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Transcription factor lineage and surgical outcomes in nonfunctioning pituitary neuroendocrine tumors: a systematic review and meta-analysis

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Transcription factor lineage and surgical outcomes in nonfunctioning pituitary neuroendocrine tumors: a systematic review and meta-analysis

Abstract

Background: The 2022 WHO classification groups pituitary neuroendocrine tumors (PitNETs) by transcription factor lineage. Whether lineage predicts invasiveness, resection and recurrence independently of tumor size and invasion is uncertain.

Methods: We searched PubMed, Europe PMC, Scopus and Web of Science to 6 September 2026, with OpenAlex citation chasing, for surgical cohorts of PitNETs classified by PIT1, TPIT and SF1 immunohistochemistry. Risk ratios (RRs) were pooled by random effects with Hartung–Knapp–Sidik–Jonkman (HKSJ) intervals.

Results: Thirty-two reports from 23 independent cohorts were included. In nonfunctioning tumors, invasion was more frequent in TPIT- than SF1-lineage tumors (54% vs 31%; RR 1.66, 95% HKSJ CI 1.44–1.92; I^2 = 0%; six cohorts) and gross total resection less frequent (75% vs 83%; RR 0.92, 0.87–0.98; I^2 = 0%; seven cohorts). Each study's own definition raised the invasion RR to 2.03 (1.35–3.06), with substantial heterogeneity (I^2 = 69%). Crude recurrence was higher in all six SF1-comparator cohorts but significant in none; pooling the three sharing an outcome definition gave RR 1.58 (HKSJ 0.63–3.96). Two adjusted hazard ratios against SF1 (2.04, 1.10–3.82; 1.29, 0.58–2.84) were not comparable. Female sex was more frequent in TPIT-lineage tumors (RR 2.83, 2.40–3.33; I^2 = 0%); evidence for PIT1-lineage and null cell tumors was inconsistent.

Conclusions: TPIT-lineage tumors were more often invasive and less completely resected than SF1-lineage tumors. Crude recurrence was consistently higher but imprecise; whether lineage predicts it independently of invasion and resection is unresolved. Future series should report surgical approach, GTR by Knosp grade, and adjusted lineage-specific estimates.

Keywords: Pituitary neuroendocrine tumors; Transcription factors; SF1; TPIT; Cell lineage; Meta-analysis;

Background

The 2022 WHO classification groups pituitary neuroendocrine tumors (PitNETs) by cell lineage, defined by PIT1, TPIT and SF1 expression; silent corticotroph (TPIT-lineage) and immature PIT1-lineage tumors are designated high risk **[1]**.

TPIT-lineage nonfunctioning tumors are often described as large, invasive and prone to recurrence, but meta-analytic evidence conflicts: a meta-analysis of silent corticotroph adenomas defined by ACTH immunostaining found no excess recurrence relative to other nonfunctioning adenomas **[2]**, whereas a 2025 systematic review reported more frequent invasion in TPIT-positive and null cell tumors than in SF1-positive tumors **[3]**.

Whether lineage predicts outcome independently of tumor size and invasion is unclear. TPIT-lineage tumors tend to be larger and more invasive, so crude recurrence differences may reflect invasion and residual tumor rather than lineage.

We asked whether, in nonfunctioning PitNETs classified by transcription factor immunohistochemistry, lineage is associated with invasiveness, gross total resection (GTR), and recurrence or progression, with and without adjustment for prognostic factors. We also summarized how completely the literature reports the information needed, and the evidence on tumors expressing more than one lineage factor.

Methods

We followed PRISMA 2020 and PRISMA-S, and incorporated MOOSE items for observational studies. The protocol was registered on OSF retrospectively, on 5 October 2026, after pilot extraction.

Eligibility criteria

- **Population:** PitNET patients undergoing surgery, predominantly by a transsphenoidal approach; primary analyses were restricted to nonfunctioning tumors, with functioning series summarized descriptively.
- **Exposure:** Lineage defined by transcription factor immunohistochemistry (PIT1, TPIT, SF1, or none), classified by WHO 2017 or 2022 criteria or reclassifiable to them.
- **Comparator:** Another lineage within the same study; SF1 lineage was the reference group for nonfunctioning tumors, and single-arm series were extracted separately.
- **Outcomes:** Invasiveness (Knosp grade 3–4 or cavernous sinus invasion), GTR on postoperative MRI, and recurrence or progression, as crude proportions, survival data or adjusted HRs.
- **Study design:** Cohort studies and case series published 2015–2026 with at least seven patients per lineage group, a threshold chosen to retain the rare PIT1-lineage groups and interpreted with caution. Reports without full text informed the narrative synthesis only.
- **Exclusion criteria:** Absence of transcription factor immunohistochemistry; revision-only cohorts; case reports; reviews; studies without lineage-specific surgical outcomes; radiosurgery or medical-therapy populations.

Information sources and search strategy

We searched PubMed, Europe PMC (full-text mode), Scopus and the Web of Science Core Collection (all editions), with forward and backward citation chasing in OpenAlex from six seed articles. Embase was not searched because institutional access was unavailable. Search strings and record counts are in Supplementary Tables S5 and S6.

Study selection and data extraction

Titles and abstracts were screened and potentially eligible articles assessed in full text where available. Screening and extraction were performed by two reviewers and adjudicated by two others.

We extracted setting, enrollment period, surgical approach, immunohistochemistry methodology, group sizes, outcome definitions and counts, follow-up and adjusted estimates. Overlapping cohorts were identified from author lists and enrollment periods; only one report per cohort contributed to each analysis.

Full text could not be obtained for four reports (one congress abstract and three subscription articles); these informed the narrative synthesis only, since an abstract permits neither risk-of-bias appraisal nor verification of cohort independence.

Risk of bias

Comparative cohorts were appraised with the Newcastle–Ottawa Scale (NOS; good 7–9, fair 5–6, poor ≤4; Table S2), prognostic studies without a discrete comparator with QUIPS (Table S3), and case series with the JBI checklist (Table S4). Two reviewers appraised each study and a third resolved disagreements (Figures S1 and S2).

Data synthesis

Binary outcomes were pooled as log risk ratios with DerSimonian–Laird random effects. Because this estimator can underestimate τ^2 when studies are few, τ^2 was also estimated by restricted maximum likelihood and Paule–Mandel; the three agreed ($\tau^2 = 0$ for the primary outcomes). Intervals are Hartung–Knapp–Sidik–Jonkman (HKSJ) with truncated variance, with Wald intervals for comparison. Leave-one-out analyses and prediction intervals ($k - 2$ degrees of freedom) are reported where at least four cohorts contributed, and absolute risk differences for GTR used the same method.

Invasiveness used the protocol definition (Knosp grade 3–4 or cavernous sinus invasion); where a study's primary analysis used a broader definition, protocol-defined counts were extracted when available and the study's own definition examined in sensitivity analysis.

Adjusted hazard ratios were pooled only when adjustment sets were comparable. Funnel plots were not constructed (fewer than 10 studies per outcome). Certainty of evidence for the main outcomes was rated with GRADE by two authors independently, starting from low for observational data (Table S7). Analyses used Python 3.12.3; code and study-level data are available at OSF registration.

Deviations from protocol

Because the protocol was registered after pilot extraction, it cannot show that analytic decisions preceded the data. Deviations were: the minimum group size was lowered from 10 to 7 to retain PIT1-lineage groups; the three cohorts sharing a recurrence definition became the primary analysis, with the registered all-cohort pooling as sensitivity; comparative cohorts were appraised with NOS as well as QUIPS; and moderator analyses were omitted. Analyses of sex, consistency, growth, age, radiotherapy and prior surgery were unregistered and exploratory.

Results

Study selection

The searches returned 3,363 records; 2,256 were unique, and 1,983 were excluded at title and abstract. Of 273 full texts assessed, 241 were excluded, leaving 32 reports (Figure 1).

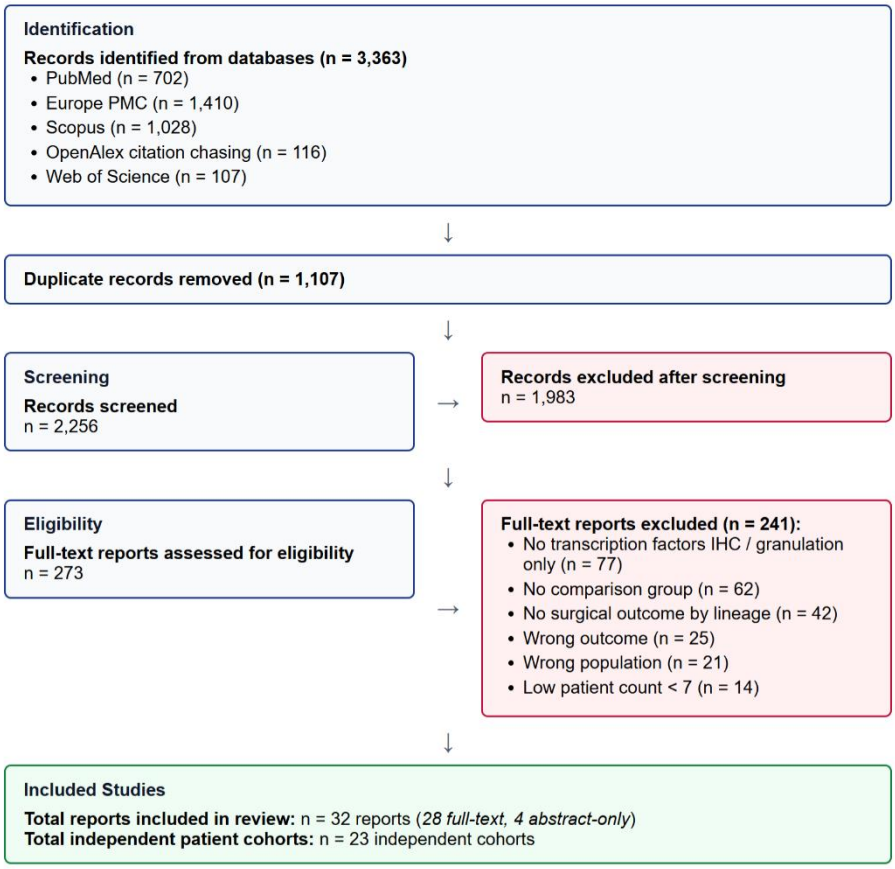


Figure 1. PRISMA flow diagram (32 included studies).

Characteristics of included studies

Sixteen of the 32 reports described endoscopic surgery in all or most patients and one predominantly microscopic surgery; the remaining 15 did not report the approach or specified it only as transsphenoidal.

Overlapping cohorts. Four reports from the University of Southern California and University of Washington were treated as one cohort, with Cheok providing the lineage comparison **[4-7]**; the Toronto subtype 3 and Barrow–Toronto null cell series were likewise combined **[8, 9]**, as were five Beijing Tiantan reports sharing an institution and probable enrolment overlap **[10-14]**. Hu 2026 (March 2020–December 2023) and Xu 2025 (January 2021–February 2023) report overlapping enrolment at the same department, so they were treated as one cohort represented by Hu 2026, with Xu's counts used only in sensitivity analysis **[15, 16]**. The two Goyal-Honavar reports come from different institutions and were kept separate **[17, 18]**. With 17 non-overlapping reports, 23 independent cohorts remained.

Lineage, invasiveness and resectability

Six cohorts provided counts for both invasiveness and GTR, and seven provided GTR counts (Woo 2024 contributed GTR counts to the primary comparisons, with its broader invasion definition examined in sensitivity analysis).

TPIT versus SF1: invasiveness

Six cohorts compared cavernous sinus invasion or Knosp grade 3–4 between TPIT-lineage and SF1-lineage tumors (Table 1). Invasion was present in 54% of TPIT-lineage and 31% of SF1-lineage tumors. The pooled RR was 1.66 (95% HKSJ CI 1.44–1.92; conventional 95% CI 1.49–1.86; $\tau^2 = 0$; $I^2 = 0\%$; prediction interval 1.42–1.94; Figure 2A), with leave-one-out estimates from 1.63 to 1.71.

Table 1. Invasiveness in TPIT-lineage versus SF1-lineage tumors

Study	Definition used	TPIT, n/N	SF1, n/N	RR (95% CI)
Fukuhara 2026	Knosp 3–4 (preoperative MRI)	18/46	17/118	2.72 (1.54–4.80)
Cheok 2025 (nonfunctioning)	Knosp 3–4	12/29	23/104	1.87 (1.06–3.29)
Taguchi 2023	Cavernous sinus invasion (MRI and surgical findings)	7/22	35/191	1.74 (0.88–3.43)
Hu 2026	Knosp 3–4	68/101	103/245	1.60 (1.31–1.96)
Jiang 2021	Knosp 3–4	43/112	45/198	1.69 (1.19–2.39)
Zhang 2026	Knosp 3–4	123/188	168/415	1.62 (1.38–1.89)
Pooled (random effects)				**1.66 (1.49–1.86);** HKSJ 1.44–1.92; $I^2 = 0\%$; $\tau^2 = 0$; prediction interval 1.42–1.94

TPIT versus SF1: gross total resection

In each study, GTR was absence of residual tumor on postoperative MRI, timed as that study reported (for example, within three months in Hu 2026) (Table 2).

Table 2. Gross total resection in TPIT-lineage versus SF1-lineage tumors

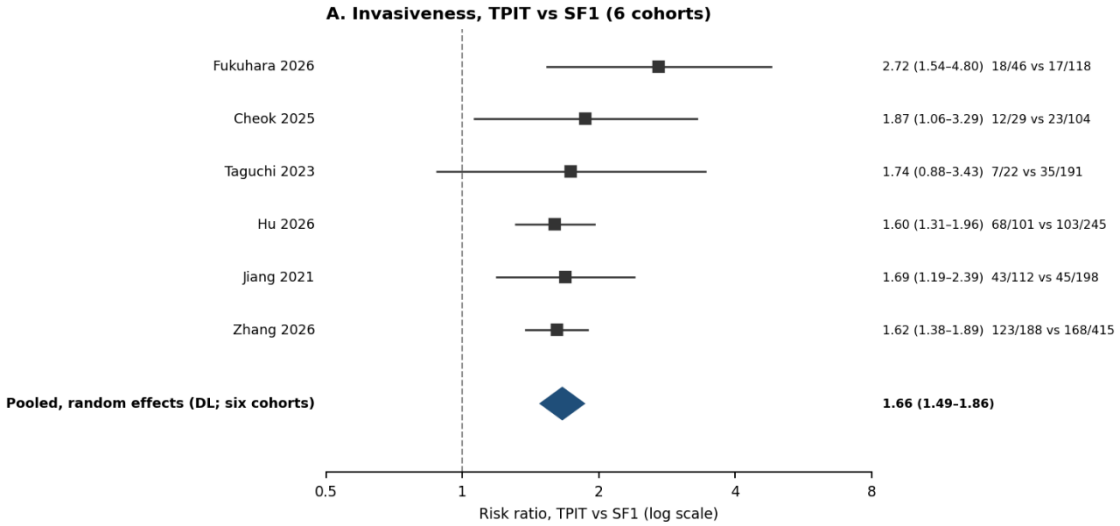
Study	TPIT, n/N	SF1, n/N	RR (95% CI)
Fukuhara 2026	31/46	95/118	0.84 (0.67–1.04)
Woo 2024	7/21	33/66	0.67 (0.35–1.28)

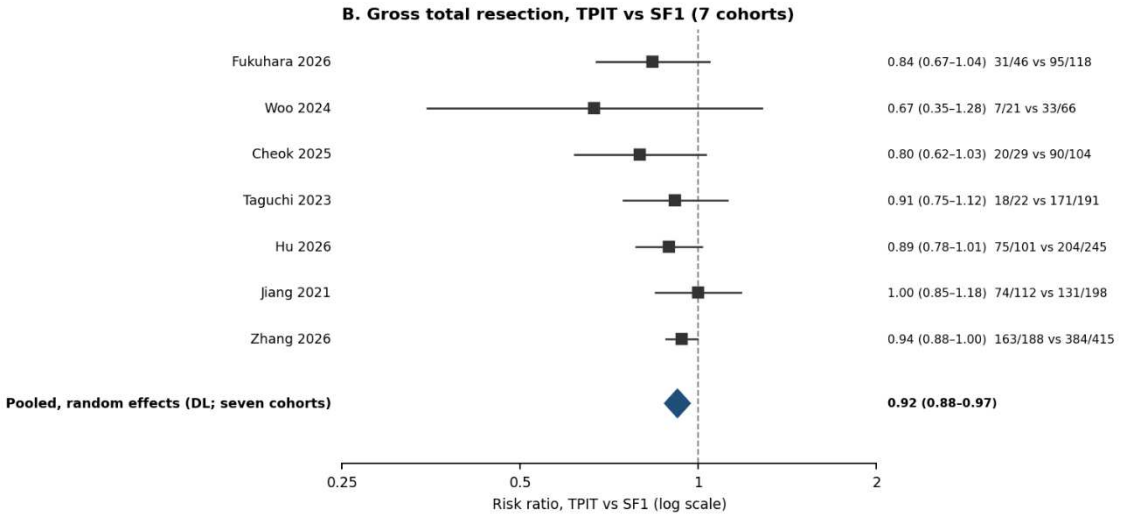
Cheok 2025 (nonfunctioning)	20/29	90/104	0.80 (0.62–1.03)
Taguchi 2023	18/22	171/191	0.91 (0.75–1.12)
Hu 2026	75/101	204/245	0.89 (0.78–1.01)
Jiang 2021	74/112	131/198	1.00 (0.85–1.18)
Zhang 2026	163/188	384/415	0.94 (0.88–1.00)
Pooled (random effects)			**0.92 (0.88–0.97)**; HKSJ 0.87–0.98; I^2 = 0%; τ^2 = 0 prediction interval 0.86–0.98

GTR was achieved in 75% of TPIT-lineage and 83% of SF1-lineage tumors. The pooled RR was 0.92 (95% HKSJ CI 0.87–0.98; conventional 95% CI 0.88–0.97; τ^2 = 0; I^2 = 0%; prediction interval 0.86–0.98; Figure 2B), a pooled absolute difference of 7.0 fewer complete resections per 100 patients (HKSJ −11.9 to −2.2; crude 8).

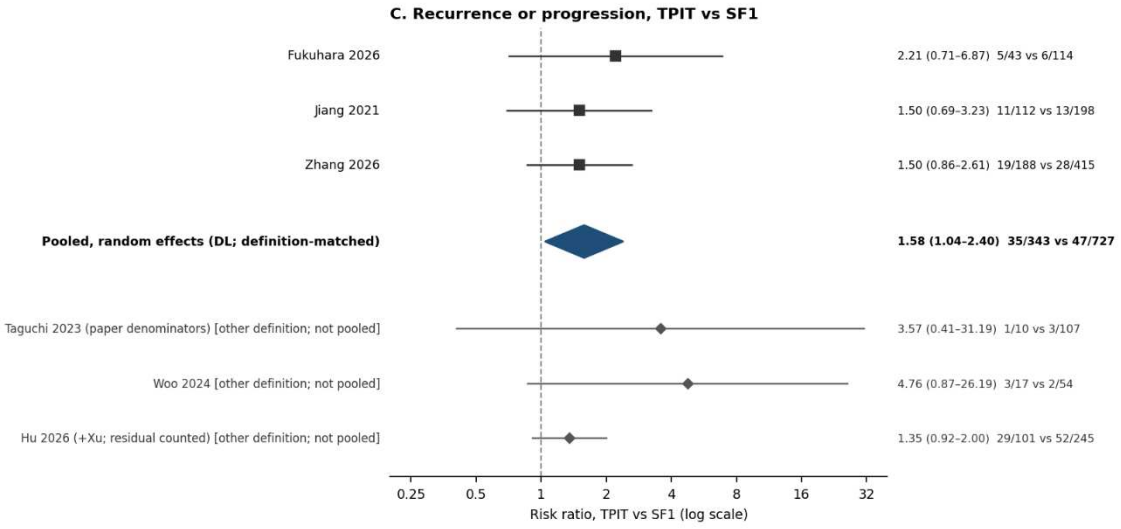
Taguchi labels the TPIT group corticotroph and the SF1 group gonadotroph. Jiang's cohort included 18 TPIT-lineage and 21 SF1-lineage patients with previous surgery, was operated predominantly microscopically, and defined invasion at any site; in Zhang's cohort, 20.2% of silent corticotroph and 23.1% of silent gonadotroph tumors were recurrent at surgery. Previously operated patients may affect GTR and recurrence estimates, so sensitivity analyses excluding them are needed where data permit.

Forest plots appear in Figure 2 and the underlying percentages in Figure 3.





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156 *Figure 2. Forest plots for TPIT-lineage versus SF1-lineage tumors: (A) invasiveness, (B) gross total*
157 *resection, (C) crude recurrence or progression.*

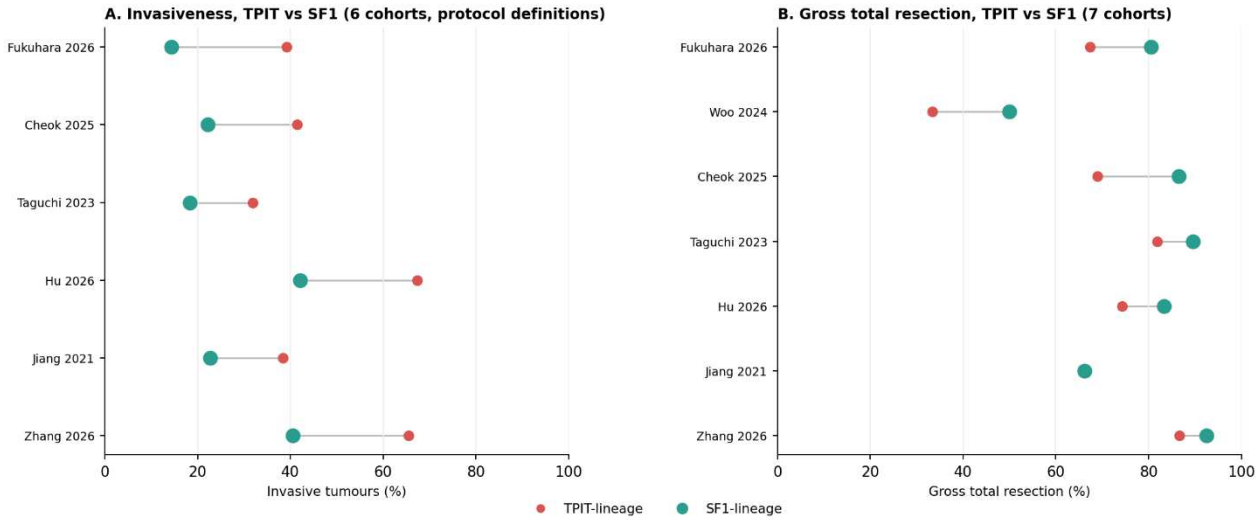


Figure 3. Percentage of invasive tumors (A) and of tumors completely resected (B) in TPIT-lineage and SF1-lineage groups, by cohort.

Sensitivity analyses

The protocol definition required substituting Jiang's Knosp grade 3–4 counts (43/112 vs 45/198; RR 1.69) for its any-site intraoperative counts (41/112 vs 15/198; RR 4.83), Fukuhara's preoperative Knosp counts (18/46 vs 17/118; RR 2.72) for its intraoperative cavernous sinus counts (20/46 vs 21/118; RR 2.44), and Zhang's Knosp counts (123/188 vs 168/415; RR 1.62) for its cavernous sinus counts (129/188 vs 169/415; RR 1.70). With each study's own definition, the pooled RR rose to 2.03 (95% CI 1.57–2.63; HKSJ 1.35–3.06) with substantial heterogeneity (I^2 = 69%). Within that set, replacing Jiang's any-site counts with its Knosp counts reduced I^2 to 0% (pooled RR 1.70, 95% CI 1.52–1.89), so the heterogeneity is attributable to that definition (Figure 4).

Other analyses left the direction and magnitude unchanged: Woo's broader definition gave RR 1.72 (I^2 = 8%); Fukuhara's intraoperative cavernous sinus counts substituted into the protocol-definition analysis, 1.66 **[19]**; Taguchi's Knosp counts 1.67 **[20]**; Xu 2025 substituted for Hu 2026, 1.67; and omitting Taguchi, where SF1 lineage was inferred from GATA3, 1.66. Adding three cohorts with all-other-nonfunctioning comparators gave 1.58 (I^2 = 15%), descriptive only.

Broader analyses that added cohorts with functioning tumors and mixed comparators gave RR 1.76 (95% CI 1.49–2.09; I^2 = 62%) for invasiveness across 13 cohorts and 0.92 (95% CI 0.87–0.96) for GTR across 10 **[17, 21-24]** (Figure 5). These answer a different question and are descriptive; the direction was unchanged, but heterogeneity increased for invasion.

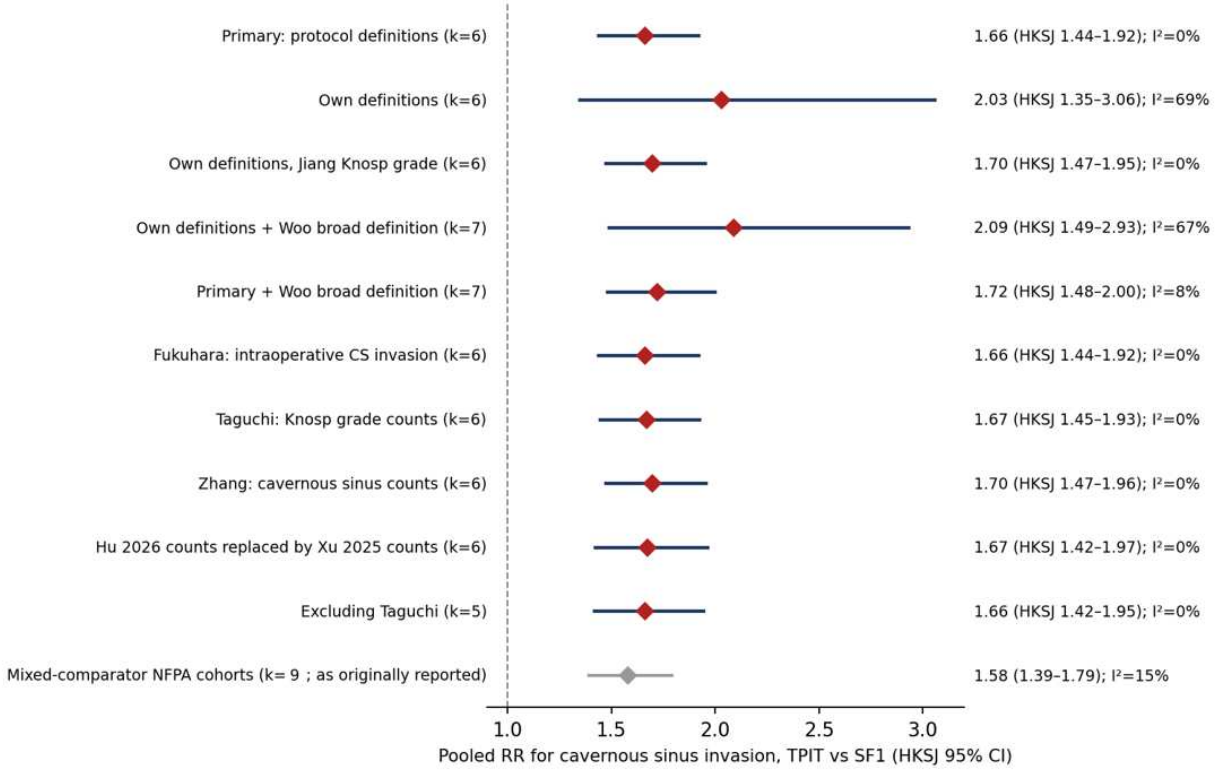


Figure 4. Robustness of the pooled estimate for cavernous sinus invasion to definition and cohort choices.

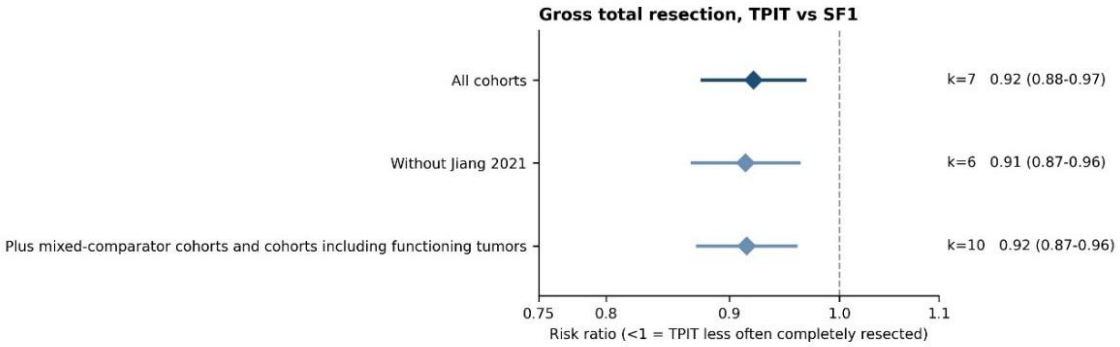


Figure 5. Robustness of the pooled estimates for TPIT-lineage versus SF1-lineage tumors under alternative sets of cohorts.

Sex distribution by lineage

Female sex was more frequent in TPIT-lineage than SF1-lineage nonfunctioning tumors in all four cohorts reporting sex by lineage (Table 3).

Table 3. Female sex in TPIT-lineage versus SF1-lineage tumors

Study	TPIT, n/N	SF1, n/N	RR (95% CI)

Jiang 2021	101/112	59/198	3.03 (2.42–3.78)
Zhang 2026	166/188	126/415	2.91 (2.49–3.39)
Hu 2026	86/101	76/245	2.74 (2.24–3.37)
Fukuhara 2026	38/46	40/118	2.44 (1.83–3.24)
Pooled (random effects)			**2.83 (2.56–3.13);** HKSJ 2.40–3.33; I^2 = 0%; τ^2 = 0; prediction interval 2.27–3.53 (four cohorts)

The pooled estimate was precise, with no heterogeneity across four independent cohorts, all from China and Japan **[14, 16, 19, 25]**; its prediction interval (2.27–3.53) was wider, reflecting the small number of cohorts. Fukuhara further found that female sex remained associated with TPIT lineage after multivariable adjustment (odds ratio 13.10, 95% CI 4.48–38.32) **[19]**.

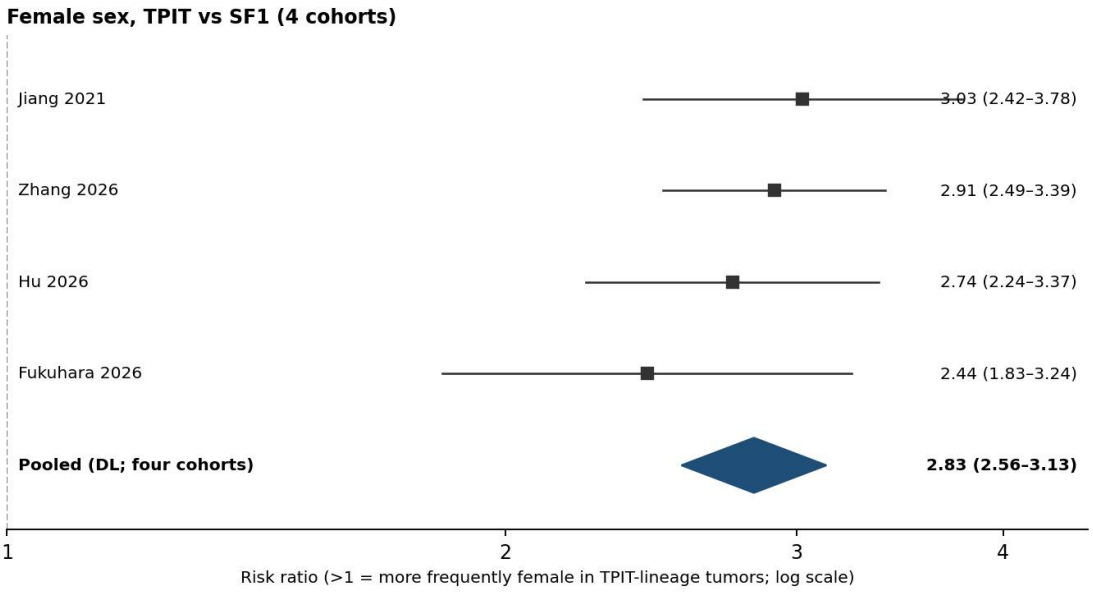


Figure 6. Forest plots for sex distribution by lineage.

Crude recurrence or progression: TPIT versus SF1

Six cohorts compared recurrence or progression with an SF1 comparator (Table 4). All favored TPIT-lineage tumors (crude RR 1.35–4.76); none was significant individually.

Table 4. Crude recurrence or progression in TPIT-lineage versus SF1-lineage and other nonfunctioning tumors

Study	Outcome as defined by authors	Follow-up	TPIT, n/N	SF1, n/N	RR (95% CI)
Recurrence or progression, all patients					
Fukuhara 2026 *TPIT vs SF-1*	Recurrence after GTR or progression of residual	Median 45 / 50 mo	5/43	6/114	2.21 (0.71–6.87)
Jiang 2021 *TPIT vs SF-1*	Recurrence after GTR or remnant regrowth	Mean 14.1 / 13.5 mo	11/112	13/198	1.50 (0.69–3.23)
Zhang 2026 *TPIT vs SF-1*	New lesion after clean first scan, or ≥2 mm growth of residual	Median 24.4 / 27 mo	19/188	28/415	1.50 (0.86–2.61)
Pooled (random effects)			**35/343**	**47/727**	**1.58 (1.04–2.40)**; HKSJ 0.63–3.96; I^2 = 0%; τ^2 = 0
Outcome defined differently — not pooled					
Taguchi 2023 *TPIT vs SF-1*	Recurrence after total resection only; denominator restricted to patients with GTR and ≥5 y follow-up	Median 92 mo	1/10	3/107	3.57 (0.41–31.2)
Woo 2024 *TPIT vs SF-1*	Recurrence after GTR only; denominator all patients with ≥2 postoperative scans	Median 5.7 y	3/17	2/54	4.76 (0.87–26.2)
Hu 2026 *TPIT vs SF-1*	Recurrence or progression during follow-up; baseline three-month MRI	Median 801 d	29/101	52/245	1.35 (0.92–2.00)
Chen 2025 *TPIT vs all*	Recurrence or progression *Comparator: all other nonfunctioning tumors*	Median 53.5 mo	18/44	29/148	2.09 (1.29–3.38)
Goyal-Honavar 2021 *TPIT vs all*	Recurrence after GTR or progression of residual	Median 48.4 / 44.8 mo	20/52	22/205	3.58 (2.12–6.05)

Three cohorts (Fukuhara, Jiang, Zhang) counted recurrence after GTR together with progression of residual tumor among all operated patients; their pooled RR was 1.58 (95% HKSJ CI 0.63–3.96; conventional 95% CI 1.04–2.40; I^2 = 0%; Figure 2C). Pooling all six gave 1.52 (95% HKSJ CI 1.06–2.20; conventional 95% CI 1.15–2.01). Both analyses have τ^2 = 0, so the wide intervals reflect few cohorts rather than heterogeneity. The three-cohort analysis does not establish a difference, and although the six-cohort HKSJ interval excludes no difference, it combines non-equivalent definitions, so the evidence remains weak. These risk ratios are unadjusted for extent of resection. Because resection may lie on the causal path from lineage to recurrence, they estimate the total association rather than a direct effect of lineage.

Follow-up ranged from a mean of 14.1 to a median of 92 months, and median follow-up does not give person-time, so no incidence-rate estimate was computed.

Two cohorts used all other nonfunctioning tumors as comparator and reported larger effects (Chen 2.09; Goyal-Honavar 3.58). A pooled estimate across all eight comparisons (1.97; 95% CI 1.44–2.68; I^2 = 38%) mixes comparators and is not interpreted.

Adjusted estimates

Crude differences may reflect size and invasion rather than lineage. Two cohorts reported lineage-specific HRs against SF1, crude and adjusted (Table 5). The crude TPIT association was significant in neither; after adjustment it was significant in Hu (HR 2.04, 95% CI 1.10–3.82) but not in Woo (1.29, 95% CI 0.58–2.84).

The adjustment sets are not comparable, and neither isolates lineage from the pathway through which it acts. Hu's lineage estimate is adjusted for age, height, weight and apoplexy only; invasiveness, diameter and volume were each modelled separately with the same covariate set, so the TPIT hazard ratio is not adjusted for invasion or size, and its Cox analyses used only the 357 primary-surgery patients **[16]**. Woo's model did include tumor volume and invasiveness, but its composite outcome of residual or recurrent disease cannot separate lineage from extent of resection **[26]**.

A third cohort adjusted for subtotal resection, and the association with silent corticotroph pathology lost significance **[21]**; because extent of resection may lie on the pathway from lineage to recurrence, adjusting for it estimates a different quantity. Directly comparable TPIT-versus-SF1 evidence therefore remains limited, and lineage's independent contribution is unresolved.

Table 5. Crude and adjusted hazard ratios for recurrence or progression versus SF1-lineage tumors

Lineage	Woo, crude	Woo, adjusted	Hu, crude	Hu, adjusted
TPIT	1.81 (0.93–3.49)	1.29 (0.58–2.84)	1.69 (0.96–2.96)	2.04 (1.10–3.82)
PIT1	1.07 (0.33–3.54)	1.10 (0.33–2.84)	2.34 (1.10–4.96)	2.56 (1.13–5.80)
No distinct lineage	3.01 (1.61–5.56)	3.44 (1.70–6.96)	0.62 (0.15–2.59)	0.70 (0.17–2.95)

Two further studies used other comparators. Silent corticotroph tumors carried an adjusted HR of 3.79 (95% CI 2.06–6.99) relative to all other nonfunctioning tumors, adjusted for male sex, Knosp grade ≥3, diameter >4 cm and MIB-1 >3% but not extent of resection **[17]**; null cell tumors had an adjusted HR of 3.64 (95% CI 1.07–12.30) relative to silent gonadotroph tumors, in a model that also included cavernous sinus invasion and AP diameter **[27]**.

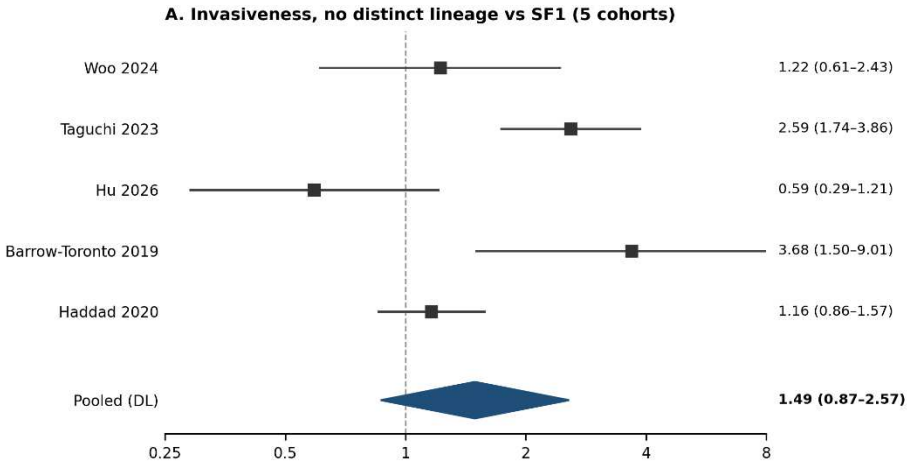
PIT1-lineage tumors and tumors without a distinct lineage

Evidence for the other lineages was limited and inconsistent (Table 6). The PIT1-lineage groups were small (seven patients each in Woo and Cheok). For null cell tumors, RRs for invasiveness ranged from 0.59 to 3.68 across five cohorts. Almeida's strictly defined null cell tumors were more often invasive (15/31 vs 5/38) and less often resected (19/31 vs 33/38) **[9]**. Taguchi reported cavernous sinus invasion in 47.5% vs 18.3% **[20]**, Hu reported Knosp grade 3–4 in 25.0% vs 42.0% **[16]**, and Haddad, defining null cell tumors by negativity for SF1, ACTH, prolactin and GH, found similar rates (43.0% vs 36.9%) **[27]**. Because these variations did not track the definition used, the

pooled estimates were not interpreted. In Li's cohort, the 12 PIT1–GH/PRL tumors had the highest invasion grade and the lowest GTR rate (58.3%) **[24]**. Forest plots appear in (Figure 7).

Table 6. Pooled comparisons of PIT1-lineage and null cell tumors with SF1-lineage tumors

Comparison with SF1	Studies	Outcome	Pooled RR (95% CI)	I^2
PIT1	4	GTR	0.89 (0.78–1.03)	0%
PIT1	4	Invasiveness	1.67 (0.76–3.65)	84%
No distinct lineage	5	GTR	0.88 (0.76–1.03)	55%
No distinct lineage	5	Invasiveness	1.49 (0.87–2.57)	81%



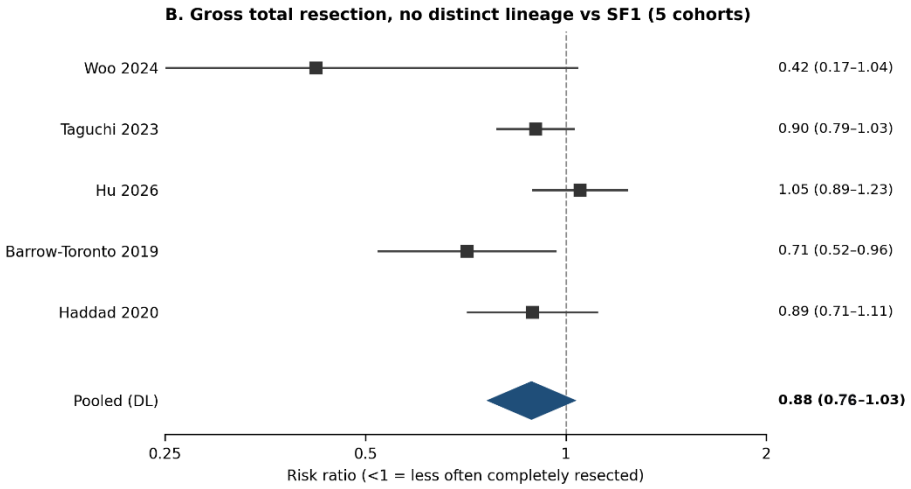


Figure 7. Forest plots for tumors without a distinct lineage versus SF1-lineage tumors: (A) invasiveness, (B) gross total resection

Transcription factor multiplicity

Tumors expressing two or more lineage factors were reported in six studies, with conflicting results. In Taracha (302 patients, all endoscopic), adjusted HRs were 2.75 for SF1/TPIT co-expression and 3.80 for triple-positive tumors, rising to 17.46 (95% CI 2.85–106.93) with Ki-67 ≥3% **[28]**. In Cheok's nonfunctioning cohort, Knosp grade 3–4 was present in 60% of dual-positive versus 22.1% of SF1-lineage tumors **[4]**.

Five Tiantan reports describing the same population were treated as one cohort. Multilineage tumors had a lower short-term complete response rate (30.0% vs 58.7%; P = 0.026) **[10]**, more Knosp grade 3–4 invasion than SF1-lineage tumors (48.3% vs 31.5%; P = 0.023) **[11]**, and, in the PIT1/SF1 subgroup, more cavernous sinus invasion (56.1% vs 27.1%; P = 0.001) **[12]**. Enrolment windows overlap (2018–2022 and 2019–2021), so these are not independent observations.

Tumors co-expressing PIT1 and SF1 (n = 32) did not differ from SF1-only tumors in invasion (invasion grade ≥2: 56.2% vs 54.7%; Knosp grade ≥3: 21.9% vs 15.8%) **[24]**. Because exposures were defined differently and studies shared institutions, these were not pooled. One report, with full text unavailable, compared plurihormonal tumors (gonadotroph factor plus other factors) with gonadotroph-only tumors: invasion, judged endoscopically, was more frequent (50% vs 16%; P = 0.002), and GTR was less frequent among nonfunctioning tumors (44% vs 86%; P = 0.004); subgroup sizes were not reported **[29]**.

Lineage and history of prior surgery

Because some cohorts included previously operated patients, we examined prior surgery descriptively (not pooled). It was 18/112 vs 21/198 (16.1% vs 10.6%) in Jiang's cohort (P = 0.212) **[25]** and 14/62 vs 18/238 (22.6% vs 7.6%) in Goyal-Honavar's cohort (Fisher P = 0.002) **[17]**. In Zhang's cohort the direction reversed (20.2% vs 23.1% already recurrent at presentation; P = 0.424); recurrent status predicted progression among silent corticotroph tumors (HR 4.92, 95% CI 1.23–19.66, P = 0.024) but not silent gonadotroph tumors (HR 1.66, 95% CI 0.75–3.72, P = 0.214) **[14]**. In Hu's cohort, 13/101 vs 34/245 (12.9% vs 13.9%) had prior surgery (P = 0.865) **[16]**. These findings point in different directions and use different comparators, so we report them descriptively.

Additional analyses for functioning tumors, and survival data are reported in the Supplementary Analyses.

GRADE Certainty of evidence

Certainty was low for greater invasion (RR 1.66) and lower resection (RR 0.92) in TPIT-lineage tumors (observational data, moderate risk of bias), very low for recurrence (imprecision, non-equivalent definitions, unequal follow-up, no adjustment for resection), and moderate for female predominance (large effect; Supplementary Table S7).

Discussion

Principal findings

In nonfunctioning PitNETs classified by transcription factor immunohistochemistry, TPIT-lineage tumors were roughly 66% more likely than SF1-lineage tumors to be invasive, and less likely to be completely resected. Recurrence was higher in every SF1-comparator cohort, yet none was individually significant and the pooled estimate was imprecise; two cohorts comparing silent corticotroph tumors with all other nonfunctioning tumors were individually significant. Among adjusted analyses that controlled for invasion or size, the association persisted for null-cell status (Woo 3.44; Haddad 3.64) and for silent corticotroph tumors versus all other nonfunctioning tumors (Goyal-Honavar 3.79), but was lost when extent of resection was added (Chen). No adjusted TPIT-versus-SF1 comparison controlling for invasion and size showed a significant association.

Comparison with previous reviews

The 2025 systematic review found more frequent cavernous sinus invasion in TPIT-positive tumors **[3]**, and our estimate points the same way; differences in magnitude may reflect definitions and cohorts. Earlier silent corticotroph meta-analyses used ACTH-based definitions and are not directly comparable **[2]**; an updated meta-analysis reported more frequent cavernous sinus invasion and progression than in other nonfunctioning tumors **[30]**. Definitions mattered: heterogeneity was substantial under each study's own definition (I^2 = 69%) and disappeared when Jiang's any-site invasion was replaced by Knosp grade, so heterogeneity in earlier syntheses may partly reflect definitions rather than biology.

Interpretation

These findings are compatible with a pathway from lineage to invasion to resectability: the invasion difference was large and consistent, the GTR difference smaller and free of heterogeneity. Complete resection remained achievable in most TPIT-lineage tumors in six of seven cohorts, the exception being Woo's, where one-third were completely resected **[26]**. Aggregate data cannot test mediation, as no study cross-tabulated GTR by invasion within both lineages; within TPIT-lineage tumors, Jiang reported GTR in 24.4% of invasive versus 90.1% of noninvasive tumors **[25]**, consistent with invasion mediating resectability but not establishing it. Because incomplete resection predicts progression **[14]**, extent of resection may also mediate the association with recurrence, so adjusting for it may underestimate the total association. The only contrary evidence is a conference abstract reporting no difference in Knosp grade or volume **[31]**.

The adjusted analyses are too few, and too differently specified, to settle the question: the association was significant univariably but not multivariably in Chen **[21]**, nonsignificant crude but significant after adjustment in Hu, and nonsignificant throughout in Woo **[26]**.

Prior surgery was more common among TPIT-lineage patients in two of four cohorts, similar in a third and reversed in a fourth, and recurrent status at presentation predicted later progression within TPIT-lineage but not SF1-lineage tumors **[14]**. TPIT lineage may therefore carry a higher baseline rate of reoperation for treatment failure, distinct from recurrence after clean surgery; lineage-only analyses cannot resolve this.

Results for PIT1-lineage and null cell tumors were too heterogeneous to interpret. Null-cell classification requires negativity for all three factors, and antibodies, thresholds and surrogate markers such as GATA3 differ between institutions, so the category is probably not comparable across centers.

Lineage-associated patient and tumor characteristics

Female predominance among TPIT-lineage tumors was the most consistent secondary finding, with no heterogeneity across four East Asian cohorts **[14, 16, 19, 25]**. It parallels the female predominance of ACTH-secreting tumors in Cushing disease and is compatible with an intrinsic feature of TPIT-lineage differentiation, although the data cannot test this **[32, 33]**. Other lineage-associated characteristics each rest on one or two cohorts and are hypothesis-generating **[15, 16, 18, 27]**.

Implications

Lineage may reasonably be used to anticipate greater invasiveness and lower rates of complete resection in TPIT-lineage tumors, but given the low certainty of the recurrence evidence it should not alone determine surveillance intensity or adjuvant therapy. Future studies should report surgical approach, GTR stratified by Knosp grade, recurrence conditional on extent of resection, and adjusted estimates with named covariates. Multicenter individual patient data would enable the mediation analyses that aggregate data cannot support.

Limitations

The review omitted Embase, CENTRAL and trial registries and lacked full text for three subscription articles, so relevant studies may be missing. Pooled estimates rest on three to seven studies and the adjusted analyses are non-equivalent, so the wide HKSJ intervals and adjusted estimates are exploratory; $\tau^2 = 0$ does not exclude clinically relevant between-study variation.

Cohort overlap and mixed comparator groups remain concerns despite our collapsing rules. Definitions of invasion, GTR, recurrence and null cell status were inconsistent, and the surgical approach was unreported or unspecified in roughly half the reports. Recurrence definitions differed over whether residual tumor counted as an event, preventing pooling of all cohorts. Follow-up ranged from 14.1 to 92 months, and several cohorts included previously operated patients.

The protocol was registered retrospectively, after the searches and pilot extraction, so it could not guide those stages and cannot show the sequence of methodological decisions.

Conclusions

TPIT-lineage nonfunctioning tumors are more often invasive and less completely resected than SF1-lineage tumors. Recurrence is probably higher, but whether lineage predicts it independently of invasion and extent of resection remains unproven. Evidence for PIT1-lineage, null cell and multilineage tumors is too inconsistent to pool. TPIT-lineage tumors also showed a consistent female predominance across four cohorts. Future series should report surgical approach, GTR by Knosp grade, and adjusted lineage-specific estimates.

List of abbreviations

ACTH: adrenocorticotropic hormone.
AP: anteroposterior.
CI: confidence interval.
CS: cavernous sinus.
DL: DerSimonian–Laird.
GATA3: GATA-binding protein 3.
GH: growth hormone.
GRADE: Grading of Recommendations Assessment, Development and Evaluation.
GTR: gross total resection.
HKSJ: Hartung–Knapp–Sidik–Jonkman.
HR: hazard ratio.
I^2: percentage of variability due to between-study heterogeneity.
JBI: Joanna Briggs Institute.
k: number of cohorts in a pooled analysis.
MIB-1: antibody clone used to measure the Ki-67 proliferation index.
MOOSE: Meta-analysis Of Observational Studies in Epidemiology.
MRI: magnetic resonance imaging.
NFPA: nonfunctioning pituitary adenoma.
NOS: Newcastle–Ottawa Scale.
OSF: Open Science Framework.
PIT1: POU class 1 homeobox 1.
PitNET: pituitary neuroendocrine tumor.
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
PRISMA-S: PRISMA extension for reporting literature searches.
PRL: prolactin.
QUIPS: Quality In Prognosis Studies.
RR: risk ratio.
SF1: steroidogenic factor 1.
TPIT: T-box transcription factor 19 (TBX19).
WHO: World Health Organization.
τ^2: between-study variance.

Declarations

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Competing interests:
The authors declare no competing interests.

Ethics approval and consent to participate:
Not applicable. This study is a systematic review and meta-analysis of previously published data and did not involve new data collection from human participants.

Consent for publication:
Not applicable.

Registration and protocol:
The review was registered retrospectively on the Open Science Framework, deviations are described in Methods.

Data and code availability:
The search strategies, screening decisions, extracted study-level data and analysis code needed to reproduce all pooled estimates and figures are available at OSF.

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Supplementary material

Supplementary analyses :

Functioning tumors

Series with functioning tumors contributed no pooled estimate and are summarized only descriptively. In Asmaro (169 first-time surgeries, 45% functioning), cavernous sinus invasion was most frequent in PIT1 tumors (53%, vs 24% for TPIT and 18% for SF1) **[23]**. In acromegaly, sparsely granulated somatotroph tumors had lower early remission than densely granulated tumors (15.0% vs 51.9%; P = 0.006) **[34]**; multi-factor tumors had lower remission than single-factor tumors (30.8% vs 71.6%) **[13]**; and PIT1/SF1 tumors remitted similarly to PIT1-only tumors (30.8% vs 27.6%) **[35]**. Two further series addressed silent PIT1-lineage tumors **[36]** and GH-secreting subtypes **[37]**. Remission in these series is biochemical and depends on medical therapy, so they can neither support nor contradict the nonfunctioning analyses; the female predominance of TPIT-lineage nonfunctioning tumors parallels Cushing disease **[32, 33]**.

Survival data

Progression-free survival could not be pooled. Median PFS was 83 vs 45 months (SF1 vs TPIT) in Cheok's cohort (P = 0.002) **[4]**; 5-year PFS was 1.00 vs 0.70 (gonadotroph vs null cell) in Almeida's cohort (P = 0.011) **[9]**; and in Chatrath's cohort, with mean follow-up of 8.8 years, no subtype differed significantly (null vs gonadotroph HR 3.6, P = 0.10) **[38]**.

Supplementary Tables :

Table S1. Characteristics of the included studies

Study	Study type	Setting	Patients analyzed	Lineage groups	Surgical approach	Use in this review
Fukuhara 2026 **[19]**	Full text	Toranomon Hospital, Tokyo (Apr 2019–Mar 2022)	164 (of 180; PIT1 16 excluded)	TPIT 46, SF1 118	Endoscopic, all	Pooled: invasion, GTR, recurrence
Woo 2024 **[26]**	Full text	Queen Mary Hospital, Hong Kong (Jan 2010–Mar 2022)	113	SF1 66, TPIT 21, PIT1 7, none 19	Transsphenoidal 90.3%; combined 8.0%; open 1.8%	Pooled: GTR, recurrence; broad-definition invasion (sensitivity)
Cheok 2025 **[4]**	Full text	Multicenter, USC-led (Jun 2017–Aug 2021)	238 (150 nonfunctioning)	Nonfunctioning: SF1 104, TPIT 29, PIT1 7, dual 10	Endoscopic 82.4%; microscopic endonasal 15.1%	Pooled: invasion, GTR
Taguchi 2023 **[20]**	Full text	Hiroshima University	292	Gonadotroph 191 (SF1 by GATA3 surrogate), null 61, PIT1 18, corticotroph (TPIT) 22	Not stated	Primary analyses retained; excluded in sensitivity analysis
Hu 2026 **[16]**	Full text	First Affiliated Hospital, Sun Yat-sen University (Mar 2020–Dec 2023); same cohort as Xu 2025	409	SF1 245, TPIT 101, PIT1 39, none 24	Not stated	Pooled: invasion, GTR; recurrence (sensitivity only)
Chen 2025 **[21]**	Full text	Fuzong Clinical Medical College, Fujian Medical University (2014–2019)	192	SCA 44; non-SCA 148	Transsphenoidal (not further specified)	Adjusted estimate; crude recurrence vs all other nonfunctioning tumors
Taracha 2026 **[28]**	Full text	Not stated in text reviewed (Jan 2020–Sep 2024)	302 primary endoscopic transsphenoidal surgeries	Transcription-factor combinations (multiplicity)	Endoscopic endonasal, all	Narrative: multiplicity; adjusted HRs
Xu 2025 **[15]**	Full text	First Affiliated Hospital, Sun Yat-sen University (Jan 2021–Feb 2023)	171 macroadenomas	SF1 113, TPIT 58	Endoscopic	Same cohort as Hu 2026; growth pattern (narrative)
Chatrath 2022 **[38]**	Full text	Washington University, St Louis; University of Virginia	239	Corticotroph, gonadotroph and null-cell groups (WHO 2017)	Not stated	Narrative: long-term outcomes (null vs gonadotroph HR 3.6)
Raub 2025 (TPIT) **[5]**	Full text	University of Washington and USC	107 TPIT-immunoreactive silent tumors (exclusions: see text)	Silent TPIT, single arm	Endoscopic endonasal 95.7%; craniotomy 2.9%; combined 1.4%	Narrative (single arm)

Bove 2024 **[7]**	Full text	USC and University of Washington (2008–2021)	27	Dual transcription-factor staining (single arm)	Endoscopic 96% (26/27)	Narrative (dual-factor)
Tang 2023 **[10]**	Full text	Beijing Tiantan Hospital (2018–2021)	723 PAs; 93 multilineage, 100 single-lineage comparators	Multilineage vs single-lineage	Not stated	Narrative (Tiantan cluster)
Zhao 2023 **[36]**	Full text	Huashan Hospital, Fudan University, Shanghai (from 2017)	146	Silent PIT1 lineage	Not stated	Narrative (PIT1 lineage)
Oksuz 2026 **[34]**	Full text	Ankara University, Turkey (15-year single centre)	90 (of 148 screened)	GH-only vs GH/PRL; sparsely vs densely granulated	Not stated	Narrative (functioning tumors)
Chong 2025 **[35]**	Full text	Nanjing Drum Tower Hospital (2017–2024)	94 (of 109)	PIT1/SF1 vs PIT1 (acromegaly)	Not stated	Narrative (functioning tumors)
Li 2026 (GH) **[37]**	Full text	Peking Union Medical College Hospital (2022–2024)	143 (acromegaly or gigantism)	GH-secreting pathological subtypes	Not stated	Narrative (functioning tumors)
Zhang 2025 (GH) **[13]**	Full text	Beijing Tiantan Hospital (2018–2022)	193 (acromegaly)	Single vs multiple transcription factors (GH-secreting)	Not stated	Narrative (functioning; remission 30.8% vs 71.6%)
Jiang 2021 **[25]**	Full text	Peking Union Medical College Hospital (Jan 2019–May 2020)	310 (112 SCA; 198 SGA)	Silent TPIT 112, silent SF1 198	Microscopic 70.6%; endoscopic 29.4%	Pooled: invasion, GTR, recurrence, sex
Asmaro 2023 **[23]**	Full text	Stanford University	169 consecutive first-time surgeries	PIT-1 64, TPIT 38, SF-1 62, null 5 (45% functioning)	Endoscopic (Table 1)	Narrative; functioning-tumor and broadened analyses
Goyal-Honavar 2021 **[17]**	Full text	Christian Medical College, Vellore	300 nonfunctioning (62 SCA; 238 other); 52 vs 205 with serial imaging	SCA vs other nonfunctioning	Transsphenoidal: 80.6% (SCA), 89.5% (other)	Adjusted estimate; crude recurrence vs all other nonfunctioning tumors
Himstead 2024 **[22]**	Full text	University of California, Irvine	91 (20 SCA; 71 other NFPA)	Silent TPIT 20; other nonfunctioning 71	Endoscopic endonasal	Narrative (invasion patterns)
Almeida 2019 **[9]**	Full text	Barrow Neurological Institute and University Health Network, Toronto (2007–2017)	69 (31 null cell; 38 gonadotroph)	Null cell 31; gonadotroph 38	Transsphenoidal (not quantified)	Narrative (null cell)
Haddad 2020 **[27]**	Full text	University of California, San Francisco	1,166 adenomas; 107 null cell, 149 silent gonadotroph	Null cell 107; silent gonadotroph 149	Endoscopic 32% (null cell), 26% (gonadotroph)	Adjusted estimate (null vs gonadotroph)

Goyal-Honavar 2025 **[18]**	Full text	NIMHANS, Bengaluru (2013–2023)	57	Silent corticotroph (single arm)	Endoscopic in most (not quantified)	Narrative (single arm)
Raub 2025 (silent ACTH) **[6]**	Full text	University of Washington and USC	186 (after excluding 91 Cushing disease)	Silent ACTH-positive (single arm)	Endoscopic 96.2%	Narrative (single arm)
Mete 2016 **[8]**	Full text	University Health Network, Toronto	954 adenomas; 31 silent subtype 3	Silent subtype 3 (PIT1 lineage)	Not stated	Narrative (PIT1 lineage)
Zhang 2026 **[14]**	Full text	Beijing Tiantan Hospital (2020–2025)	603 (188 SCA; 415 SGA)	Silent TPIT 188, silent SF1 415	Endoscopic endonasal 94.1% (SCA), 88.2% (SGA)	Pooled: invasion, GTR, recurrence, sex
Li 2026 **[24]**	Full text	Tongji Hospital, Wuhan	274 primary resections	TF lineages (TPIT group = ACTH-secreting; SF1; PIT1 subgroups)	Transsphenoidal, extra-pseudocapsular	Narrative; not pooled (TPIT group ACTH-secreting)
Sugata 2026 **[31]**	Congress abstract	Kagoshima, Japan (2012–2023)	201 treatment-naïve	SF1 141, TPIT 39, PIT1 6, SF1/PIT1 4, triple-negative 11	Not stated	Narrative (abstract only)
Bie 2024 **[11]**	Full text not retrieved (abstract only)	Beijing Tiantan Hospital, Capital Medical University (Jan 2019–Oct 2021)	369	SF1 89, TPIT 79, multilineage 87	Not stated	Narrative (abstract only)
Wang 2024 **[12]**	Full text not retrieved (abstract only)	Beijing Tiantan Hospital, Capital Medical University (2018–2022)	57 Pit1/SF1; 88 Pit1; 70 SF1	Pit1/SF1 57, Pit1 88, SF1 70	Not stated	Narrative (abstract only)
Micko 2021 **[29]**	Full text not retrieved (abstract only)	Single centre, Vienna	73 TFGA-positive (22 TFGA-plus; 51 TFGA-only)	TFGA-plus 22; TFGA-only 51	Not stated (direct endoscopic inspection for invasion)	Narrative (abstract only)

Abbreviations: DGST, densely granulated somatotroph tumor; GH, growth hormone; GTR, gross total resection; HR, hazard ratio; PFS, progression-free survival; PRL, prolactin; SGST, sparsely granulated somatotroph tumor.

Table S2. Risk of bias assessed with the Newcastle–Ottawa Scale for comparative cohorts

Study	Design / sample	Selection	Comparability	Outcome	Total
Himstead et al., 2024 **[22]**	Retrospective comparative cohort; 91 patients comprising 20 SCAs and 71 other NFPAs (study excluded functional tumours, reoperations and prior apoplexy)	4/4	2/2	2/3	8/9
Fukuhara et al., 2026 **[19]**	Single-center retrospective comparative cohort; 180 clinically nonfunctioning PitNETs; 164 TPIT/SF1 comparison after exclusions (46 TPIT, 118 SF1)	3/4	1/2	3/3	7/9
Asmaro et al., 2023 **[23]**	Retrospective comparative cohort; 169 consecutive first-time pituitary surgeries; 45% functional; TF groups PIT1 n=64, SF1 n=62, TPIT n=38, nonstaining n=5	4/4	2/2	2/3	8/9
Cheok et al., 2025 **[4]**	Retrospective multicenter comparative cohort; 238 surgically resected PAs; 150 nonfunctional, with multiple TF-defined lineages	3/4	0/2	2/3	5/9
Tang et al., 2023 **[10]**	Retrospective comparative cohort; 723 PAs reviewed, 93 multiple-cell-lineage tumours identified and compared with a random sample of 100 drawn from the 589 single-cell-lineage tumours; 19 cases excluded for unavailable data	3/4	1/2	1/3	5/9
Xu et al., 2025 **[15]**	Retrospective comparative cohort; 171 NFPA macroadenomas; 113 SF1-expressing and 58 TPIT-expressing after exclusions (same cohort as Hu 2026)	4/4	1/2	1/3	6/9
Jiang et al., 2021 **[25]**	Retrospective comparative cohort; 112 SCA and 198 SGA patients operated January 2019–May 2020	3/4	2/2	2/3	7/9
Li et al., 2026 (Tongji) **[24]**	Retrospective cohort with comparative TF-lineage groups; 294 eligible resections; 274 primary surgeries and 20 reoperations, with 274 primary cases used for main analyses	3/4	1/2	2/3	6/9
Almeida et al., 2019 **[9]**	Retrospective comparative cohort; Barrow and University Health Network, 2007–2017; 31 null cell and 38 gonadotroph adenomas (the latter reclassified from null cell by SF1 on retesting); transcription factors stained retrospectively at Barrow	4/4	1/2	2/3	7/9
Zhang et al., 2025 **[13]**	Retrospective comparative cohort; 193 patients with acromegaly operated 2018–2022 at Beijing Tiantan Hospital; single versus multiple transcription factor expression; endocrine remission outcome	3/4	1/2	2/3	6/9
Oksuz et al., 2026 **[34]**	Retrospective comparative cohort; 90 of 148 screened patients with acromegaly (58 excluded, 18 for absent follow-up) at a tertiary center; GH-only versus GH/PRL and sparsely versus densely granulated tumors	3/4	2/2	2/3	7/9
Chong et al., 2025 **[35]**	Retrospective comparative cohort; Nanjing Drum Tower Hospital, 2017–2024; 94 of 109 patients with acromegaly after exclusions; PIT1/SF1 versus PIT1 tumors	3/4	1/2	3/3	7/9
Li et al., 2026 (GH-secreting) **[37]**	Retrospective comparative cohort; Peking Union Medical College Hospital, 2022–2024; 143 patients with acromegaly or gigantism; 25 lost to follow-up for the remission analysis	3/4	2/2	3/3	8/9

Table S3. Risk of bias assessed with QUIPS for prognostic cohorts

Study	Design / sample	Participation	Attrition	PF measurement	Outcome measurement	Confounding	Analysis	Overall
Taguchi et al., 2023 **[20]**	Retrospective prognostic cohort; 292 NF-PitNETs; recurrence analysis restricted to patients with >5-year follow-up or recurrence within 5 years; 113 had qualifying follow-up	Low	High	Low	Low	Moderate-High	Moderate-High	High
Chatrath et al., 2022 **[38]**	Retrospective prognostic cohort; 239 NFPA patients; 23 excluded for insufficient tissue/apoplexy/unavailable blocks; 216 underwent TF/pathology reassessment	Low	Low	Low	Low	Low	Low	Low
Haddad et al., 2020 **[27]**	Retrospective prognostic cohort; 1166 total pituitary adenomas; 107 null cell adenomas (9.2%) compared with 149 silent gonadotroph adenomas (12.8%)	Low	Low-Moderate	Low	Low	Low-Moderate	Low-Moderate	Low-Moderate
Goyal-Honavar et al., 2021 **[17]**	Retrospective prognostic/comparative cohort; 300 nonfunctional adenomas; outcome analysis included 52 SCA and 205 other nonfunctional adenomas with serial imaging	Low	Low-Moderate	Low	Low	Moderate	Low-Moderate	Moderate
Woo et al., 2024 **[26]**	Retrospective prognostic cohort; 113 NF-PitNETs with follow-up at Queen Mary Hospital	Low-Moderate	Low-Moderate	Low	Low	Moderate	Low	Low-Moderate
Zhang et al., 2026 **[14]**	Retrospective prognostic/comparative cohort; 603 NFPA patients: 188 SCA and 415 SGA	Low	Low-Moderate	Low	Low	High	Low	Moderate-High
Chen et al., 2025 **[21]**	Retrospective prognostic cohort; 192 NFPA patients operated 2014–2019; SCA n=44 and non-SCA n=148	Low	Low	Low	Low	Moderate	Low	Low-Moderate
Hu et al., 2026 **[16]**	Retrospective prognostic cohort; 409 NF-PitNETs: SF1 245, TPIT 101, PIT1 39, no distinct lineage 24	Low	Low-Moderate	Low	Low	Moderate	Low-Moderate	Moderate
Zhao et al., 2023 **[36]**	Retrospective prognostic cohort; 146 patients with silent PIT1-lineage PitNETs from a tertiary-center database	Low-Moderate	Moderate	Low	Low-Moderate	High	High	High
Taracha et al., 2026 **[28]**	Retrospective prognostic cohort; 302 primary endoscopic endonasal transsphenoidal surgeries	Low	Low	Low	Low	Low-Moderate	Low	Low-Moderate

Table S4. Risk of bias assessed with the JBI checklist for case series (single-arm series)

Study	Design / sample	Q1–Q5	Q6–Q10	Yes	Overall
Raub et al., 2025 (TPIT) **[5]**	Retrospective review of prospectively maintained databases, University of Washington and USC, 2011–2023; 70 silent TPIT-lineage PitNETs after excluding 37 Cushing disease cases	Y Y Y U U	Y Y Y Y Y	8/10 (80%)	Low
Raub et al., 2025 (silent ACTH) **[6]**	Retrospective study, University of Washington and USC, 2011–2023; 186 silent ACTH-positive PitNETs after excluding 91 Cushing disease cases; identification by ACTH rather than transcription factor staining	Y Y U U U	Y Y Y Y Y	7/10 (70%)	Low
Bove et al., 2024 **[7]**	Retrospective chart review of a prospectively collected USC multi-institutional database, 2008–2021; 27 patients with dual transcription factor staining; follow-up of 3 months or more in 20	Y Y Y U N	Y Y Y Y Y	8/10 (80%)	Low
Mete et al., 2016 **[8]**	Retrospective review of pathology records, University Health Network, 2001–2015; 31 silent subtype 3 adenomas among 954; clinical information incomplete for some cases	Y Y U N N	Y Y U Y Y	6/10 (60%)	Moderate
Goyal-Honavar et al., 2025 **[18]**	Retrospective single-center series (NIMHANS, Bengaluru), all patients operated for silent corticotroph tumors 2013–2023; 57 patients; those without follow-up or postoperative imaging excluded	Y U U Y U	Y Y Y Y Y	7/10 (70%)	Low

Table S5. Records count by source

Source	Records	Already in PubMed set	New
PubMed	702	Not applicable	702
Europe PMC	1,410	320	1,090
OpenAlex citation chasing	116	71	45
Scopus	1,028	625	403
Web of Science	107	91	16

548 **Table S6.** Search strategies (PRISMA-S)

PubMed (2015–2026):

```
(("Pituitary Neoplasms"[Mesh] OR "pituitary adenoma"[tiab] OR "pituitary adenomas"[tiab] OR "pituitary neuroendocrine tumor"[tiab] OR "pituitary neuroendocrine tumors"[tiab] OR "pituitary neuroendocrine tumour"[tiab] OR "pituitary neuroendocrine tumours"[tiab] OR PitNET[tiab] OR PitNETs[tiab] OR "pituitary tumor"[tiab] OR "pituitary tumors"[tiab] OR "pituitary tumour"[tiab] OR "pituitary tumours"[tiab]) AND ("transcription factor"[tiab] OR "transcription factors"[tiab] OR TPIT[tiab] OR "T-PIT"[tiab] OR TBX19[tiab] OR SF1[tiab] OR "SF-1"[tiab] OR NR5A1[tiab] OR PIT1[tiab] OR "PIT-1"[tiab] OR POU1F1[tiab] OR lineage[tiab] OR lineages[tiab] OR "silent corticotroph"[tiab] OR "silent corticotrophs"[tiab] OR Crooke[tiab] OR "sparsely granulated"[tiab] OR "densely granulated"[tiab] OR "immature PIT1"[tiab] OR "silent subtype 3"[tiab] OR "null cell"[tiab]) NOT ("Case Reports"[pt] OR Editorial[pt] OR Letter[pt]) NOT (animals[mh] NOT humans[mh])) AND 2015:2026[dp]
```

Scopus:

```
TITLE-ABS-KEY ( ( "pituitary adenoma" OR "pituitary neuroendocrine tumor" OR "pituitary neuroendocrine tumour" OR pitnet OR "pituitary tumor" OR "pituitary tumour" ) AND ( "transcription factor" OR tpit OR "t-pit" OR tbx19 OR sf1 OR "sf-1" OR nr5a1 OR pit1 OR "pit-1" OR pou1f1 OR lineage OR "silent corticotroph" OR crooke OR "sparsely granulated" OR "densely granulated" OR "immature pit1" OR "null cell" ) ) AND PUBYEAR > 2014 AND NOT DOCTYPE ( le ) AND NOT DOCTYPE ( ed ) AND NOT DOCTYPE ( no )
```

Web of Science Core Collection (all editions):

```
TS=(("pituitary adenoma*" OR "pituitary neuroendocrine tumo*" OR PitNET* OR "pituitary tumo*") AND ("transcription factor*" OR TPIT OR "T-PIT" OR TBX19 OR SF1 OR "SF-1" OR NR5A1 OR PIT1 OR "PIT-1" OR POU1F1 OR lineage* OR "silent corticotroph*" OR Crooke OR "sparsely granulated" OR "densely granulated" OR "immature PIT1" OR "null cell")) AND PY=2015-2026
```

Europe PMC (MEDLINE, PMC, and preprints):

```
("pituitary adenoma" OR "pituitary adenomas" OR "pituitary neuroendocrine tumor" OR "pituitary neuroendocrine tumors" OR "pituitary neuroendocrine tumour" OR "pituitary neuroendocrine tumours" OR PitNET OR PitNETs OR "pituitary tumor" OR "pituitary tumors" OR "pituitary tumour" OR "pituitary tumours") AND ("transcription factor" OR "transcription factors" OR TPIT OR "T-PIT" OR TBX19 OR SF1 OR "SF-1" OR NR5A1 OR PIT1 OR "PIT-1" OR POU1F1 OR lineage OR "silent corticotroph" OR Crooke OR "sparsely granulated" OR "densely granulated" OR "immature PIT1" OR "null cell") AND (SRC:MED OR SRC:PMC OR SRC:PPR) AND (PUB_YEAR:[2015 TO 2026])
```

Not searched: Embase (no institutional access), CENTRAL, trial registries.

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Supplementary Table S7. GRADE Certainty of evidence

Outcome	Studies (patients)	Effect	Certainty	Reasons
Invasion, TPIT vs SF1	6 cohorts (498 vs 1,271)	RR 1.66 (HKSJ 1.44–1.92); crude 54% vs 31%	Low	Moderate risk of bias (Taguchi high, Zhang moderate-to-high; estimate 1.66 without Taguchi); I^2 0%; precise; definitions differ (I^2 69% under own definitions); RR below 2, so no upgrade
Gross total resection	7 cohorts (519 vs 1,337)	RR 0.92 (0.87–0.98); 7.0 fewer per 100 (−11.9 to −2.2)	Low	MRI timing and approach vary; I^2 0%; precise; invasion may mediate
Crude recurrence or progression (definition-matched)	3 cohorts (343 vs 727)	RR 1.58 (HKSJ 0.63–3.96); crude 10.2% vs 6.5%	Very low	Interval spans no effect; follow-up 14–50 months; unadjusted for resection
Adjusted recurrence HR	2 cohorts, not pooled	Hu 2.04 (1.10–3.82); Woo 1.29 (0.58–2.84)	Very low	Non-comparable adjustment sets; Hu not adjusted for invasion or size
Female sex, TPIT vs SF1	4 cohorts (447 vs 976)	RR 2.83 (HKSJ 2.40–3.33)	Moderate	Upgraded one level for large effect; I^2 0%; all East Asian cohorts

Supplementary Figures:

Figure S1. Methodological quality of the included comparative cohort studies, assessed with the Newcastle–Ottawa Scale (NOS)

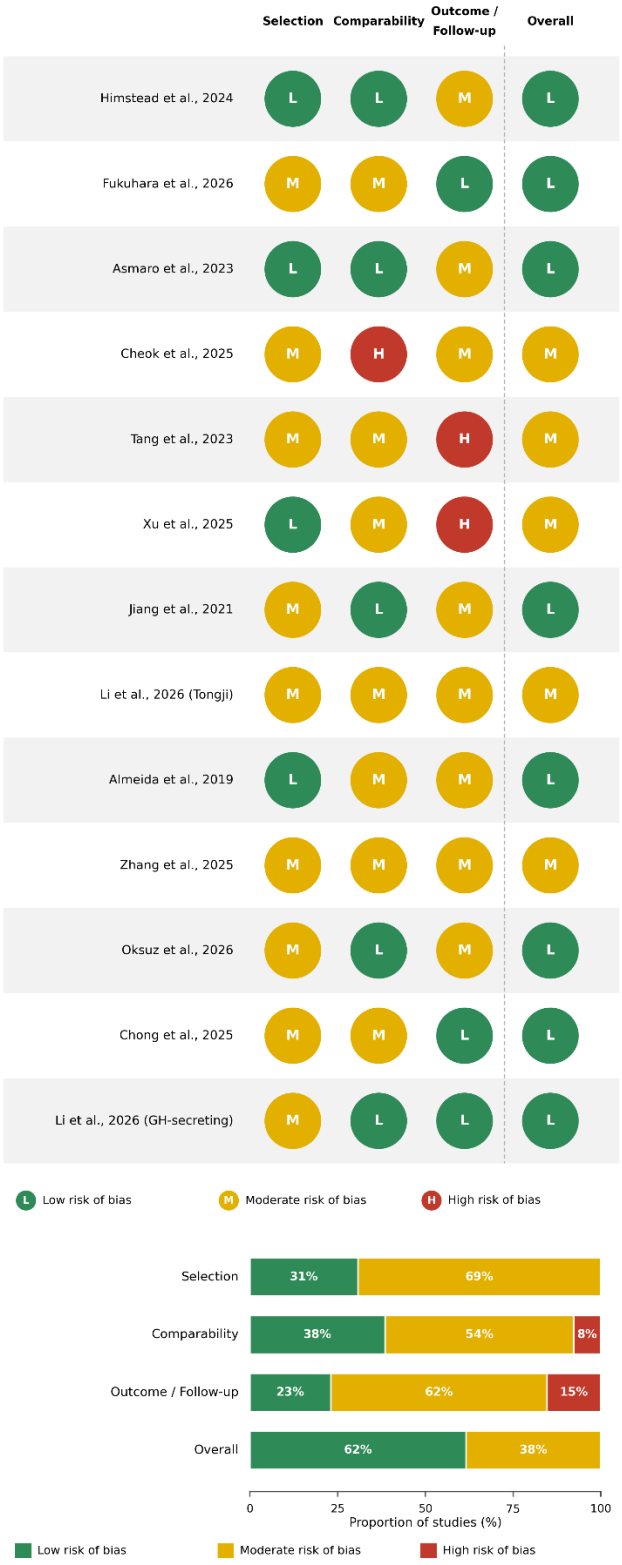


Figure S2. Risk of bias in the included prognostic cohort studies (QUIPS)

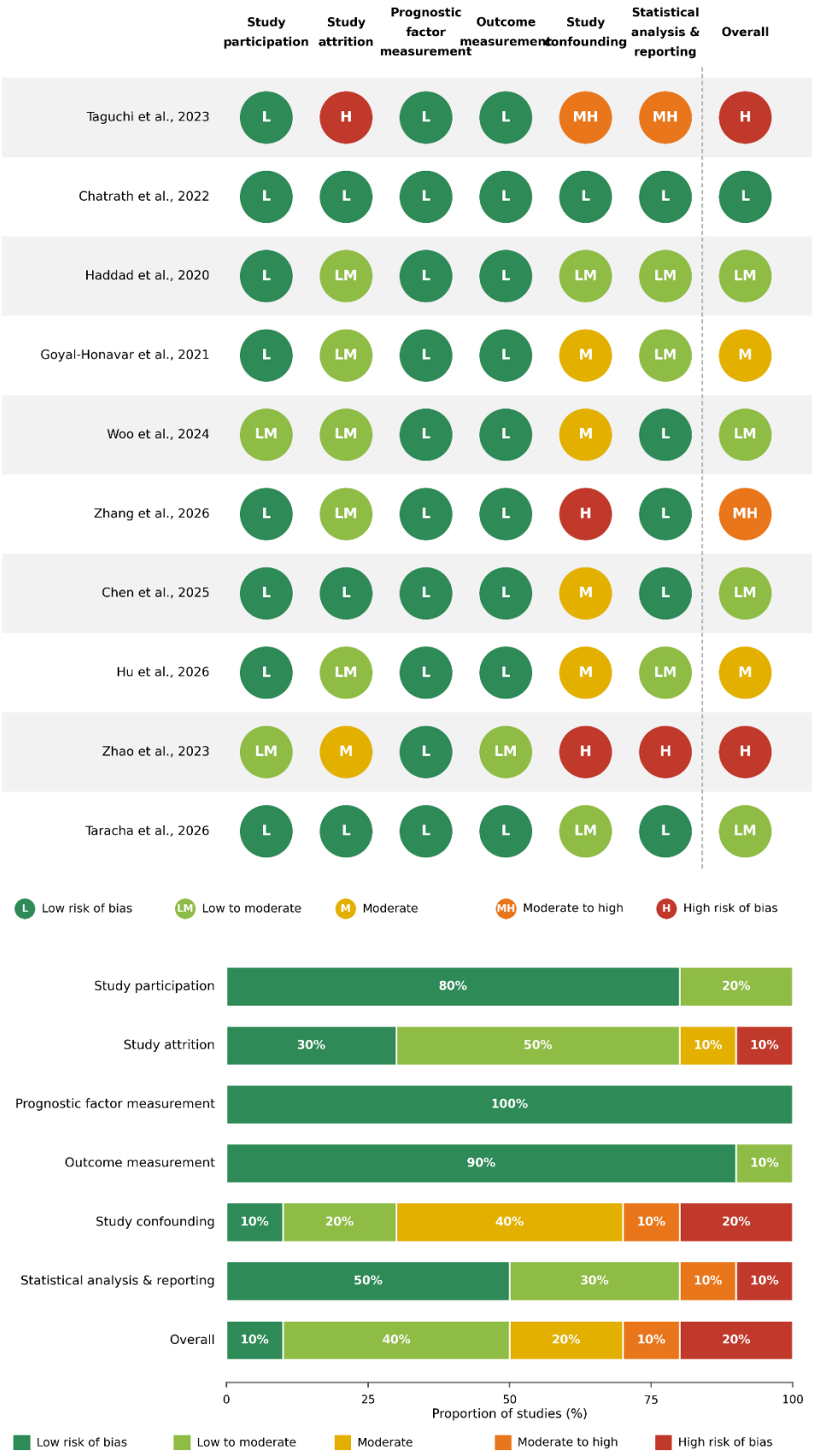


Figure S3. Risk of bias in the included prognostic cohort studies (*JBI*)

