers a straightforward explanation. Six of the ten malignancies were keratinocyte carcinomas of the eyelid, four squamous cell and two basal cell. For these tumours the dominant aetiological factor is cumulative ultraviolet exposure²², with basal cell carcinoma linked to intense exposure in childhood and squamous cell carcinoma to chronic exposure over decades³⁸. Risk stratification for keratinocyte cancers rests on ultraviolet dose, phenotype, and immunosuppression rather than on metabolic variables³⁹. If most of the malignancy in an ocular oncology clinic is ultraviolet-driven skin cancer, then a systemic adipokine should not be expected to discriminate, and our result is what the biology predicts.

The one case where an adiposity link is defensible is the orbital lymphoma. Obesity has been proposed as a lymphoma risk factor with leptin as the mediating adipokine²³, a pooled analysis of six United States cohorts found sustained high BMI more than doubled the risk of diffuse large B-cell lymphoma⁴⁰, and Mendelian randomisation supports a causal contribution of genetically determined BMI to that subtype⁴¹. Population data also associate lymphoma incidence with obesity prevalence at country level⁴². A single case cannot test any of this.

The contrast with systemic oncology is instructive. Large cohorts consistently find BMI associated with cancer risk, whether in 4.1 million Swedes⁸, 620 000 Asian adults⁴³, or pooled European cohorts⁴⁴, and the pattern held across 18 cancer types in Catalonia⁷. Those studies achieve their precision through sample sizes three to five orders of magnitude larger than ours and through outcomes with far higher event counts. Serum leptin in melanoma is the closest published analogue to our design, where raw and BMI-adjusted leptin predicted sentinel node positivity in 72 patients³⁶, supported by murine work showing leptin accelerates melanoma growth³⁷. Melanoma differs from keratinocyte carcinoma in both biology and metastatic behaviour, so that finding does not transfer directly to our cases.

The correlation between BMI and leptin was the most robust finding in this study, and its value lies in what it rules out. Coefficients of 0.634 overall, 0.672 in cases, and 0.663 in controls sit almost exactly on published population estimates of 0.698 in men and 0.626 in women³¹, and are consistent with the reference curves derived from 12 629 individuals across 16 European cohorts³². An assay that reproduces the expected physiological gradient in three independent subsets is measuring leptin. The null finding for tumour status therefore cannot be dismissed as analytical failure. The correlation should not, however, be presented as a discovery. That leptin tracks adiposity has been known since the hormone was characterised⁹, and reporting it as a study result would inflate a positive control into a finding.

BMI itself remains an imperfect proxy. At any given level of adiposity, leptin concentrations vary widely between individuals, and those with relatively elevated leptin show reduced insulin sensitivity irrespective of BMI⁴⁵. Asians carry a higher percentage of body fat than Europeans at the same BMI⁴⁶, which is why the Asia-Pacific thresholds were applied here^{27,28}; the same reasoning underpins their use in Indonesian cardiovascular research⁴⁷, although the optimal national cut-off is still debated²⁹. Sex adds a further layer, since hormone receptors are expressed throughout ocular tissue⁴⁸ and women had higher leptin in both of our groups.

The practical conclusion is a negative one, and it is worth stating plainly: serum leptin should not be ordered as an adjunct in the assessment of ocular or adnexal masses. With an area under the curve of 0.40 there is no threshold at which the test would perform better than not testing. Nor does BMI identify patients requiring closer ocular oncological surveillance in this setting.

That conclusion should not be dressed up as an obesity paradox. A paradox describes an inverse association between adiposity and outcome that survives adjustment; what we observed is an absence of association with a confidence interval wide enough to accommodate modest effects in either direction. The obesity paradox literature itself has grown considerably more cautious, with detection bias, collider bias, and reverse causation all offered as explanations²⁴. When examined directly in renal cell carcinoma, the apparent protective effect of low BMI dissolved into weight loss around the time of diagnosis⁴⁹, and BMI has been criticised as too crude a measure of adiposity to support paradox claims at all⁵⁰. Waist circumference adds information beyond BMI for site-specific cancer risk⁵¹, and weight change across adulthood outperforms BMI measured at a single time point⁵². Our single BMI measurement is the weakest version of the exposure.

What the study does provide is a design specification. A future study needs 138 participants per group to detect a 1.5-fold difference in leptin, should separate keratinocyte carcinoma from lymphoid and melanocytic tumours rather than pooling them, and should measure leptin alongside adiponectin so that the leptin/adiponectin ratio can be computed. That ratio distinguished breast cancer patients from controls when neither adipokine alone was decisive⁵³, and circulating adiponectin is reduced across many malignancies⁵⁴.

Five limitations bound these conclusions. The first and most consequential is the timing of blood sampling in the malignant group, discussed above: measurement after excision means the study addresses leptin in patients who have had an ocular malignancy rather than leptin as a preoperative marker. Second, ten malignant cases is a small number, and the precision analysis quantifies the consequence directly, since only differences of 2.48-fold or larger were detectable. Third, the controls were younger patients attending for refractive error rather than a general-population sample; age was adjusted for in every regression model and emerged as the only variable associated with malignancy, but residual confounding by age cannot be excluded at this sample size. Fourth, although all samples were drawn in the fasting state, which removes the postprandial fall in leptin that follows a high-fat meal³⁰, the

time of day was not standardised and sleep in the preceding night was not recorded, and both influence circulating leptin⁵⁵. Fifth, diagnostic classification relied on records rather than central review, and sebaceous and poorly differentiated squamous carcinoma of the eyelid overlap sufficiently that even experienced pathologists disagree⁵⁶, while the differential diagnosis of basal cell carcinoma against its mimics requires immunohistochemistry that was not uniformly available²⁶. Leptin was also measured once, without adiponectin, insulin, or inflammatory markers, and waist circumference and body composition were not assessed, so the broader metabolic context that links systemic dysfunction to ocular disease⁵⁷ was not captured.

CONCLUSION

Serum leptin and body mass index did not distinguish patients with ocular or ocular adnexal tumors from tumor-free controls attending the same clinic, and separating malignant from benign lesions did not alter that result. Age was the only variable associated with malignancy. The expected correlation between leptin and body mass index was preserved in cases, in controls, and in the pooled sample, which indicates that the absence of a signal reflects the biology sampled rather than a failure of measurement. Because most malignancy in this cohort was ultraviolet-driven keratinocyte carcinoma of the eyelid, a disease in which metabolic factors play little part, an absent adipokine signal is what the aetiology would predict.

Two qualifications frame the practical value of this result. Blood was drawn after excision in the malignant group, so these data speak to circulating leptin in patients who have had an ocular malignancy rather than to leptin as a preoperative diagnostic aid; and with an area under the curve of 0.40, no threshold in this dataset performs better than not testing at all. On present evidence there is no basis for adding serum leptin to the routine assessment of ocular or adnexal masses. For research, these estimates specify what a larger study must do: sample before any intervention, enroll 138 participants per group to detect a 1.5-fold difference in leptin, analyze keratinocyte, lymphoid, and melanocytic tumors separately rather than pooling them, and measure adiponectin alongside leptin so that the ratio of the two can be examined.

Declarations

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Authors' Contributions: *Delfi*: supervision of clinical conduct and diagnostic classification, critical revision of the manuscript for important intellectual content. All authors approved the final version and agree to be accountable for all aspects of the work. *Effendi AP*: conceptualisation, protocol design,

ethics submission, patient recruitment, data collection, data curation, manuscript drafting. *Lubis RR*: conceptualisation, supervision of study design and methodology, critical revision of the manuscript for important intellectual content.

Data Availability Statement: The de-identified participant dataset, comprising serum leptin concentration, body mass index, age, sex, and diagnostic category for all 55 participants, together with the analysis scripts, is available from the corresponding author on reasonable request from 12 months after publication for a period of 5 years. Requests should state the intended analysis and will be reviewed by all authors.

Use of AI-Generated Content: Generative artificial intelligence tools were used in the preparation of this manuscript in the following ways: independent reproduction and extension of the statistical analysis (effect sizes, confidence intervals, logistic regression, receiver operating characteristic analysis, and sensitivity analyses) in Python; literature searching and screening; generation of Figures 1 and 2 from the raw dataset; and English language editing. No text, data, or numerical result was generated without verification against the primary data by the authors. The authors reviewed all AI-assisted output, take full responsibility for the integrity of the data, the accuracy of the analysis, and the content of the manuscript, and confirm that no AI tool is listed as an author.

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Figures

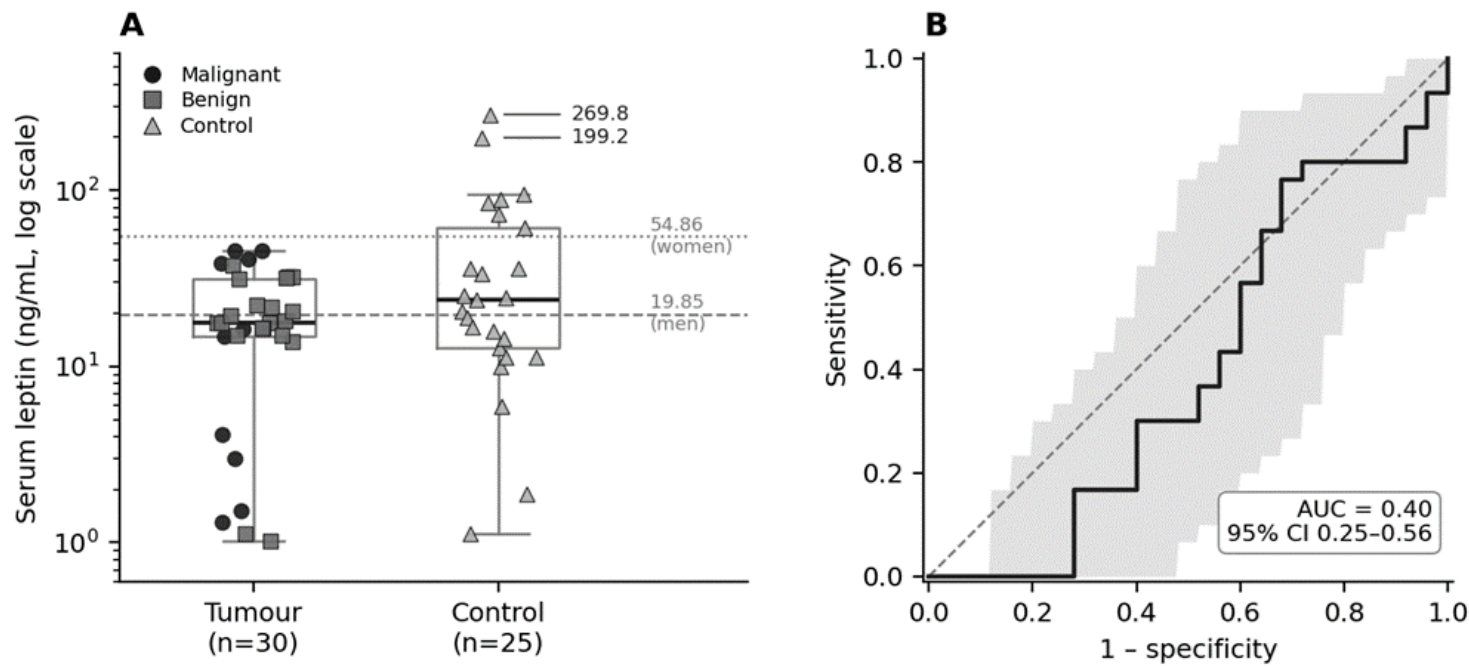


Figure 1

Serum leptin neither separated the groups nor discriminated tumour status. A: Individual serum leptin concentrations by group on a logarithmic axis. Symbols distinguish malignant cases, benign cases, and controls; box plots show median and interquartile range with whiskers to the most extreme value within 1.5 interquartile ranges. Horizontal lines mark the published upper reference limits of 54.86 ng/mL for women (dotted) and 19.85 ng/mL for men (dashed)³¹. The two control values above those limits are labelled with their concentrations. B: Receiver operating characteristic curve for serum leptin as a marker of ocular tumour status (solid line) with its bootstrap 95% confidence band (shading) and the diagonal line of no discrimination (dashed).

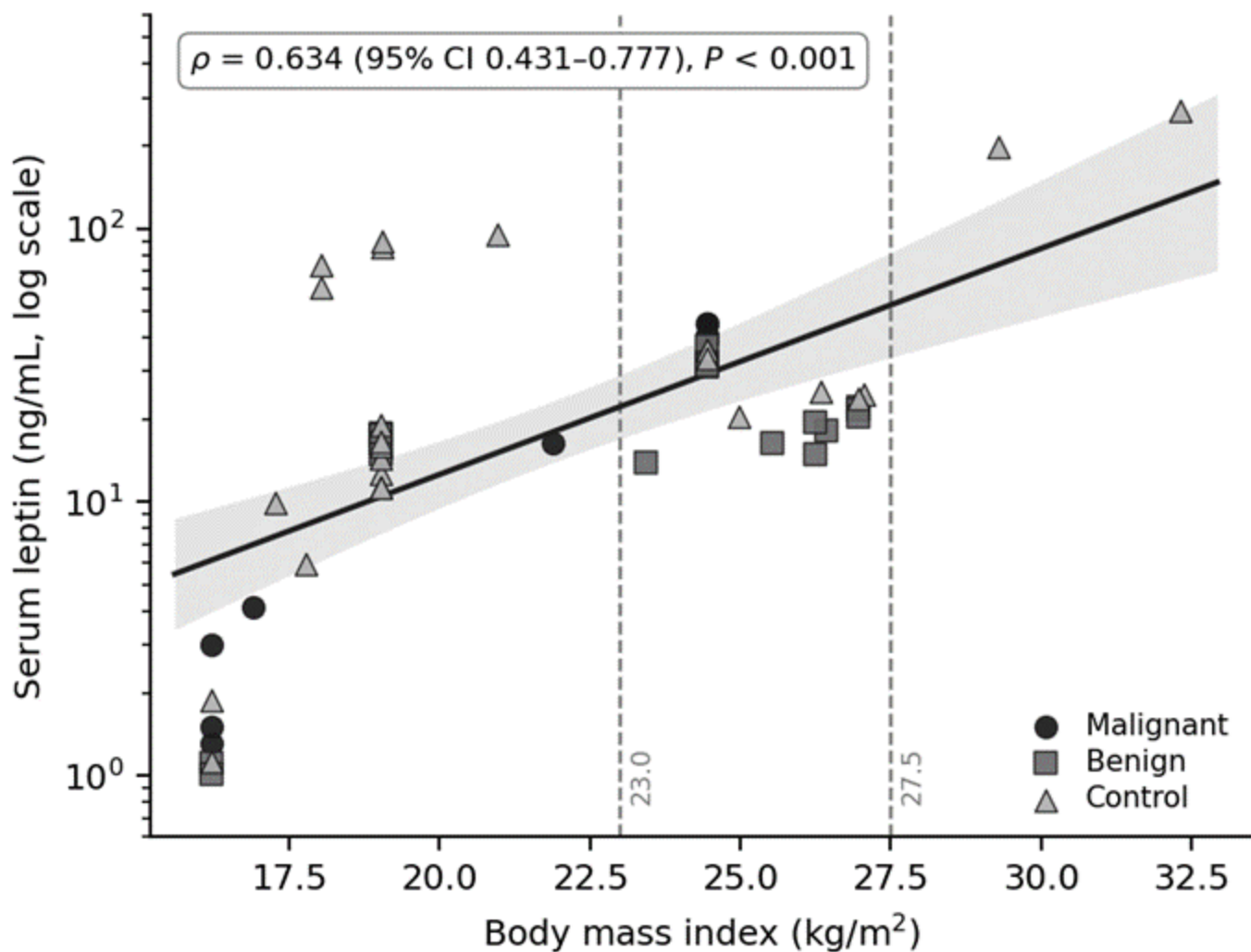


Figure 2

Serum leptin rose with body mass index in cases and controls alike. Each point is one participant, with separate symbols for malignant cases, benign cases, and controls. Leptin is plotted on a logarithmic axis; the solid line is the least-squares fit of the natural logarithm of leptin on body mass index, shown with its 95% confidence band, and corresponds to a 2.59-fold rise in leptin per 5 kg/m². Vertical dashed lines mark the Asia-Pacific thresholds of 23.0 and 27.5 kg/m²²⁷. Spearman's rank correlation for all 55 participants is inset.