# The role of metabolically active brown adipose tissue in patients with phaeochromocytoma and paraganglioma

DOCTORAL (PH.D.) THESIS BOOKLET

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***NOTE:*** *For space-saving reasons, this booklet represents a condensed version of the dissertation and therefore does not include references. Please refer to the* ***full dissertation*** *where all references for the text are provided.*

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# 1. Introduction

## 1.1. Phaeochromocytoma and paraganglioma

Catecholamines are sympathomimetic hormones derived from tyrosine, synthesised mainly in the adrenal medulla and sympathetic neurons via enzymatic steps converting tyrosine to DOPA, dopamine, then norepinephrine and epinephrine. These substances mediate stress responses—positive chronotropy and inotropy, vasoconstriction, bronchodilation, lipolysis, gluconeogenesis, diaphoresis, and reduced gastrointestinal motility, via α- and β-adrenergic receptors. Epinephrine and norepinephrine activate both, while dopamine acts mainly on dopaminergic receptors but can also stimulate adrenergic receptors at high levels.

In adults, catecholamine-secreting neoplasms include phaeochromocytomas and paragangliomas (PPGLs). Phaeochromocytomas (PCCs) originate within the adrenal medulla, whereas paragangliomas (PGLs) develop outside the adrenal glands, commonly along the sympathetic chain or within parasympathetic tissues. Although rare (2–8 cases/million/year), these tumours are significant due to catecholamine overproduction and possible dissemination.

### *1.1.1. Pathogenesis & inherited syndromes*

The pathogenesis of phaeochromocytomas (PCCs) and paragangliomas (PGLs) relates to embryological origins and genetic mutations. These tumours derive from neural crest cells, which form chromaffin cells in the adrenal medulla and paraganglia in extra-adrenal sites. Sympathetic PGLs typically secrete catecholamines; parasympathetic PGLs are usually nonfunctioning.

Molecular abnormalities in PPGLs affect cell proliferation and survival, primarily via two pathways: the pseudohypoxic and kinase signalling pathways. In the pseudohypoxic pathway ("cluster 1"), mutations affect oxygen-sensing mechanisms, stabilising HIFs, which drive angiogenesis and catecholamine production. *VHL* mutations prevent HIF degradation; *SDHx* mutations disrupt mitochondrial function, allowing succinate accumulation and further HIF stabilisation.

The kinase signalling pathway ("cluster 2") involves *RET* and *NF1* gene mutations. *RET* gain-of-function mutations activate PI3K/AKT/mTOR and RAS/RAF/MEK/ERK pathways. *NF1* mutations remove neurofibromin's tumour-suppressive function, leading to sustained MAPK/ERK signalling and tumour growth.

Due to their association with genetic disturbances, PPGLs may also arise as part of familial cases. In contrast to sporadic cases, it is estimated that up to 40% of PPGLs can be linked to inherited patterns of pathogenesis. MEN2, caused by germline RET mutations, includes MEN2A, MEN2B, and FMTC. All involve medullary thyroid carcinoma (MTC); PCCs are adrenal and bilateral in ~2/3 of cases. MEN2A involves parathyroid hyperplasia; MEN2B features marfanoid habitus and mucosal neurinomas. Von Hippel-Lindau (VHL) disease, due to VHL gene mutations, features PPGLs in 10–25% of cases, mostly as adrenal PCCs secreting noradrenergic catecholamines; bilateral PCCs occur in 43.5%, with PGLs in ~1/7 of patients. Neurofibromatosis type 1 (NF1), caused by *NF1* gene mutations, manifests with neurofibromas, café-au-lait spots, and optic gliomas. PPGLs occur in ~3% of NF1 patients, usually as unilateral adrenal PCCs. Hereditary paraganglioma-phaeochromocytoma syndromes, caused by *SDHx* mutations (*SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2*), result in mitochondrial complex II dysfunction and succinate accumulation, activating hypoxia pathways. *SDHB* mutations carry high malignancy risk and involve functioning sympathetic PGLs. *SDHD* mutations cause head and neck PGLs, maternally imprinted and nonfunctioning. *SDHC*, *SDHA*, and *SDHAF2* mutations are rare and linked to benign HNPGLs.

### 1.1.3. Clinical manifestations

Typical clinical manifestations of PPGLs result from excessive catecholamine production (mainly norepinephrine and epinephrine), leading to symptoms of sympathetic overactivity. The classic triad—headache, diaphoresis, and palpitations—may occur alone or together, though most patients lack all three. Triggers for catecholamine release include exertion, stress, posture changes, and activities raising intraabdominal pressure, often presenting as paroxysmal episodes ("spells") with abrupt symptoms that resolve spontaneously.

Hypertension is a major manifestation, appearing episodically in about half of patients and potentially causing severe hypertensive crises. Others may have sustained, treatment-resistant hypertension. Rarely, orthostatic hypotension occurs due to α-receptor downregulation from prolonged catecholamine exposure. Cardiovascular effects can include tachycardia, arrhythmias, and coronary vasospasm. PPGL symptoms may mimic psychiatric disorders, especially when autonomic features are present.

Not all PPGLs secrete significant catecholamines; nonfunctioning PPGLs (NF-PPGLs), often paragangliomas in the head and neck, may produce little or no catecholamines. These patients typically lack classic symptoms and are often diagnosed incidentally or via mass effect symptoms like abdominal discomfort or urinary obstruction. NF-PPGLs present diagnostic challenges and may be detected later than functioning tumours.

### 1.1.4. Diagnosis

The diagnostic approach to PPGLs involves biochemical testing and imaging with the aim of confirming excess catecholamine production and localising the tumour, respectively. Due to potential heredity, performing genetic assessment may influence further management.

The gold standard for diagnosing functioning PPGL is biochemical testing to detect elevated catecholamines or their metabolites. As catecholamine secretion

can be episodic, specific measurement of their *stable* metabolites (nor)metanephrines is essential for accurate diagnosis; therefore, measurement of plasma-free metanephrine and normetanephrine is the most sensitive test, as these metabolites are continuously produced by the breakdown of catecholamines within the tumour. For patients where plasma testing is impractical or in cases where further confirmation is needed, 24-hour urinary measurements of fractionated catecholamines can be used. It must be noted that some medications can interfere with assays. Plasma 3-MT measurement is clinically useful for detecting rare dopamine-producing PPGLs.

Computed tomography (CT) is used for proper localisation of both adrenal and extra-adrenal tumours. The protocol for assessing adrenal masses includes a non-contrast (native) CT scan, followed by intravenous contrast administration if the benign nature of the mass cannot be confirmed. Magnetic resonance imaging (MRI) is an alternative to CT and is particularly useful for patients with allergy to intravenous contrast (iodine) agents or with contraindications to ionising radiation. Furthermore, MRI is most sensitive for imaging HNPGL due to its superior soft tissue resolution.

Positron emission tomography (PET) using $^{68}$Ga-DOTATATE (DOTA-[Tyr$^3$]-octreotate) and $^{18}$F-FDG (fluorodeoxyglucose), as well as single-photon emission computed tomography (SPECT) using $^{123}$I-MIBG (metaiodobenzylguanidine), are used for detecting PPGLs. Selection and performance of these imaging modalities is affected by tumour differentiation, catecholamine storage, expression of receptors, and tumour's metabolic activity. $^{68}$Ga-DOTATATE PET targets somatostatin receptor expression and has recently shown excellent results in PPGL imaging. It is particularly effective for detecting tumours with *SDHD*/*SDHC* mutations, i.e. well-differentiated, localised PPGLs and HNPGLs due to their high somatostatin receptor density, but also for metastatic disease. $^{123}$I-MIBG SPECT, which relies on catecholamine transport and vesicular storage, may be used as a method for functional adrenal phaeochromocytomas, although with variable performance in impaired catecholamine storage. $^{18}$F-FDG is a less specific tracer

which reflects glucose metabolism via glycolysis, and is therefore superior for aggressive, metastatic or *SDHB*-mutated PPGLs, which show high glycolytic activity. It outperforms both MIBG and CT/MRI for metastatic disease detection.

### *1.1.5. Management*

The only definitive treatment for PPGLs is surgical resection of the tumour. For patients with a confirmed diagnosis, preoperative medical management is initiated and should be based on sequential α- and β-adrenergic blockades.

A laparoscopic or laparotomic approach is used for localised phaeochromocytomas and abdominal PGLs, while PGLs located in other regions require specialised approaches. In patients with hereditary phaeochromocytomas, a bilateral cortex-sparing adrenalectomy can be performed. Postoperative follow-up surveillance should be individually based on multiple factors, including genetic background and biochemical activity of the disease.

Metastatic disease can be cured only if all tumours are resectable; in all other cases, the management is oriented towards management of symptoms and systemic therapy (by $^{131}$I-MIBG ablation or chemotherapeutic agents).

## 1.2. Brown adipose tissue

Adipose tissue in humans and other mammals can be categorised into two primary subtypes: white (WAT) and brown adipose tissue (BAT). WAT predominantly serves as an energy reservoir by sequestering surplus dietary calories in the form of triglycerides. Beyond its storage capacity, WAT operates as an active endocrine organ, releasing cytokines and other signalling molecules that modulate energy metabolism and assist in maintaining overall physiological homeostasis. BAT, in contrast, is specialised for thermogenesis, with this activity being linked to elevated mitochondrial density and the expression of uncoupling protein-1 (UCP1), which facilitates heat production independent of adenosine triphosphate (ATP) synthesis. Although adult humans primarily produce heat via shivering mechanisms, the thermogenic role of BAT is vital in neonatal mammals

(including human neonates), where heat production is necessary to counteract heat loss and preserve core body temperature in the context of underdeveloped muscular system. Similarly, hibernating species rely on BAT's capacity for rapid heat generation to endure extended periods of reduced ambient temperatures. Notwithstanding its relevance in neonates and hibernators, BAT also persists in adult humans, albeit in smaller quantities.

During the early stages of human development, BAT predominantly localises to specific anatomical regions, such as the neck, mediastinum, axilla, and retroperitoneum. As individuals progress through childhood and into adolescence, the quantity of BAT in these depots tends to decrease and reflect reduced thermogenic demands and shifts in metabolic regulation. Nevertheless, residual BAT may remain dispersed in various sites with retained capacity to undergo thermogenic activation under particular physiological and pathological conditions. The regulation of BAT mass and function in later life appears to be influenced by various endocrine signals.

### *1.2.1. Catecholamine-mediated activation*

Of all the potential stimuli for BAT activation, catecholamines are best described. Norepinephrine binds to $\beta_3$-adrenergic receptors on brown adipocytes, triggering a signalling cascade that activates adenylyl cyclase and increases cAMP production. Elevated cAMP stimulates protein kinase A (PKA), which phosphorylates hormone-sensitive lipase and perilipin, enhancing lipolysis and releasing free fatty acids that fuel thermogenesis and activate UCP1. PKA also induces thermogenic gene transcription, upregulating UCP1.

UCP1 functions as a proton channel, allowing protons to re-enter the mitochondrial matrix independently of ATP synthase, dissipating the proton gradient as heat—termed non-shivering thermogenesis—and increasing glucose uptake.

Beyond classical BAT activation, "WAT browning" refers to the emergence of "beige" adipocytes within white adipose tissue. These cells display multilocular

lipid droplets, high mitochondrial content, and express UCP1, though they arise in response to stimuli rather than developmental programming.

### *1.2.2. Regulatory factors*

A potent activator of human BAT is cold exposure via norepinephrine-mediated UCP1 upregulation. Upon sensing a drop in temperature, thermoregulatory centres in the hypothalamus increase sympathetic stimulation to brown adipocytes. BAT activation is inversely correlated with outdoor temperature and body fat percentage, suggesting individuals with lower fat rely more on BAT for thermoregulation.

Beyond catecholamines, several physiological factors—ambient temperature, diet, energy status, and hormone-associated signalling—modulate BAT activity, often overlapping with catecholamine pathways. Thyroid hormones, especially triiodothyronine ($T_3$), synergise with adrenergic signalling to enhance thermogenesis via TR-α and TR-β receptors. Deiodinase type 2 converts thyroxine ($T_4$) to more active $T_3$ in brown adipocytes, amplifying local thermogenic responses.

Insulin signalling also promotes BAT activity. Cold exposure enhances insulin sensitivity, upregulating insulin receptor signalling components and facilitating glucose uptake. The PI3K/Akt pathway, activated by insulin, intersects with adrenergic signalling and promotes thermogenic gene expression.

Capsaicin stimulates BAT thermogenesis by activating TRPV1 channels and the sympathetic nervous system. Other bioactive substances—resveratrol, curcumin, caffeine, catechins, menthol, and omega-3 fatty acids—are increasingly associated with BAT activation, often synergising with catecholamines.

BAT also secretes cytokines ("batokines") that regulate energy expenditure, including FGF21, $T_3$, and microRNAs, contributing to BAT remodelling.

The hypothalamus integrates signals such as temperature and energy status to modulate sympathetic outflow to BAT. Leptin increases sympathetic activity to BAT, promoting thermogenesis.

Circadian rhythms influence BAT activation, with non-shivering thermogenesis and fat oxidation more pronounced in the morning, reflecting both circadian and seasonal patterns in BAT function.

### 1.2.3. Detection

FDG-PET imaging, as mentioned in the previous chapter, is commonly used for detecting abnormally metabolically active tissues, and can therefore incidentally reveal aBAT due to its high glucose uptake—often presenting as areas of intense FDG accumulation that may be mistaken for malignancy and lead to false-positive reporting of tumours. This phenomenon has important diagnostic implications in patients with PPGLs as the adrenergic stimulation associated with PPGLs promotes BAT activation and subsequent FDG uptake, leading to aBAT as an incidental finding on PET imaging in these patients. This is particularly relevant as FDG-PET in these patients is typically used when aggressive disease is suspected.

Research on FDG-PET imaging in patients with PPGL has reported aBAT detection, correlating with elevated plasma catecholamine levels. However, no clear association has been established between aBAT incidence and specific germline mutations within PPGL patients, though one study indicated that aBAT presence might be linked to poorer survival outcomes. The propensity of aBAT to show up on FDG-PET, particularly in cases of catecholamine excess, emphasises the need for standardised imaging criteria and diagnostic cut-offs to differentiate between true tumour tissue and aBAT in clinical settings. Currently, the standardised uptake value (SUV) cut-off for aBAT identification varies, though it is often set between 1.0 and 2.0, with some PPGL studies employing a threshold of > 1.5. Despite these guidelines, the relationship between aBAT and PPGL remains underexplored, and there is minimal consensus on its precise clinical significance.

In addition to diagnostic challenges, a deeper understanding of the aBAT and PPGL relationship could offer better understanding of the potential prognostic value of aBAT detection. However, not much is known from sources above

primary research about the precise relationship of aBAT with PPGL and catecholamine levels. The limited available research hints at a potential association between aBAT incidence and the severity of catecholamine excess, yet many questions remain about whether aBAT could serve as a marker for tumour burden, metabolic dysfunction, or adverse outcomes in patients with PPGL.

Our study aims to expand the current knowledge pool related to aBAT and its association with PPGLs, investigating its prevalence, biochemical associations, and clinical implications. By performing an observational cohort study, we hope to clarify how aBAT detection correlates with patient characteristics, biochemical markers, tumour characteristics, and survival outcomes. Afterwards, through performing a comprehensive systematic review of original research studies and meta-analysis, we aim to raise the evidence of these findings through the inclusion of previously conducted research along with our original research.

Ultimately, our goal is to determine whether aBAT could serve as a meaningful clinical indicator to aid in prognostication and potentially even guide therapeutic approaches for patients with PPGL.

# 2. Cohort study

## 2.1. Methods

We conducted a retrospective observational study across a single tertiary academic institution (King's College Hospital NHS Foundation Trust, London, United Kingdom), evaluating the presence of aBAT in patients who had undergone FDG-PET imaging for suspected PPGL. The selection criteria for FDG-PET included patients with presumed disseminated or extra-adrenal disease, or those with intermediate lesions based on strong clinical or radiological suspicion (e.g., findings on CT imaging). These cases were reviewed in adrenal multidisciplinary team meetings, where the indication for FDG-PET was determined. Guideline recommendations for imaging in PPGL were followed.

### *2.1.1. Patient characteristics and clinical assessment*

The PPGL patients included had their baseline FDG-PET scans reviewed by two nuclear medicine consultant physicians experienced in FDG-PET CT reporting. Cases were independently scored for the presence of aBAT in predetermined locations (supraclavicular, paravertebral, perirenal). Any discrepant cases were mediated by a third such experienced nuclear medicine consultant physician.

### *2.1.2. Statistical analysis*

Continuous data were assessed for normality using the Shapiro–Wilk test. Normal data were expressed as the mean value with its respective standard deviation ($A_r \pm SD$). Non-normal data is presented as the median with interquartile range in square brackets (MED [IQR]). We reported categorical data using ratios and percentages. Missing data within the dataset were imputed using the *missRanger* package (version 2.4.0), employing a random forest algorithm for iterative imputation. The function was iterated 1,000 times, with each random forest consisting of 100 trees.

To investigate the potential association of covariates with the incidence of aBAT, we conducted a multivariate analysis using a logistic regression. The model was fitted with Firth's bias reduction method to address issues of small sample sizes and rare events. The analysis incorporated pre-defined clinical covariates, while the results were presented as adjusted odds ratios (OR) for each covariate, with their respective 95% confidence intervals (95%–CI) and *P*-values ($\alpha = 0.05$), alongside non-adjusted (crude) ORs. The *logistf* package (version 1.26.0) was used for the multivariate logistic regression analysis. We defined statistically insignificant trends as $P < 0.2$.

To assess statistical significance in difference of observed numerical variables, we implemented an R function for non-parametric bootstrap *P*-value calculation due to relatively small sample size. The function performed iterative resampling (10,000 iterations) to compute t-statistics for two-group comparisons, determining the *P*-value based on the proportion of resampled statistics. Statistical significance of independence of categorical data was tested using Fisher's exact tests for count data.

We produced Kaplan–Meier plots to compare the OS and PFS times between the investigated and control group. Due to the sample size, the significance of survival differences was assessed using a univariate Cox model.

All analyses were performed in the *R* statistical software, version 4.4.0.

### 2.1.3. Ethics

Ethical approval from a Regional Ethical Committee (REC) in the United Kingdom (UK) was not required as the data generated for the purposes of this project were fully anonymised, collected in line with the standard of care protocols for treating patients with PPGL at the King's College Hospital, and are processed and presented retrospectively. The study was discussed within Research Delivery Unit 6 (RDU6) meeting – Renal/Endo Research Group Board (RRGB) at King's College Hospital NHS Foundation Trust (Governance Arrangements for Research

Ethics Committees [GafREC]: Endo203). The study is registered with ClinicalTrials.gov, with registration number NCT06440122.

## 2.2. Results

An initial list of 93 patients with suspected PPGL having undergone FDG-PET imaging was obtained from the nuclear medicine department covering the time period from 2013 to 2021. After exclusion of duplicate patients and reviewing electronic notes for the inclusion of only those with a PPGL diagnosis confirmed after discussion in multidisciplinary team meetings, this list was reduced to 62 patients (22 male, 40 female), of whom 8 were later classified as aBAT-positive and 54 as aBAT-negative.

The results of demographic and clinical data analysis and laboratory, imaging, pathology, treatment, and follow-up information, are also presented in the patient characteristics table (Table 1) with respect to the presence or absence of aBAT. Except for the plasma metanephrine concentration, which was significantly negatively associated with aBAT, the differences in categorical and continuous data between the groups did not reach statistical significance in the univariate analysis.

Penalised multivariate analysis with multiple clinical covariates indicated that male sex (adjusted OR 0.1; CI 0.00, 1.05), tumour type (adjusted OR 2.10; CI 0.37, 16.41), hypertension (adjusted OR 0.26; CI 0.03, 1.42), and increased plasma metanephrine levels (adjusted OR 0.00; CI 0.00, 1.06) were not significantly associated with the presence of aBAT. In contrast, increased plasma normetanephrine levels (adjusted OR 2.85; CI 1.11, 10.35) showed a statistically significant trend towards aBAT presence.

Overall, mortality rates were 25.0% in aBAT-positive patients and 22.2% in aBAT-negative patients ($P$ = 1.000). The median progression-free survival was 41.0 months [22.5, 60.0] in aBAT-positive patients and 36.0 months [24.3, 55.3] in aBAT-negative patients ($P$ = 0.913). Overall survival medians were 41.0 months [23.3, 60.8] for aBAT-positive patients and 47.5 months [32.8, 95.3] for aBAT-

negative patients ($P = 0.136$). The univariate Cox proportional hazards model indicated hazard ratios of 1.77 (CI 0.38, 8.18) and 1.38 (CI 0.30, 6.34) for overall and progression-free survival probabilities, respectively.

While statistically insignificant, the aBAT-positive group showed trends (defined as $P < 0.2$) in association with lower age, absence of prior cardiovascular disease, lower number of antihypertensive medications, and lower overall survival. In our study, although no patients with detectable aBAT were taking adrenoreceptor blockade, we found no statistical association between aBAT and either alpha- or beta-blocking medication ($P = 0.581$ and $P = 1.000$, respectively).

One of our patients in the aBAT-positive cohort had a confirmed diagnosis of MEN2A proceeding to a right adrenalectomy for phaeochromocytoma and total thyroidectomy for medullary thyroid carcinoma (MTC); both in 2014 with satisfactory surgical clearance. Areas of aBAT uptake on FDG-PET were retrospectively correlated with brown adipose tissue on histology specimens.

**Table 1.** Patient characteristics table

| | **aBAT-positive** (N = 8) | **aBAT-negative** (N = 54) | ***P*-value** |
|---|---|---|---|
| **Demographic information** | | | |
| Age [years] | 46.0 [29.8, 51.0] | 54.5 [39.8, 60.8] | 0.126 |
| Sex | | | 0.240 |
| — Female | 7 (87.5%) | 33 (61.1%) | |
| — Male | 1 (12.5%) | 21 (38.9%) | |
| **Clinical data** | | | |
| Body mass index [kg/m$^2$] | 25.8 ± 4.82 | 26.9 ± 5.23 | 0.548 |
| Prior cardiovascular disease | 0 (0%) | 13 (24.1%) | 0.186 |
| Hypertension | 2 (25%) | 29 (53.7%) | 0.255 |
| Number of antihypertensives | 0.389 ± 0.737 | 0.903 ± 1.090 | 0.083 |
| — Alpha blockade | 0 (0%) | 8 (14.81%) | 0.581 |
| — Beta blockade | 0 (0%) | 5 (9.26%) | 1.000 |
| Positive family history | 1 (12.5%) | 6 (11.1%) | 1.000 |
| **Laboratory parameters** | | | |
| Plasma metanephrine [pmol/L] | 279 [202, 913] | 505 [169, 1920] | 0.034 |
| Plasma normetanephrine [pmol/L] | 7740 [674, 14700] | 2320 [1010, 10100] | 0.434 |
| Ratio of plasma normetanephrine / metanephrine | 14.3 [3.66, 25.90] | 6.45 [3.03, 17.70] | 0.472 |
| Plasma 3-methoxytyramine [pmol/L] | 131 [120, 231] | 120 [120, 232] | 0.876 |
| **Imaging and pathology** | | | |
| Number of aBAT locations | 3.90 ± 2.78 | not applicable | |
| Highest aBAT $SUV_{max}$ | 5.69 [3.87, 12.70] | not applicable | |
| Tumour type | | | 1.000 |
| — Phaeochromocytoma | 5 (62.5%) | 34 (63.0%) | |
| — Paraganglioma | 3 (37.5%) | 20 (37.0%) | |
| Size of largest tumour [mm] | 57.5 [48.7, 70.3] | 49.5 [30.0, 64.3] | 0.876 |

| | **aBAT-positive** (N = 8) | **aBAT-negative** (N = 54) | ***P*-value** |
|---|---|---|---|
| Cluster | | | 1.000 |
| — No mutation | 4 (50.0%) | 17 (31.5%) | |
| — Cluster 1 (*SDHx*, *VHL*) | 1 (12.5%) | 9 (16.7%) | |
| — Cluster 2 (*MEN*, *RET*) | 0 (0%) | 2 (3.7%) | |
| — Unknown | 3 (37.5%) | 26 (48.1%) | |
| AJCC staging | | | 0.374 |
| — 1 | 1 (12.5%) | 16 (29.6%) | |
| — 2 | 1 (12.5%) | 14 (25.9%) | |
| — 3 | 3 (37.5%) | 8 (14.8%) | |
| — 4 | 3 (37.5%) | 16 (29.6%) | |
| Metastatic disease | 3 (37.5%) | 16 (29.6%) | 0.692 |
| **Treatment** | | | |
| Chemotherapy | 1 (12.5%) | 4 (7.41%) | 0.511 |
| Surgery | 6 (75%) | 46 (85.2%) | 0.604 |
| Radiotherapy | 0 (0%) | 3 (5.56%) | 1.000 |
| MIBG therapy | 1 (12.5%) | 8 (14.8%) | 1.000 |
| **Follow-up** | | | |
| RECIST v1.1 criteria | | | 0.292 |
| — Complete response (CR) | 1 (12.5%) | 11 (20.4%) | |
| — Partial response (PR) | 0 (0%) | 6 (11.1%) | |
| — Stable disease (SD) | 0 (0%) | 2 (3.7%) | |
| — Progressive disease (PD) | 3 (37.5%) | 5 (9.3%) | |
| — No data | 4 (50.0%) | 30 (55.6%) | |
| Mortality | 2 (25.0%) | 12 (22.2%) | 1.000 |
| Progression-free survival [months] | 41.0 [22.5, 60.0] | 36.0 [24.3, 55.3] | 0.913 |
| Overall survival [months] | 41.0 [23.3, 60.8] | 47.5 [32.8, 95.3] | 0.136 |

*Legend: aBAT, active brown adipose tissue; $SUV_{max}$, maximum standardised uptake value; SDH(x), succinate dehydrogenase complex (subunit x); VHL, Von Hippel-Lindau; RET, "rearranged during transfection"; MEN, multiple endocrine neoplasia; RECIST, Response Evaluation Criteria in Solid Tumours; MIBG, metaiodobenzylguanidine.*

# 3. Systematic review of literature

## 3.1. Methods

The design of this study was set as a systematic review and meta-analysis of original research studies. A protocol was created using PICO (population, intervention, control, outcomes) framework and registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the number CRD42021276073 and was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020.

### *3.1.1. Study eligibility*

The review assessed only peer-reviewed publications in English. We used all of the following inclusion criteria:

- All prospective and retrospective studies examining BAT in patients with PPGL (randomised controlled trials [RCTs], observational, cohort, and other).
- Diagnosis of PPGL based on biochemistry, pathognomonic imaging, and/or histology.
- Patients to have completed FDG-PET imaging.

### *3.1.2. Statistical analysis*

We used the random-effects model with the inverse variance method and restricted maximum-likelihood (REML) tau-estimation to pool such quantitative data and calculate the summary results based on effect sizes. Subsequently, the results were expressed using forest plots as standardised mean differences (SMD) with respective 95%–confidence intervals (CI). Afterwards, a cumulative meta-analysis, using the chronological criterion, was also performed in order to assess the evolution and trends in the data over time, with results plotted on a cumulative forest plot.

Studies were also analysed using a meta-analysis of proportions with respective 95%–CIs, both as standard and cumulative meta-analytical methods, after each of which a forest plot was generated.

## 3.2. Results

### *3.2.1. Search and selection*

A total of 145 records were identified through database searches, including MEDLINE (35 records), Embase (59 records), and Scopus (51 records). After the removal of 83 duplicate records, 62 records remained for screening (κ = 1.00). During the screening phase, 53 records were excluded: 34 were case reports, 12 were reviews, and 7 were excluded for other reasons. Consequently, 9 reports were sought for retrieval, and all 9 reports were successfully retrieved for assessment. Ultimately, six studies were included in the review.

### *3.2.2. Synthesis*

The included studies were primarily conducted on a retrospective basis, with a PPGL diagnosis being made multi-modally. Cohort samples analysed ranged from 28 to 205 patients. The included studies revealed a clear correlation between the elevation of catecholamine tracers and the predisposition to increased BAT activity. For 12 out of 12 patients with non-secreting PPGLs (normal catecholamine assessment) across two studies, BAT activation was absent.

The meta-analysis of pooled data showed a statistically significant positive difference in isolated normetanephrine/norepinephrine (SMD = 0.70; CI 0.37, 1.03) catecholamine levels between the aBAT-positive ($N$ = 69) and negative ($N$ = 210) groups, with a low level of heterogeneity ($I^2$ = 20%, $P$ = 0.29). Isolated metanephrine/epinephrine levels indicated a negative, albeit statistically insignificant, mean difference between the groups (SMD -0.15; CI -0.47, 0.16). When combined, however, normetanephrine/norepinephrine and metanephrine/epinephrine levels also showed statistically significant positive difference between

the aBAT-positive ($N$ = 67) and negative ($N$ = 188) groups (SMD 0.51; CI 0.18, 0.85) with low, statistically insignificant heterogeneity ($I^2$ = 24%, $P$ = 0.26).

The test for overall heterogeneity was statistically significant (Q = 26.65, df = 13, $P$ = 0.0139), indicating a non-negligible inter-study variability that should be accounted for when interpreting the findings. Despite these variations, the directionality of the effect remained consistent across most studies.

After performing a cumulative meta-analysis on the combined groups of metabolites in chronological order, the SMD showed notable variation as new studies were added, with an initial large effect size decreasing and stabilising over time, with initially substantial heterogeneity ($I^2$ = 57%) reducing over time to low ($I^2$ = 24%). The addition of data from our study led to a pooled estimate of SMD = 0.51 (95% CI: 0.18, 0.85), with a further reduction in heterogeneity to $I^2$ = 24.1%. Over time, the confidence interval of the effect size narrowed, and the $P$-value decreased, despite only one study in isolation reached statistical significance.

The proportion of phaeochromocytoma patients who also had aBAT was 26% (CI 20%, 32%), with moderate, albeit statistically insignificant heterogeneity ($I^2$ = 32%, $P$ = 0.18).

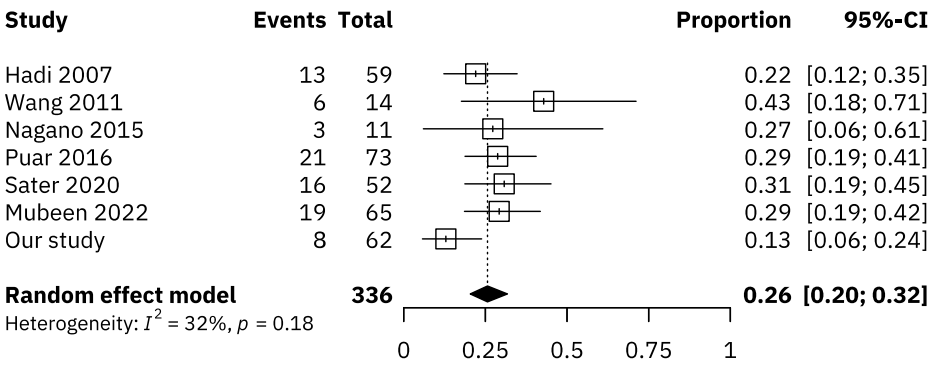


**Figure 1.** Forest plot showing proportions of PPGL patients with aBAT

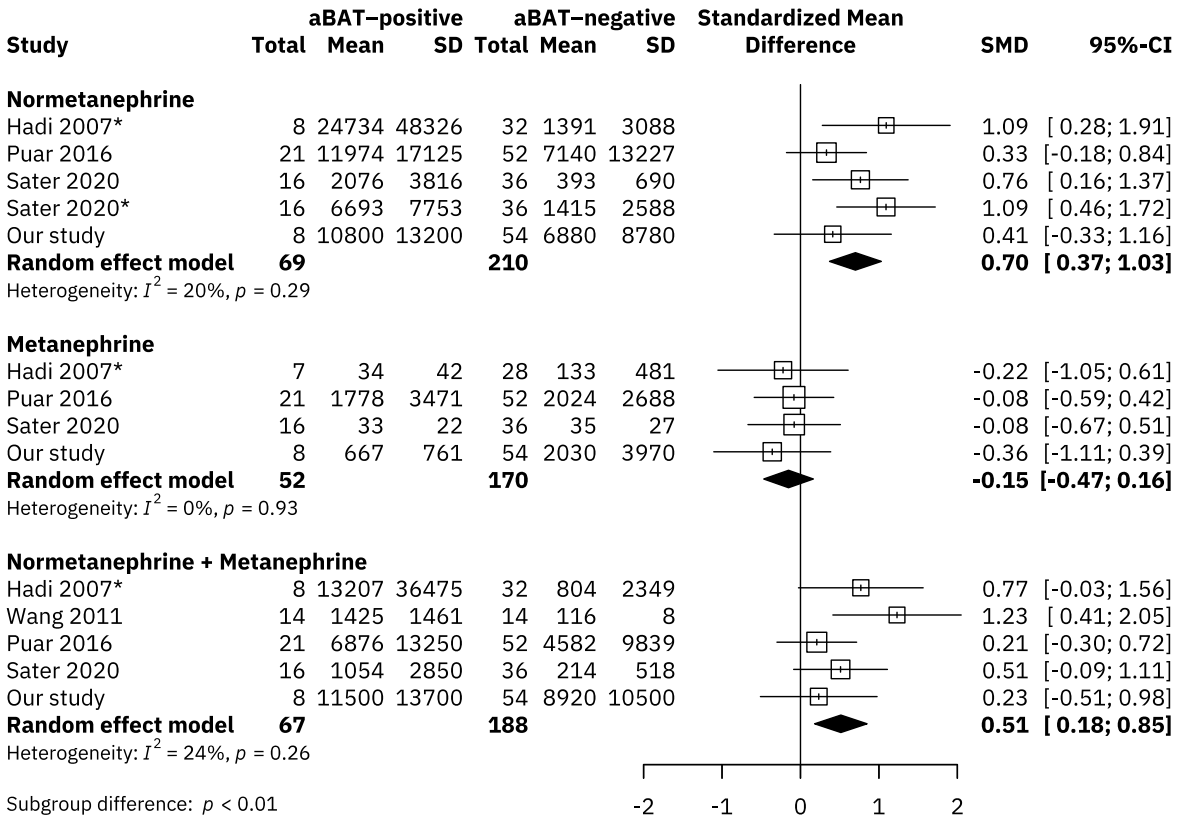


**Figure 2.** Forest plot showing mean differences in levels of different catecholamines.

# 4. Discussion

The interplay between PPGLs and brown adipose tissue (BAT) represents a complex and evolving area of research, linked together in the context of catecholamine excess. Given that BAT is primarily activated by sympathetic stimulation, its incidental detection on FDG-PET imaging in patients with PPGLs has raised questions about its underlying metabolic interactions, clinical significance, and potential prognostic value. To comprehensively investigate this relationship, we used a dual approach: (1) conducting a retrospective cohort study to assess the prevalence and clinical correlates of BAT activation in PPGL patients, and (2) performing a systematic review with meta-analysis (SR/MA) to integrate our findings with existing literature and previously available data. Our cohort study provided a deeper insight into the association between aBAT and specific biochemical markers (particularly plasma normetanephrine), while the SR/MA allowed us to contextualise these findings within a broader evidence base.

Past studies have reported aBAT in PPGL patients with a prevalence of 7.8% to 42.8% using lenient $SUV_{max}$ cut-offs. Using a stricter 1.5 cut-off, we found 13% (8/62) with aBAT. While FDG-PET suggests BAT presence via metabolic activity, it does not confirm it. In one patient with MEN2A, histopathology validated BAT adjacent to the tumour, correlating with PET findings.

Trends ($P < 0.2$) indicated that aBAT-positive patients were younger, had fewer cardiovascular comorbidities, used fewer antihypertensives, had more advanced AJCC staging, and lower survival, though these were not statistically significant. Age is often key in BAT activation, but our limited age range may have obscured this. Other PPGL cohorts found no major differences in tumour characteristics or locations. aBAT can also be seen with other imaging modalities due to sympathetic innervation.

More females had aBAT (87.5% vs 61.1%), suggesting sex hormones may influence BAT activation. Prior studies have shown sex-based differences in BAT function and thermogenesis, potentially impacting aBAT prevalence in females.

Our meta-analysis found that including our cohort's lower aBAT proportion had minimal effect on pooled results, supporting a stable ~25% prevalence. Demethylated metabolites, especially normetanephrine, were significantly higher in aBAT-positive groups. Preclinical work links norepinephrine stimulation with BAT activity through $\beta_3$-receptors, driving thermogenesis. In our study, higher normetanephrine levels were significant in multivariate analysis; metanephrine was inversely associated in univariate analysis, suggesting a preference for increased normetanephrine-to-metanephrine ratio in BAT activation. Phaeochromocytoma and paraganglioma distributions were similar between groups.

BAT's metabolic activity may clear catecholamines, altering plasma metabolite profiles. aBAT patients may represent a subgroup with distinct hormonal or tumour profiles. Most (86%) of our cohort lacked aBAT, raising the question of other browning mechanisms. BAT activation has been linked to malignancies, but its role remains controversial. While BAT is thought to act via $\beta_3$-adrenoreceptors, $\beta_2$-mediated thermogenesis is also proposed. No aBAT-positive patients were on adrenoreceptor blockers, and medications were not associated with aBAT, though undetected effects cannot be ruled out.

Catecholamines may influence tumour growth and resistance via receptor-mediated pathways. Similarly, BAT activation and WAT browning may also result from other factors (e.g., thyroxine, bile acids, IL-6, PTH-rP, and natriuretic peptides). PPGLs can secrete growth factors like adrenomedullin, known to induce lipolysis and browning in other tumour models. This suggests browning factors beyond catecholamines warrant further investigation. Increased plasma normetanephrine was associated with aBAT, but not with imaging, pathology, or treatment features. No associations were found with specific germline mutations. More aBAT-positive patients were stage 3–4 (75% vs 44.4%), possibly explaining lower survival, although not statistically significant. Limited sample size restricted matched control comparisons.

Solid tumours often lie near adipose tissue, enabling tumour–adipocyte interactions that promote tumour growth via lipid and adipokine transfer. BAT,

although protective in metabolic diseases, may contribute to cancer cachexia. Studies have long suggested BAT contributes to weight loss in cancer, and recent work links BAT activation to BMI and cachexia. An inverse aBAT–BMI relationship was found in our review, possibly reflecting cancer hypermetabolism via UCP1-driven thermogenesis. However, large retrospective studies haven't confirmed significant links to cachexia or mortality. While preclinical studies support these associations, clinical evidence is limited and further study is needed. It can be hypothesised that BAT's role in weight regulation may even offer therapeutic options for obesity.

Our cohort's Kaplan–Meier plots showed trends toward reduced survival in aBAT-positive patients, but the small sample and strict $SUV_{max}$ cut-off limited statistical power. Prior studies found that higher norepinephrine levels and BAT activity on PET correlated with reduced survival, suggesting norepinephrine may independently predict mortality. Interest is growing in prognostic biomarkers for PPGL outcomes. aBAT may worsen prognosis through hypermetabolism, cachexia, malnutrition, and cardiovascular risk. Catecholamine excess exacerbates metabolic instability and cardiomyopathy, while BAT-induced hypermetabolism may lower treatment tolerance and surgical eligibility, reducing survivability.

In PPGL, catecholamine excess not only activates BAT but may worsen outcomes through its systemic effects. These pathways linking hypermetabolism, cachexia, and cardiovascular strain support aBAT as a potential independent survival determinant, though further prospective research is needed.

## 4.1. Strengths and limitations

To our knowledge, this is the first *clinical* cohort study assessing BAT activation on FDG-PET with histopathological confirmation in PPGL patients. Although based on a single patient, this confirmation supports the correlation between imaging findings and true aBAT. Unlike previous cohort studies on aBAT in PPGL, ours uses a multivariate statistical approach, enhancing generalisability.

Limitations stem from the retrospective design and small sample size. Histological confirmation was possible in only one patient, as multiple biopsies pose ethical and practical challenges. The observational nature restricted systematic analyses, and some records lacked full data, particularly from out-of-region cases. To address this, we applied a random forest algorithm with 1,000 iterations and 100 trees to impute missing data. Still, due to the rarity of these tumours and limited FDG-PET use for characterisation, findings must be interpreted cautiously.

In the meta-analysis, increased catecholamine levels consistently appeared, reducing heterogeneity and increasing statistical significance. Including our study lowered the pooled *P*-value to 0.0025 and reduced heterogeneity by 12%, especially for catecholamine variability. Sensitivity analyses with and without our data supported the trends and robustness of findings. This held even though normetanephrine levels in our cohort lacked significance in univariate analysis.

Pooling data was challenging, as not all studies assessed the same catecholamine parameters, and some combined or reported them differently. We standardised values prior to analysis. Despite including only six eligible studies with varied designs, our study enhanced the statistical power and meta-analytical clarity regarding aBAT prevalence and biochemical associations.

# 5. Future perspectives

The exploration of catecholamine-secreting tumours in association with BAT activation opens several areas for future research, particularly given the potential prognostic implications of activated BAT in these patients. This study has established the foundation for univariately and multivariately identifying the biochemical markers—most notably normetanephrine—that correlate with aBAT presence. However, the association between aBAT and patient outcomes, specifically in terms of disease progression and survival, requires further investigation.

Expanding our understanding of the molecular pathways involved in BAT activation within the PPGL population could provide significant insights into this field. Although catecholamine excess is likely a primary driver of BAT activation, other factors may also contribute. Investigating these "browning" factors—such as inflammatory cytokines, adrenomedullin, and parathyroid hormone-related peptide (PTH-rP)—could clarify whether BAT activation in patients with PPGL reflects broader metabolic dysregulation. Future studies might benefit from employing high-throughput "omics" approaches (i.e., genomics, proteomics, metabolomics) to identify novel biomarkers and pathways involved in BAT activation.

Another potential area for future research is to refine imaging criteria for aBAT detection. Given that FDG-PET imaging can reveal intense BAT activity, which may mimic malignancy, establishing robust diagnostic criteria (including SUV cut-offs) for aBAT would enhance the accuracy of aBAT identification. Additional insights may be obtained by assessing alternative imaging options which directly target sympathetic innervation (e.g., F-DA PET). Integrating multimodal imaging strategies could also provide a more nuanced understanding of BAT activity and potentially aid in differential diagnosis and risk stratification.

The prognostic role of aBAT in patients with PPGLs requires further investigation. Although preliminary data suggest that the presence of aBAT may correlate with more advanced disease stages, larger prospective studies are needed to

confirm whether aBAT serves as a reliable marker of tumour burden and adverse clinical outcomes. Moreover, investigating whether interventions targeting BAT (e.g., $\beta_3$-adrenergic antagonists) could modulate disease progression presents a promising yet untested therapeutic approach.

Finally, it would be valuable to explore BAT activation's role in broader oncologic and metabolic contexts, particularly given the hypothesised link between BAT activation and cancer-associated cachexia (CAC). Future studies should investigate whether BAT contributes to the hypermetabolic state observed in CAC and whether the aBAT prevalence varies across different cancer types to identify tailored therapeutic strategies for metabolic management in oncology.

Advancing our understanding of BAT activation in PPGLs requires a multifaceted approach involving multiple dimensions. Future research should prioritise large-scale, prospective cohort studies to validate the current findings and investigate BAT's role as a potential prognostic biomarker. Additionally, mechanistic studies exploring non-sympathetic pathways of BAT activation and intervention trials targeting BAT modulation may offer new perspectives for managing PPGLs and other metabolically influenced cancers.

# 6. Summary of findings

The key findings of this research are as follows:

1. In contrast to prior studies that univariately linked general catecholamine levels or single catecholamines with aBAT, our results revealed a statistically significant association between elevated plasma normetanephrine levels and aBAT presence in a *multivariate* analysis. This confirms plasma normetanephrine as a specific biomarker for aBAT presence in PPGL.
2. Our study identified an inverse relationship between plasma metanephrine levels and aBAT presence, as observed in the univariate analysis, which implies a possible association with a higher normetanephrine-to-metanephrine ratio suggesting the presence of aBAT.
3. This study is the first *clinical* study to provide histopathological confirmation of brown adipose tissue adjacent to phaeochromocytoma, thereby further validating FDG-PET imaging as a reliable method for identifying BAT in this patient group.
4. Our study showed that aBAT-positive patients more frequently presented with advanced stage (3–4) disease, implying that this association might suggest the potential of aBAT as a marker of disease burden or progression in PPGL.
5. Our meta-analytical synthesis of catecholamine data, both before and after the inclusion of our study's results, indicated a consistent positive association between combined catecholamine levels and aBAT, with a reduction in heterogeneity across studies. This analysis strengthens the reliability of currently available but limited evidence for catecholamine excess as a key factor for the presence of aBAT in PPGL.

# 7. Publications & author-level research metrics

## 7.1. Author metrics

as of 7 May 2025

| Journal ranking | Number of full-text publications |
|---|---|
| Q1 | 13 |
| (D1) | (5) |
| Q2 | 4 |
| Q3 | 2 |
| Q4 | 3 |

| | |
|---|---|
| **Cumulative impact factor (IF)** | 84.696 |
| ***h*-index** | 8 |

## 7.2. Publications related to the dissertation

1. **Oštarijaš E**, Onyema M, Zair Z, Taylor DR, Lajeunesse-Trempe F, Reynolds S, Mullholland N, Corcoran B, Halim M, Drakou EE, Grossman A, Vincent RP, Aylwin S, Dimitriadis GK, Canecki-Varžić S. *Metabolically active brown adipose tissue in PPGL: an observational cohort study*. Endocr Relat Cancer. 2025 Mar 07;32(4):e240200. doi: 10.1530/ERC-24-0200. (2023 Q1, IF 4.1)

2. Onyema MC, **Oštarijaš E**, Zair Z, Roy A, Minhas R, Lajeunesse-Trempe F, Kearney J, Drakou EE, Grossman AB, Aylwin SJ, Canecki-Varžić S, Dimitriadis GK. *The Role of Active Brown Adipose Tissue in Patients With Pheochromocytoma or Paraganglioma*. Endocr Pract. 2024 Nov 16:S1530-891X(24)00828-0. doi: 10.1016/j.eprac.2024.11.003. (2023 Q1, IF 3.7)

## 7.3. Other full-text publications

1. Llewellyn D, Nuamek T, **Ostarijas** E, Logan Ellis H, Drakou EE, Aylwin SJ, Dimitriadis GK. Low-dose tolvaptan for the treatment of SIADH-associated hyponatremia: a systematic review, meta-analysis, and meta-regression analysis of clinical effectiveness and safety. Endocr Pract. 2025 Apr 25:S1530-891X(25)00131-4. doi: 10.1016/j.eprac.2025.04.012. (2023 Q1, IF 3.7)

2. Llewellyn DC, **Oštarijaš E**, Sahadevan S, Nuamek T, Byrne C, Taylor DR, Vincent RP, Dimitriadis GK, Aylwin SJ. *Efficacy and safety of low-dose tolvaptan (7.5mg) in the treatment of inpatient hyponatraemia: a retrospective study.* Endocr Pract. 2025 Apr;31(4):419-425. doi: 10.1016/j.eprac.2024.12.019. (2023 Q1, IF 3.7)

3. Lajeunesse-Trempe F, Okroj D, **Ostarijas E**, Ramalho A, Tremblay EJ, Llewellyn D, Harlow C, Chandhyoke N, Chew NWS, Vincent RP, Tchernof A, Piché ME, Poirier P, Biertho L, Morin MP, Copeland CS, Dimitriadis GK. *Medication and Supplement Pharmacokinetic Changes Following Bariatric Surgery: A Systematic Review And Meta-Analysis*. Obesity Reviews. 2024. doi: 10.1111/obr.13759. (2023 Q1/D1, IF 8.0)

4. Samarasinghe SNS, **Ostarijas E**, Long MJ, Erridge S, Purkayastha S, Dimitriadis GK, Miras AD. *Impact of insulin sensitization on metabolic andfertility outcomes in women with polycystic ovary syndrome and overweight or obesity—A systematic review, meta-analysis, and meta-regression*. Obesity Reviews. 2024;e13744. doi:10.1111/obr.13744 (2023 Q1/D1, IF 8.0)

5. Petursson P, **Oštarijaš E**, Redfors B, Råmunddal T, Angerås O, Völz S, Rawshani A, Hambraeus K, Koul S, Alfredsson J, Hagström H, Loghman H, Hofmann R, Fröbert O, Jernberg T, James S, Erlinge D, Omerovic E. *Effects of pharmacological interventions on short- and long-term mortality in patients with takotsubo syndrome: a report from the SWEDEHEART registry*. ESC Heart Failure. 2024. doi: 10.1002/ehf2.14713. (2023 Q1, IF 3.2)

6. Kukuljan M, Mršić E, **Oštarijaš E**. *CT-guided transthoracic core needle biopsies of focal pleural lesions smaller than 10 mm: a retrospective study.* Cancer Imaging. 23, 48 (2023). doi: 10.1186/s40644-023-00569-4. (2023 Q1, IF 3.5)

7. Palčevski D, Belančić A, Mikuličić I, **Oštarijaš E**, Likić R, Dyar O, Vlahović-Palčevski V. *Antimicrobial Prescribing Preparedness of Croatian Medical Students-Did It Change between 2015 and 2019?* Medicines (Basel). 2023 Jun 29;10(7):39. doi: 10.3390/medicines10070039. (2023 Q4)

8. Llewellyn DC, Logan Ellis H, Aylwin SJB, **Oštarijaš E**, Green S, Sheridan W, Chew NWS, le Roux CW, Miras AD, Patel AG, Vincent RP, Dimitriadis GK. *The efficacy of GLP-1RAs for the management of postprandial hypoglycemia*

*following bariatric surgery: a systematic review*. Obesity. 2023 Jan;31(1):20-30. doi: 10.1002/oby.23600. (2022 Q1/D1, IF 6.9)

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10. Martonosi AR, Pázmány P, Kiss Sz, Dembrovszky F, **Oštarijaš E**, Szabó L. *Urodynamics in Early Diagnosis of Diabetic Bladder Dysfunction in Women: A Systematic Review and Meta-Analysis.* Medical Science Monitor. 2022. doi: 10.12659/MSM.937166. (2022 Q2, IF 3.1)

11. Simon O, Görbe A, Hegyi P, Szakó L, **Oštarijaš E**, Dembrovszky F, Kiss Sz, Czopf L, Erőss B, Szabó I. *Helicobacter pylori Infection is Associated with Carotid Intima and Media Thickening. A Systematic Review and Meta-Analysis.* Journal of the American Heart Association. 2022 Feb;11(3). doi: 10.1161/JAHA.121.022919 (2022 Q1/D1, 2021 IF 6.106).

12. Omran A, Leca BM, **Oštarijaš E**, Graham N, Dasilva A, Zair Z, Miras A, le Roux C, Vincent RP, Cardozo L, Dimitriadis GK. *Metabolic syndrome is associated with prostate hyperplasia in patients with lower urinary tract symptoms: a systematic review, meta-analysis and meta-regression analysis.* Ther Adv Endocrinol Metab. 2021 Dec 8;12. doi: 10.1177/20420188211066210. (2021 Q2, IF 4.435)

13. Zádori N, Szakó L, Váncsa Sz, Vörhendi N, **Oštarijaš E**, Kiss Sz, Frim L, Hegyi P, Czimmer J. *Six autoimmune disorders are associated with increased incidence of gastric cancer: A systematic review and meta-analysis of half a million patients.* Front Immunol. 2021 Nov 23;12:750533. doi: 10.3389/fimmu.2021.750533. (2021 Q1, IF 8.786)

14. Borodavkin P, Sheridan W, Coehlo C, **Oštarijaš E**, Zaïr ZM, Miras AD, McGowan B, le Roux CW, Vincent RP, Dimitriadis GK. *Effects of glucagon-like peptide-1 receptor agonists on histopathological and secondary biomarkers of non-alcoholic steatohepatitis: A systematic review and meta-analysis.* Diabetes Obes Metab. 2021 Oct 4; 1-6. doi: 10.1111/dom.14565. (2020 Q1/D1, IF 6.577)

15. Boros E, Sipos Z, Hegyi P, Teutsch B, Frim L, Váncsa Sz, Kiss Sz, Dembrovszky F, **Oštarijaš E**, Shawyer A, Erőss B. *Prophylactic transcatheter arterial embolization reduces rebleeding in non-variceal upper gastrointestinal bleeding: A meta-analysis.* World J Gastroenterol. 2021 Oct; 27(40). doi: 10.3748/wjg.v27.i40.0000. (2020 Q1, IF 5.742)

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*systematic review and meta-analysis.* Clin Obes. 2021:e12450. doi: 10.1111/cob.12450. (2020 Q3)

17. Braut T, Krstulja M, Marijić B, Maržić D, Kujundžić M, Zamolo G, Vučinić D, **Oštarijaš E**. *Tip of the iceberg: Immunohistochemical markers reveal malignant transformation underneath a vocal polyp surface.* Medicina fluminensis. 2021;57(2):171-176. doi: 10.21860/medflum2021_371640. (2021 Q4)

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