**PANOMEN-3 grading score is reliable in predicting pituitary adenoma behavior and prognosis: a single center cohort study**

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# Supplementary Data

### *Age and sex analyses*

The PANOMEN-3 panelists recognized a prognostic role of these features in pituitary adenomas but were not included in the score due to a variable effect on different adenoma subtypes. We decided to assess their role in our cohort, together with the PANOMEN grade.
Female sex predicted initial surgical remission (*Supplementary Table 4*), but on the long-term it was also related to an increased risk of recurrence (grade distribution did not differ among sexes in our cohort, p=0.28) (*Supplementary Figure 4*); in case of persisting disease after surgery females were also more frequently referred to further adjuvant treatments (*Supplementary Figure 4*).
Age did not provide useful information in the whole cohort regarding postoperative behaviour.
Age and sex were not relevant in predicting final disease status after a multimodal therapeutic approach (whole cohort) or response to medical treatment.

### *Grade items analyses*

We also performed analyses on grade items in order to define whether some of them played a pivotal role in specific settings (e.g., surgical outcome, recurrence risk).
Considering a multimodal therapeutic approach in our whole cohort, some items of the grade could predict disease remission at the last available visit at the Pituitary Unit: patients with Cushing's Disease (CD) were more prone to reach remission, while cavernous sinus invasion predicted a persisting disease on the long-term.
Regarding the surgically treated patients, grade could not predict the outcome. From the analysis of items used for grade calculation a significant role of adenoma phenotype and cavernous sinus invasion emerged (*Supplementary Figure 5*), without any significant interaction between these two parameters. Regarding cases achieving disease remission following first-line surgery, preoperative biochemical control in secreting adenomas led to a recurrence risk reduction (*Supplementary Figure 6*). Moreover, Cox regression highlighted a pivotal role of phenotype, with operated CD patients presenting a higher risk of recurrence and, in case of persistent disease, an increased probability of further treatments (*Supplementary Table 3*).
Regarding primary medical treatment, prolactinomas presented a higher response rate at 1 year (i.e., biochemical control) than acromegaly (OR 3.77, 95%CI [1.44; 10.02], p<0.01); CD presence trended to the need of second-line curative approaches following medical treatment failure (OR 12.5, 95%CI [1.2; 211.8], p=0.05). Regarding disease remission after medical treatment discontinuation, only non-significative trends to remission in case of prolactinomas, microadenomas, and non-invasive adenomas emerged (p=0.07, 0.05 and 0.08 respectively) without reciprocal interactions.
Note that genetic syndrome was excluded from these analyses due to the limited data available.

### *Cushing's Disease*

Most patients with CD underwent pituitary surgery as the initial treatment. 15 patients reached UFC normalization prior to first-line surgery via preoperative medical treatment, but only one presented a downgrade. Surgery achieved remission at one year in 65% (73/112) of cases. Initial disease grade, sex and age did not predict surgical outcome (*Supplementary Table 4*); considering single items included in the grade calculation (excluding genetic syndrome due to the lack of data), we did not find effective predictors of the outcome, although a trend towards unsuccessful surgery emerged in case of cavernous sinus invasion (OR 0.01, IC95% = [<0.01; 1.12], p=0.09). Reaching eucortisolism preoperatory did not influence surgery outcome. Grade items did not predict relapse after successful

surgery (*Supplementary Table 5*), except for patients reaching eucortisolism in the preoperative period (*Figure 5*). Also, age and sex did not predict recurrence. The need for additional treatments in persistent cases was addressed in 32 out of 38 (84%) patients. Regarding persistent cases, single items used for grade calculation were not related to the need of further treatments (*Supplementary Table 5*); age and sex were uninfluential as well. Surgical downgrade was seen in 4 patients, but it did not influence the need for additional curative interventions (p=0.61).
Regarding patients undergoing primary medical treatment, 5/7 and 6/7 reached normal UFC levels respectively after 1 year of medical treatment and at last available follow-up (median 74 [23; 125] months). During follow-up 4 patients underwent curative treatments, resulting in durable remission in 50% of cases (2/4). Due to the small sample, no further statistical analysis was performed.
The single patient that received primary pituitary irradiation reached durable remission after medical treatment discontinuation without developing pituitary deficits (total follow-up of 60 months).
Overall, independently of the number or type of treatment used, 54% (65/120) of CD patients reached remission at the last follow-up considered, after a median period of 97 months [58.5; 160]. Baseline grade, age and sex did not influence the final outcome; single items used in the grade calculation were uninfluential as well.

***Acromegaly***

Regarding pituitary surgery in acromegaly, 3 out of 49 patients reached normal hormonal values preoperatively, leading to a grade reduction in a single patient. Surgery was effective in 21 cases and unlike grade, age and sex were not predictive of the outcome (*Supplementary Table 4*). When considering each item used to calculate the grade, only cavernous sinus invasion resulted relevant to the outcome; genetic syndrome was not included due to limited data. Biochemical control prior to surgery did not influence the outcome (p=0.79). Regarding patients in remission after one-year, longer follow-up was available for 20 out of 21 patients; 2 recurrences were registered over a median follow-up period of 51 months [25.5; 89.5]. A trend to increased risk of relapse for the female sex emerged (p=0.05), while grade and age were not relevant; items of the grade were not related to recurrence as well (*Supplementary Table 6*). Persistent disease required further curative interventions in 11 out of 28 cases (39%) over a median follow-up of 108 months [29.8; 189.3]. There was a trend to intervention in women (p=0.082), while postoperative grade and sex did not predict it. Considering single items included in the grade we found that hypopituitary patients tended to undergo further treatments more frequently (*Supplementary Table 6*). Despite failed surgery, 9 patients (32%) experienced a score downgrade, although this did not significantly reduce the need for additional interventions (p=0.14).
29 cases underwent primary medical treatment, 3 of which patients underwent additional curative interventions (10%) during follow-up, none leading to disease remission. Neither initial grade (or its components), nor 1-year downgrade, nor age, nor sex could predict the need for second tier interventions (p>0.05). Initial grade (and its components), 1-year downgrade, age and sex did not predict long-term response to medical treatment (p>0.05). Interestingly, a single patient (grade 2 disease) reached remission via medical treatment alone, despite not presenting an initial response at 1 year.
Considering a multimodal therapeutic approach, at last visit at the Pituitary Unit, 23 out of 78 patients with acromegaly (29%) were in remission after a median follow-up of 109 months [63; 172]. A higher baseline grade just tended to have a worse outcome without reaching significance (grade 3, OR 0.34,

IC95% = [0.09; 1.11], p=0.09), age and sex were uninfluential as well. On the contrary, considering single items used for grade calculation, the presence of cavernous sinus invasion predicted persisting disease in the long-term (p=0.04).

***TSH secreting pituitary adenomas***

All 9 patients with TSH-oma underwent primary pituitary surgery. All patients presented the same baseline features regarding grade calculation, resulting in a grade 2 disease (*Table 2*). 4 out of 9 cases (44%) reached biochemical control prior to surgery with the use of somatostatin analogues, none resulting in a re-grading. First surgery was effective in two thirds of patients (67%, 6/9) and preoperative hormonal control did not influence the outcome (p=1.00). Among cured cases, only one relapsed over a follow-up of median 28 months [17.3; 139]. For the persistent cases, the one presenting a surgical score downgrade was the only one to not require additional curative interventions. Overall, a multimodal therapeutic approach provided a remission rate of 67% (6/9) at last available follow-up (median duration of 114 months [28; 136,5]). Due to the small sample and homogenous features, no further statistical analyses were performed for this group.

***Prolactinomas***

No first-line pituitary surgery, irrespectively of preoperative medical treatment leading to normoprolactinemia, achieved cure for prolactinomas (remission rate 0%, 0/16), preventing an analysis on predictors of surgical outcome or relapse. Following surgery half of the patients presented a score downgrade (6/18). Further curative treatments were used in 38% of cases (6/16), over a median follow-up of 174 months [115.8; 220]. Age, sex, postoperative grade and score downgrade did not influence the need for additional interventions, although a trend to intervention for females emerged (p=0.062). Single items used for grade calculation did not influence the need for further treatments (*Supplementary Table 7*).

Regarding primary medical therapy, age, sex or baseline grade failed to predict 1-year hormonal response (*Supplementary Table 4*). Considering grade items, also adenoma size, invasiveness and the presence of hypopituitarism or mass effect symptoms were not relevant. Hormonal control at last on treatment follow-up (median treatment time 96 months [53; 140]) did not depend on baseline grade, sex or age, but an early response (1-year) and consequent score downgrade favoured long-term control. During follow-up, 3 patients (3%) required a curative treatment following medical treatment failure, which resulted in lasting remission in one case (33%). Age, sex, baseline grade (and its components) and 1-year biochemical control did not influence the need for second-tier curative approaches (p>0.05). Excluding patients undergoing second tier curative treatments, 25 out of 92 were cured by medical treatment alone (i.e., no prior irradiation, no ongoing medical treatment, normal radiological and biochemical findings). Although remission with medical therapy tended to be more frequent in case of low grade (grade 1 36%, grade 2 and 3 15%, p=0.05), logistic regression failed to find significant predictors among baseline grade, age, sex and 1-year hormonal response. When considering single items used for grade calculation, microadenomas were more prone to remission with medical therapy (OR 4.0, 95%CI [1.16; 18.4], p=0.04).
Overall, independently of the number or type of treatment used, 26% (22/111) of patients reached remission at the last follow-up considered, after a median follow-up of 112 months [70; 168]. Baseline

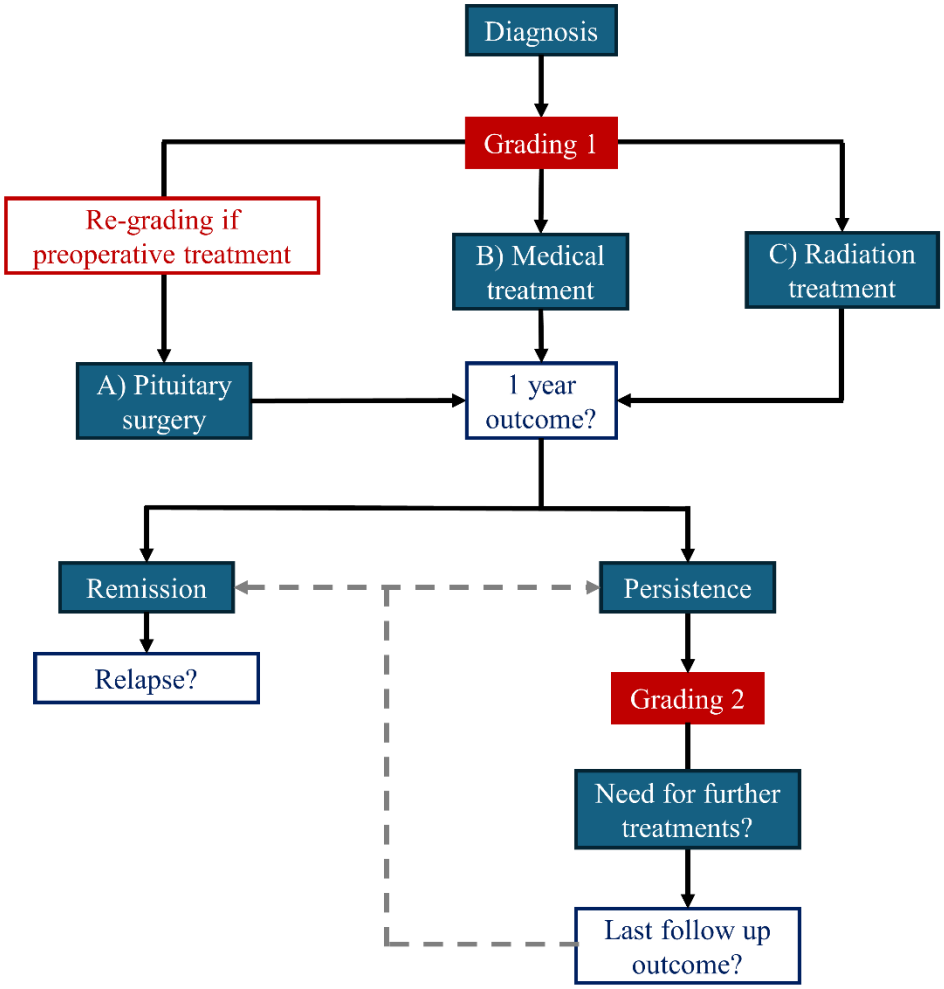
grade, age and sex did not influence the final outcome, but among single items of the grade a microadenoma at baseline predicted remission at last follow-up (OR 5.6, 95%CI [1.7; 25.7], p <0.01).

***Non-functioning pituitary adenomas***

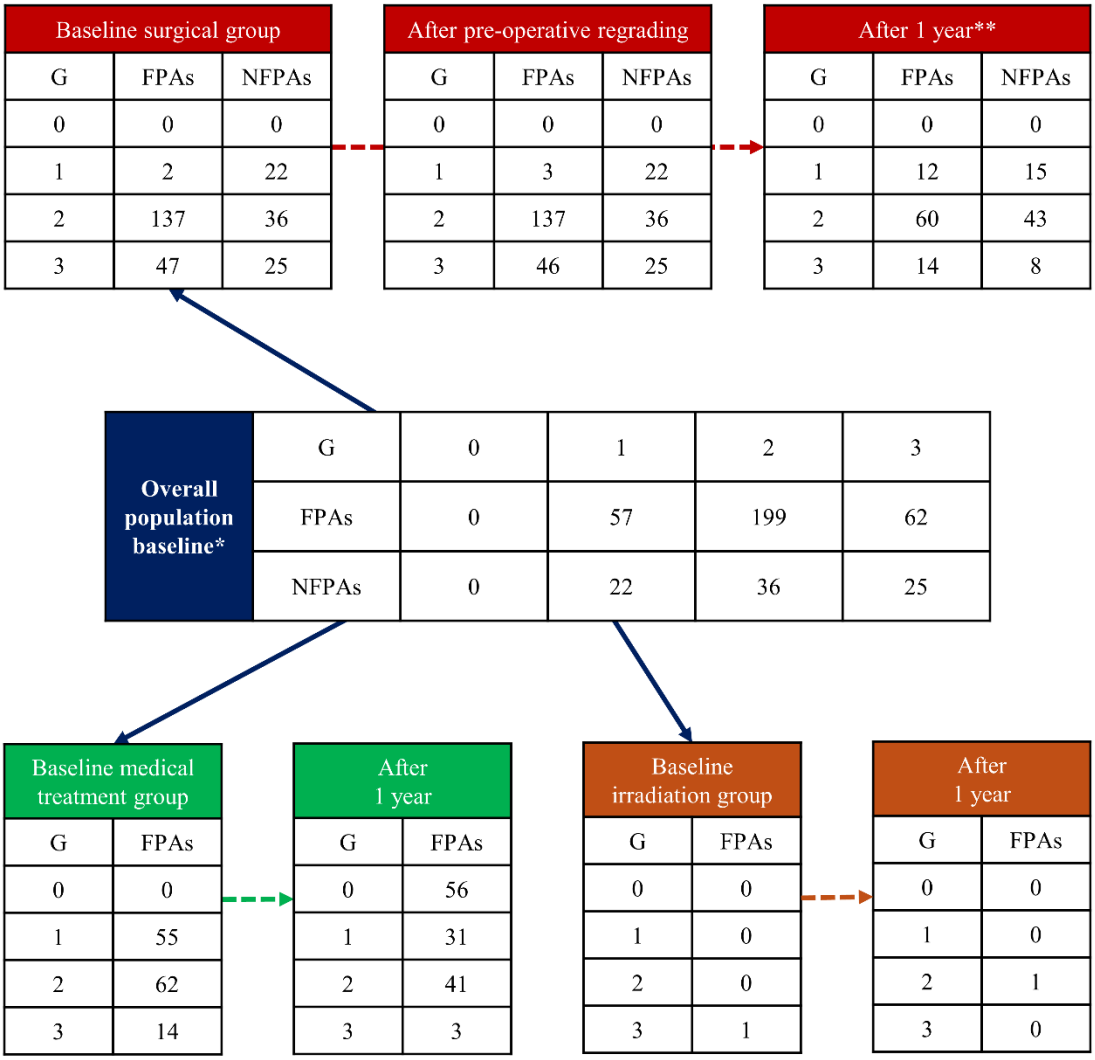
Sex and age did not influence the outcome of initial surgery. Logistic regression on single items included in the grade calculation (hypopituitarism, adenoma size, Knosp grade and mass effect symptoms) failed to reveal significant predictors of surgery outcome. Regarding cured cases at one year with follow-up longer than 12 months (n=14), only one case relapsed at 29 months (baseline grade 3), therefore no further statistical analysis was carried out. For persisting cases, further curative treatments were necessary for more than half of them (55%, 31/57). Postoperative grade and sex did not influence the need for further treatments, while a younger age favoured additional intervention. Among single grade items used, the presence of mass effect symptoms pointed towards additional intervention (*Supplementary Table 8*). Despite surgical failure, 22 patients (39%) presented a downgrade after the intervention, but this result was not relevant in relation to further treatments (p>0.05).

Considering a multimodal therapeutic approach, 22% of NFPA patients (18/83) reached remission at last ambulatory visit, considering a median follow-up of 80 months [27; 128]. High grade patients were less likely to reach remission, while age, sex and items considered in grade calculation were uninfluential.

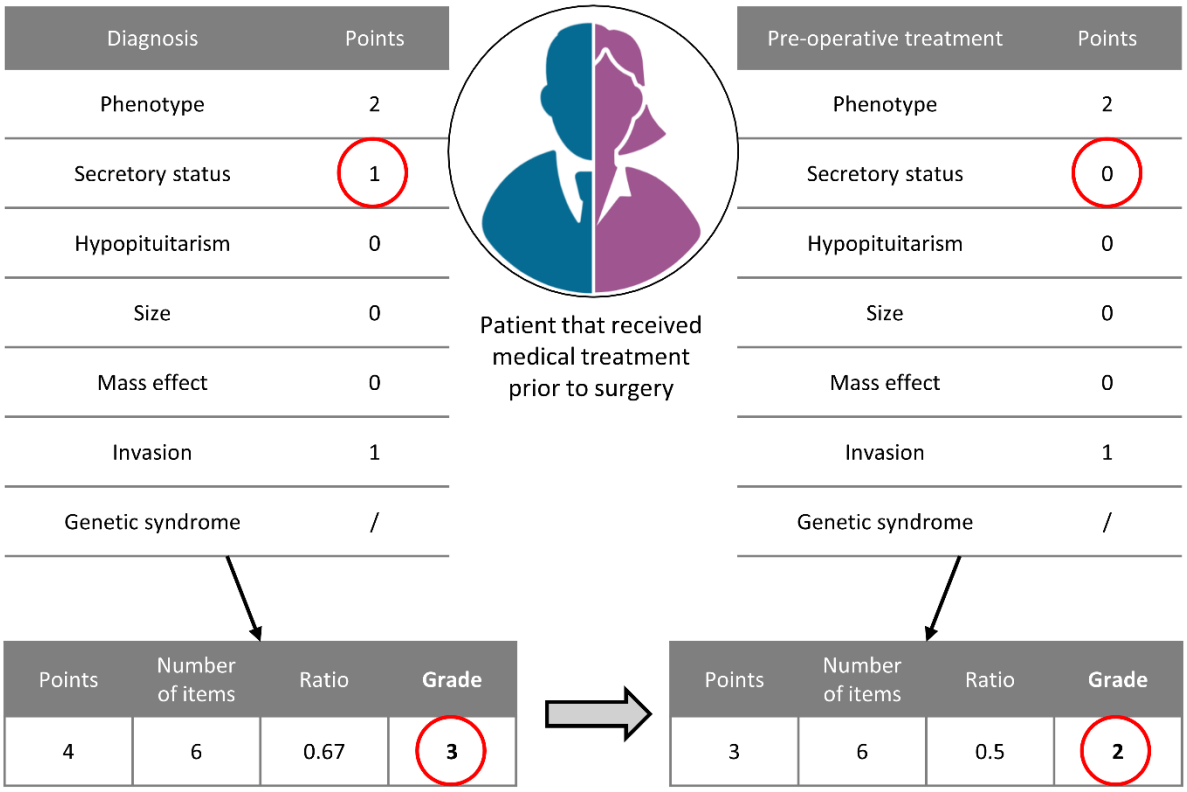
***Supplementary Figure 1.*** A first grading was assigned at diagnosis, with patients undergoing surgery receiving a re-grading if preoperatively treated based on biochemical control. Treatment's outcome was evaluated at 1 year and, in case of persisting disease, a second grading was performed. Patients were further evaluated based on their 1-year outcome, analysing recurrences in cured patients and the need for further curative treatments (see methods) in persisting cases. Disease status (i.e., disease remission or persistence) and disease control (for persisting cases) were assessed at the last follow-up.



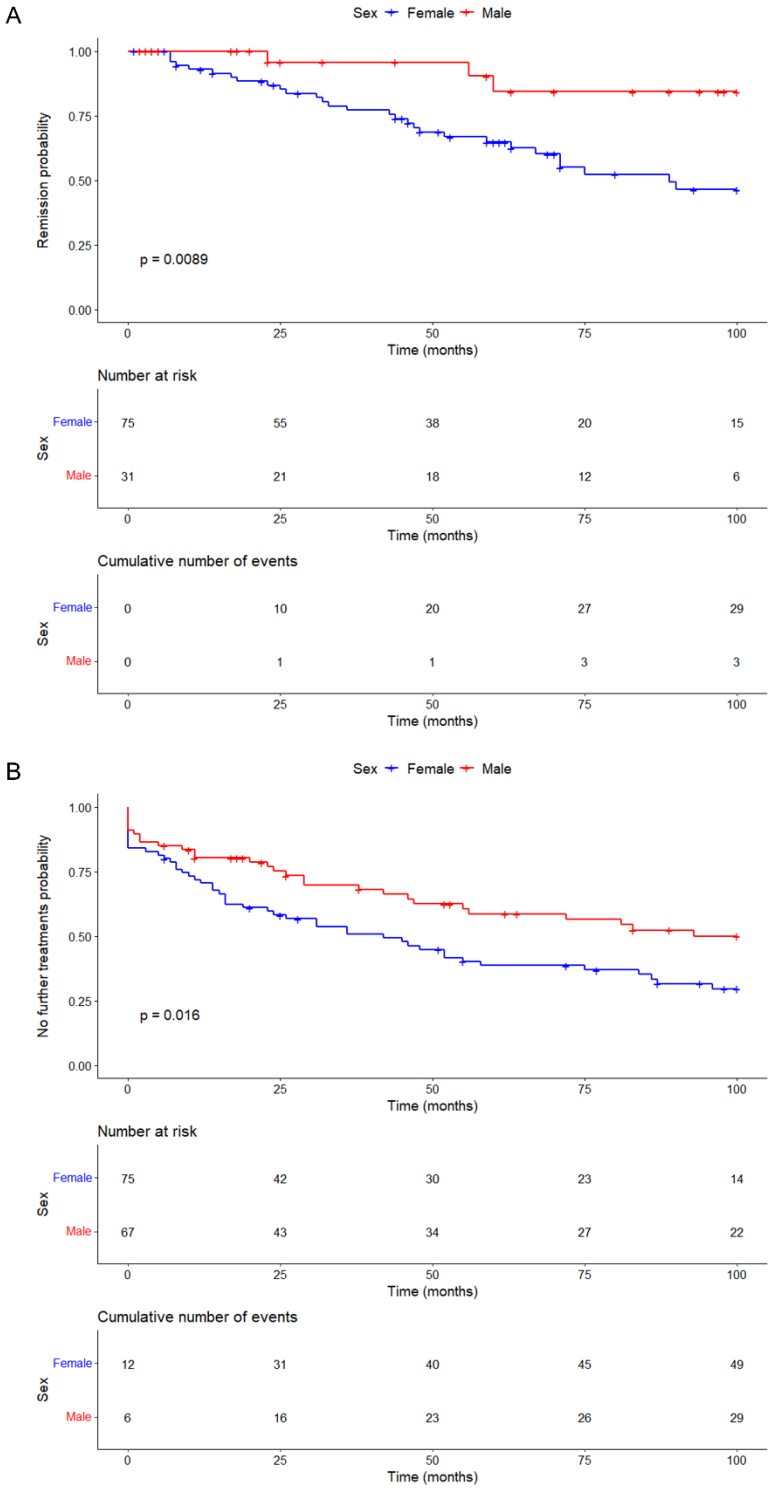
***Supplementary Figure 2.*** Grade distribution at baseline and 1 year after first line treatment based on the primary treatment chosen; for the surgical group the effect of preoperative treatment is also reported. *401 included patients. **only the 152 patients with persisting disease were assigned a grade at this time point in the surgical cohort as the others achieved disease remission. G: PANOMEN-3 grade; FPA: functioning (i.e., secreting) pituitary adenomas; NFPA: non-functioning pituitary adenomas.



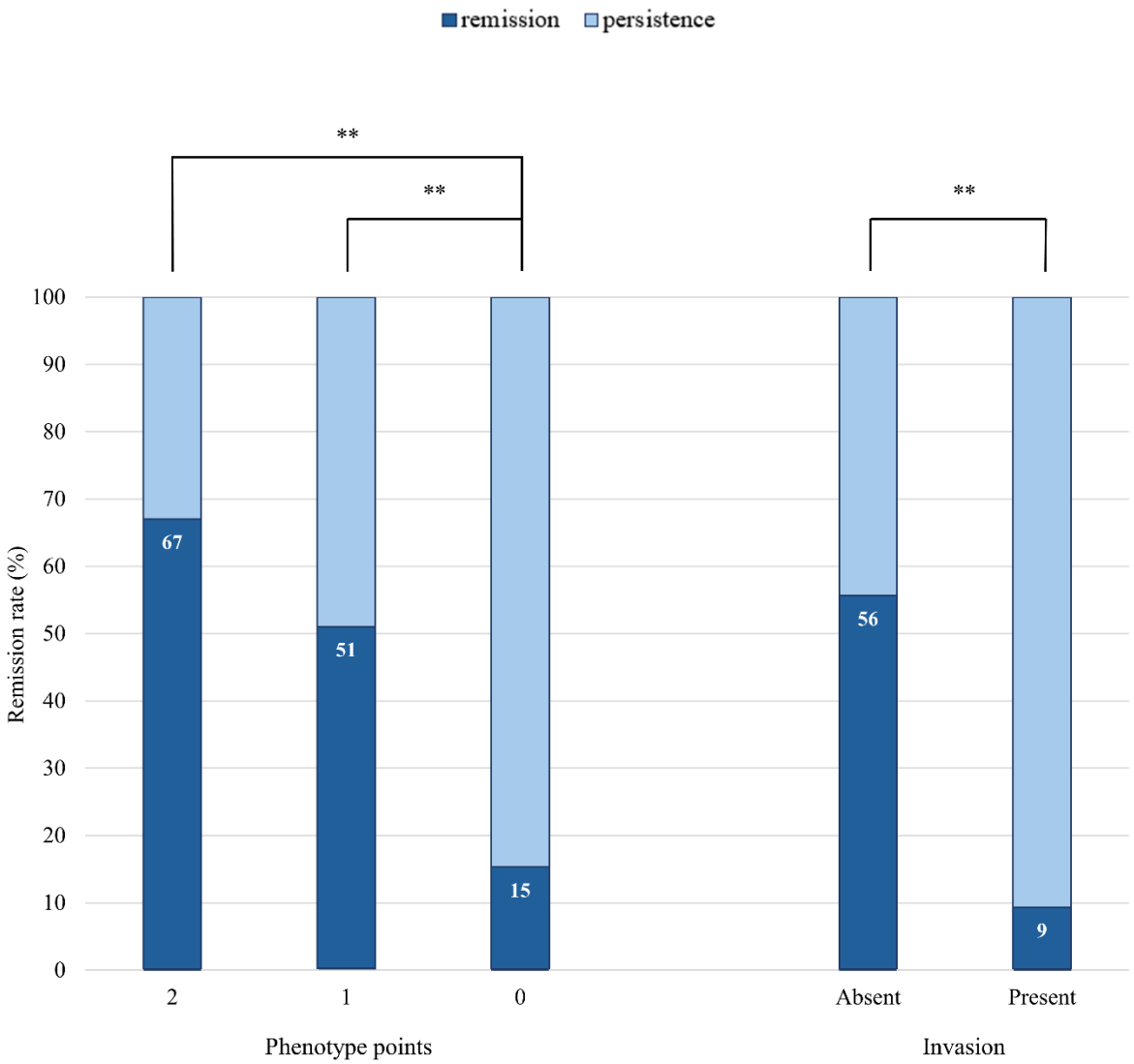
***Supplementary Figure 3**. Illustrative case of preoperative re-grading (grade 3 to 2) following biochemical control via preoperative medical treatment. Created with biorender.com.*



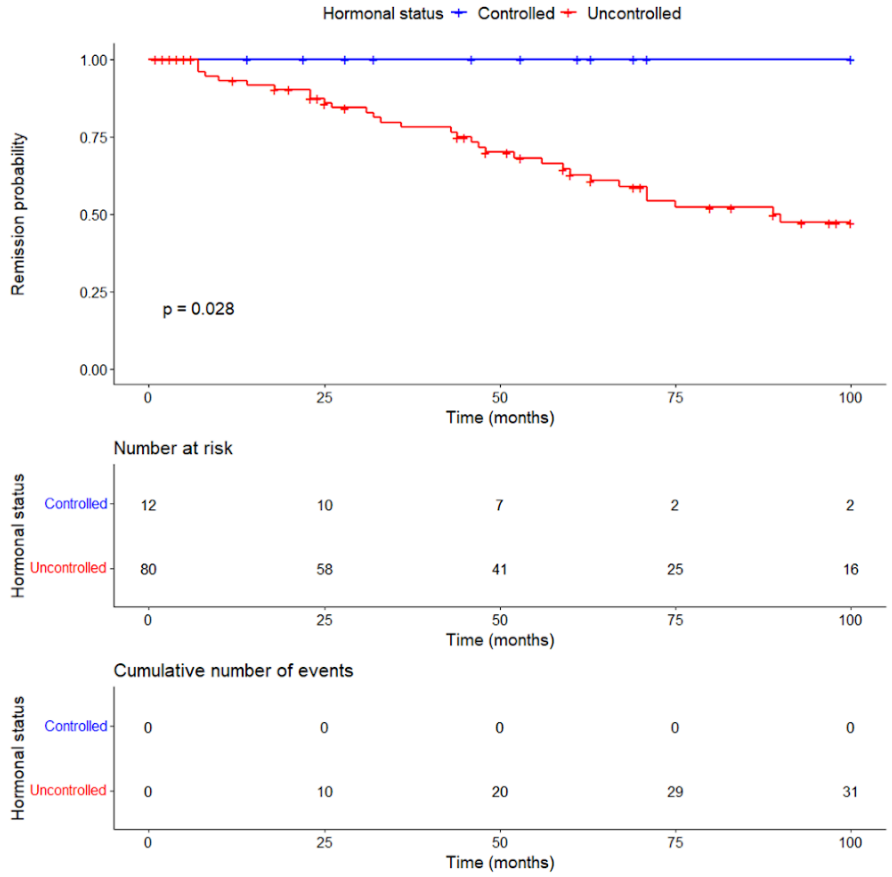
***Supplementary Figure 4.*** *Kaplan Meier curves for the probability of lasting disease remission following successful surgery (A) and of not needing additional curative treatments following surgical failure (B) based on sex. Curves were censored at 100 months in order to ensure adequate residual numerosity.*



***Supplementary figure 5.*** *Patients with Cushing's disease (2) or acromegaly/TSH secreting adenoma (1) presented significantly better surgical outcomes (OR 19.9, 95%CI [5.8; 80.3] and OR 6.0, 95%CI [2.4; 16.1], respectively) than prolactinomas/non-functioning pituitary adenomas (0). Cavernous sinus invasion significantly worsened surgical outcome (OR 0.1, 95%CI [<0.1; 0.3]). ** p <0.01.*



***Supplementary Figure 6.*** *Kaplan Meier curve for the probability of lasting remission following effective surgery based on hormonal control prior to surgery (secreting pituitary adenomas only). Curves were censored at 100 months in order to ensure adequate residual numerosity.*



***Supplementary Table 1.*** *Methodological details regarding diagnosis, treatments, grading and statistical analyses.*

| **Diagnosis** |
|---|
| • In case of co-secreting adenomas including concomitant TSH or prolactin excess in addition to growth hormone excess, patients were included in the acromegaly group.<br>• In case of a patient switching from silent corticotroph adenoma to overt Cushing's disease during follow-up, we considered the patient in the Cushing's disease group but with a normal hormone level at baseline. |
| **Treatment** |
| • Surgery outcome was assessed 1 year after surgery, in order to include "late" disease remissions.<br>• If an initial medical treatment was carried out for less than 12 months prior to pituitary surgery "indication" (i.e., not to the surgery itself), it was be considered as the preoperative treatment of a patient undergoing a first line surgery; if an initial medical treatment was carried out for more than a year prior to surgical indication, surgery was considered a second line approach after primary medical therapy failure.<br>• If a patient with persistent disease following pituitary surgery received the indication for a further curative treatment (i.e., pituitary surgery, pituitary irradiation and/or temozolomide treatment), but refused to undergo it for personal reasons, the patient was considered in the "need for further curative treatment" group to avoid bias and to correctly address a worse prognosis.<br>• In case of preoperative medical treatment, if the hormonal control was not assessed we prudently addressed an uncontrolled secretory status.<br>• A patient receiving a bilateral adrenalectomy as the third (or further) line of treatment was included in the study, but his/her follow-up was stopped at the time of the adrenal surgery considering it as a "persistent" Cushing's Disease at last available follow-up. Further analyses regarding the risk of Nelson's syndrome were not carried out. |
| **Grading** |
| • In case of Cushing's Disease with negative magnetic resonance imaging at baseline, even if not biochemically ascertained, we assumed the absence of pituitary deficits due to the supposedly very small adenoma.<br>• For non-functioning pituitary adenoma, the "null cell" histotype was addressed only in case of ascertained absence of staining for all pituitary hormones and at least 3 transcription factors.<br>• In case of prolactinomas, the presence of central hypogonadism was addressed only if the pituitary deficit persisted upon biochemical control amelioration.<br>• Headache was considered a mass effect symptom in case of suggestive clinical features and/or in case of resolution or amelioration upon tumor volume reduction. |
| **Statistical analysis** |
| • In case of first line surgery, Kaplan Meier curves and cox regression analyses for relapses and for the need of further curative treatments were started 1 year after surgery (i.e., at the time of surgery outcome evaluation). As for patients presenting ascertained persistence in the postoperatory and undergoing further curative treatments within 1 year from surgery, they were considered as receiving the treatment 12 months after surgery for the purpose of statistical analysis.<br>• Dichotomization of the age parameter was based on the median age of the group considered.<br>• When analysing biochemical control at the last available follow-up for medically treated patients, we considered:<br>  ○ For persistent disease at last follow-up: the hormonal values at the last visit. |

- For patients reaching disease remission (with effective curative second line approaches or following medical treatment withdrawal): the hormonal values prior to the second line approach or to drug discontinuation.

***Supplementary Table 2.*** *Predictors of 1 year outcome with logistic regression detailed based first-line treatment: A) surgical outcome (disease remission), B) biochemical control on medical treatment. * As compared to grade 1. OR: odds ratio; CI: confidence interval.*

| ***A) 1-year surgical outcome (disease remission)*** | | | |
|---|---|---|---|
| ***Feature*** | ***OR*** | ***95%CI*** | ***p*** |
| *Grade 2** | *0.90* | *0.37 – 2.22* | *0.82* |
| *Grade 3** | *0.48* | *0.18 – 1.32* | *0.14* |
| *Age* | *n.a.* | *n.a.* | *0.11* |
| *Male* | *0.48* | *0.28 – 0.81* | ***0.01*** |
| ***B) 1-year hormonal control on primary medical treatment*** | | | |
| ***Feature*** | ***OR*** | ***95%CI*** | ***p*** |
| *Grade 2** | *0.52* | *0.17 – 1.55* | *0.25* |
| *Grade 3** | *0.32* | *0.07 – 1.55* | *0.15* |
| *Age* | *n.a.* | *n.a.* | *0.86* |
| *Male* | *2.16* | *0.82 – 5.98* | *0.12* |

***Supplementary Table 3*** *Single items of the grade predicting relapse (baseline grade) or need for further curative treatments (postoperative grade) analysed via cox regression in the whole cohort. * Genetic syndrome was not included due to the limited data available. ** Preoperative secretory status was analysed with a dedicated log rank for secreting pituitary adenomas. (Supplementary Figure 6). *** Except prolactinomas as no case presented successful surgery in our cohort. **** All persisting cases were defined based on uncontrolled hormonal secretion after surgical failure for hypersecreting adenomas, thus this item was not analysed. OR: odds ratio; CI: confidence interval, CD: Cushing's Disease.*

| ***Relapse*, ****** | | | | | |
|---|---|---|---|---|---|
| ***Item*** | ***Value*** | ***OR*** | ***95%CI*** | ***p*** | ***Number*** |
| ***Hypopituitarism*** | *Absent* | *Reference* | | *0.92* | *85* |
| | *Present* | *0.93* | *0.22 – 3.94* | | *8* |
| ***Adenoma size*** | *Microadenoma* | *Reference* | | *0.08* | *55* |
| | *Macroadenoma* | *2.70* | *0.89 – 8.33* | | *38* |
| ***Mass effect*** | *Absent* | *Reference* | | *0.54* | *88* |
| | *Present* | *2.09* | *0.29 – 21.67* | | *5* |
| ***Invasion*** | *Absent* | *Reference* | | *0.59* | *91* |
| | *Present* | *1.88* | *0.19 – 18.60* | | *2* |
| ***Phenotype*** | *Others**** | *Reference* | | ***<0.01*** | *61* |
| | *CD* | *12.5* | *2.22 – 50.0* | | *32* |
| ***Need for further treatments*, ******** | | | | | |
| ***Item*** | ***Value*** | ***OR*** | ***95%CI*** | ***p*** | ***Number*** |
| ***Hypopituitarism*** | *Absent* | *Reference* | | *0.57* | *57* |

| | | | | | |
|---|---|---|---|---|---|
| | *Present* | *1.25* | *0.58 – 2.66* | | *36* |
| ***Adenoma size*** | *Macroadenoma* | *Reference* | | *0.10* | *48* |
| | *Microadenoma* | *0.52* | *0.24 – 1.13* | | *45* |
| ***Mass effect*** | *Absent* | *Reference* | | *0.05* | *81* |
| | *Present* | *2.28* | *1.00 – 5.17.* | | *12* |
| ***Invasion*** | *Absent* | *Reference* | | *0.84* | *64* |
| | *Present* | *0.93* | *0.47 – 1.83* | | *29* |
| ***Residual tumor*** | *Absent* | *Reference* | | *0.11* | *15* |
| | *Present* | *2.11* | *0.85 – 5.22* | | *78* |
| ***Aggressive histology*** | *Absent* | *Reference* | | *0.61* | *83* |
| | *Present* | *1.25* | *0.54 – 2.85* | | *10* |
| ***Phenotype*** | *Others* | *Reference* | | ***<0.01*** | *66* |
| | *CD* | *7.69* | *3.33 – 16.67* | | *27* |

***Supplementary Table 4.*** *Predictors of 1-year surgical outcome and 1-year biochemical control on primary medical treatment analysed with logistic regression, detailed based on the type of secreting pituitary adenoma: * Compared to grade 2. ** Compared to grade 1. CD: Cushing's Disease; OR: odds ratio; CI: confidence interval; n.a.: not available.*

| ***1-year surgical outcome (disease remission)*** | | | | | | |
|---|---|---|---|---|---|---|
| | ***CD*** | | | ***Acromegaly*** | | |
| | ***OR*** | ***95%CI*** | ***p*** | ***OR*** | ***95%CI*** | ***p*** |
| *Grade 3* | *1.05** | *0.39 – 2.95* | *0.94* | *0.21** | *0.05 – 0.83* | ***0.04*** |
| *Age* | *n.a.* | *n.a.* | *0.72* | *n.a.* | *n.a.* | *0.32* |
| *Males* | *0.46* | *0.17 – 1.20* | *0.11* | *3.09* | *0.87 – 12.5* | *0.09* |
| ***1-year hormonal control on primary medical treatment*** | | | | | | |
| | ***Acromegaly*** | | | ***Prolactinoma*** | | |
| | ***OR*** | ***95%CI*** | ***p*** | ***OR*** | ***95%CI*** | ***p*** |
| *Grade 2* | */* | */* | */* | *1.02*** | *0.18 – 7.13* | *0.98* |
| *Grade 3* | *2.71** | *0.41 – 25.46* | *0.33* | *0.23*** | *0.02 – 3.33* | *0.27* |
| *Age* | *n.a.* | *n.a.* | *0.77* | *n.a.* | *n.a.* | *0.46* |
| *Males* | *0.42* | *0.07 – 2.12* | *0.31* | *2.3* | *0.31 – 18.4* | *0.41* |

***Supplementary Table 5.*** *Single items of the grade predicting relapse (baseline grade) or need for further curative treatments (postoperative grade) analysed via cox regression in the Cushing's Disease cohort. * Genetic syndrome was not included due to the limited data available. ** Preoperative secretory status was analysed with a dedicated log rank (see main text) as no eucortisolemic patient presented a recurrence. *** Hypopituitarism and mass effect symptoms were not included in the as no patient presented them 1 year after the surgery. OR: odds ratio; CI: confidence interval.*

| ***Relapse*, **** | | | | | |
|---|---|---|---|---|---|
| ***Item*** | ***Value*** | ***OR*** | ***95%CI*** | ***p*** | ***Number*** |
| ***Hypopituitarism*** | *Absent* | *Reference* | | *0.34* | *58* |
| | *Present* | *2.66* | *0.36 – 19.66* | | *3* |
| ***Adenoma size*** | *Microadenoma* | *Reference* | | *0.85* | *52* |
| | *Macroadenoma* | *1.19* | *0.20 – 7.10* | | *9* |
| ***Mass effect*** | *Absent* | *Reference* | | *0.07* | *60* |
| | *Present* | *12.17* | *0.79 – 187.82* | | *1* |
| ***Invasion*** | *Absent* | *Reference* | | *0.11* | *60* |
| | *Present* | *9.10* | *0.61 – 134.90* | | *1* |
| ***Preoperative secretory status*** | *Controlled* | *n.a.* | | ***0.04*** | *8* |
| | *Uncontrolled* | | | | *59* |

| *Need for further treatments*, **** | | | | | |
|---|---|---|---|---|---|
| ***Item*** | ***Value*** | ***OR*** | ***95%CI*** | ***p*** | ***Number*** |
| ***Hormonal status*** | *Controlled* | *Reference* | | *0.30* | *5* |
| | *Uncontrolled* | *2.01* | *0.59 – 6.89* | | *23* |
| ***Adenoma size*** | *Macroadenoma* | *Reference* | | *0.50* | *4* |
| | *Microadenoma* | *1.84* | *0.37 – 9.10* | | *24* |
| ***Invasion*** | *Absent* | *Reference* | | *0.30* | *24* |
| | *Present* | *2.13* | *0.44 – 10.24* | | *4* |
| ***Residual tumor*** | *Absent* | *Reference* | | *0.10* | *12* |
| | *Present* | *2.25* | *0.86 – 5.89* | | *16* |
| ***Aggressive histology*** | *Absent* | *Reference* | | *0.90* | *4* |
| | *Present* | *1.08* | *0.90 – 3.86* | | *24* |

***Supplementary Table 6.*** *Single items of the grade predicting relapse (baseline grade) or need for further curative treatments (postoperative grade) analysed via cox regression in the acromegaly cohort. * Genetic syndrome was not included due to the limited data available. ** No cured patient presented cavernous sinus invasion or mass effect symptoms at baseline, and no uncured patient presented an aggressive histology, so these items were not included in the analysis. *** No hypopituitary patient presented a relapse and no patient without a visible residue received further curative treatments, so a dedicated log rank was performed indicating non-significant differences. OR: odds ratio; CI: confidence interval; n.a.: not available.*

| ***Relapse*, ***** | | | | | |
|---|---|---|---|---|---|
| ***Item*** | ***Value*** | ***OR*** | ***95%CI*** | ***p*** | ***Number*** |
| ***Hypopituitarism ****** | *Absent* | *n.a.* | | *0.49* | *16* |
| | *Present* | | | | *3* |
| ***Adenoma size*** | *Macroadenoma* | *Reference* | | *0.10* | *15* |
| | *Microadenoma* | *9.38* | *0.58 – 151.3* | | *4* |
| ***Need for further treatments*, **** | | | | | |
| ***Item*** | ***Value*** | ***OR*** | ***95%CI*** | ***p*** | ***Number*** |
| ***Hormonal status*** | *Uncontrolled* | *Reference* | | *0.90* | *25* |
| | *Controlled* | *1.13* | *0.13 – 10.0* | | *2* |
| ***Adenoma size*** | *Microadenoma* | *Reference* | | *0.37* | *14* |
| | *Macroadenoma* | *1.89* | *0.47 – 7.69* | | *13* |

| | | | | | |
|---|---|---|---|---|---|
| ***Invasion*** | *Present* | *Reference* | | *0.58* | *8* |
| | *Absent* | *1.56* | *0.33 – 7.14* | | *19* |
| ***Residual tumor****** | *Absent* | *n.a.* | | *0.18* | *3* |
| | *Present* | | | | *24* |
| ***Hypopituitarism*** | *Absent* | *Reference* | | ***0.01*** | *23* |
| | *Present* | *11.37* | *1.62 – 79.91* | | *4* |

***Supplementary Table 7.*** *Single items of the postoperative grade predicting need for further curative treatments analysed via cox regression in the prolactinoma cohort. * High-risk histopathology and mass effect symptoms were not included as no patient presented them one year after the surgery; few patients were evaluated for the presence of genetic syndromes (only 3 patients, with one presenting an AIP mutation), therefore this item was also excluded from the analysis. ** As all further treatments in the macroadenoma group were performed earlier than those of the microadenoma group, Cox's hazard ratio resulted in infinite value preventing a correct analysis; therefore, a dedicated log-rank test was conducted pointing towards a non-significant result (p=0,63). OR: odds ratio; CI: confidence interval.*

| ***Need for further treatments*, ** ** | | | | | |
|---|---|---|---|---|---|
| ***Item*** | ***Value*** | ***OR*** | ***95%CI*** | ***p*** | ***Number*** |
| ***Hormonal status*** | *Controlled* | *Reference* | | *1.00* | *3* |
| | *Uncontrolled* | *1.05* | *0.10 – 10.83* | | *13* |
| ***Invasion*** | *Absent* | *Reference* | | *0.80* | *9* |
| | *Present* | *1.40* | *0.17 – 11.26* | | *7* |
| ***Residual tumor*** | *Present* | *Reference* | | *1.00* | *2* |
| | *Absent* | *1.33* | *0.10 – 16.67* | | *14* |
| ***Hypopituitarism*** | *Absent* | *Reference* | | *0.70* | *12* |
| | *Present* | *1.50* | *0.20 – 11.05* | | *4* |

***Supplementary Table 8.*** *Single items of the postoperative grade predicting need for further curative treatments analysed via cox regression in non-functioning pituitary adenomas. * Only one patient underwent genetic testing resulting thus this item was not included. ** No patient presented a microadenoma therefore we confronted giant and non-giant macroadenomas. OR: odds ratio; CI: confidence interval.*

| ***Need for further treatments**** | | | | | |
|---|---|---|---|---|---|
| ***Item*** | ***Value*** | ***OR*** | ***95%CI*** | ***p*** | ***Number*** |
| ***Hypopituitarism*** | *Absent* | *Reference* | | *0.20* | *9* |
| | *Present* | *0.44* | *0.13 – 1.54* | | *23* |
| ***Adenoma size*** ** | *Giant* | *Reference* | | *0.13* | *1* |
| | *Non-giant* | *7.56* | *0.54 – 105.41* | | *31* |
| ***Mass effect*** | *Absent* | *Reference* | | *0.01* | *21* |
| | *Present* | *3.93* | *1.38 – 11.16* | | *11* |
| ***Invasion*** | *Absent* | *Reference* | | *0.69* | *16* |
| | *Present* | *0.82* | *0.31 – 2.17* | | *16* |
| ***Aggressive histology*** | *Present* | *Reference* | | *0.32* | *5* |
| | *Absent* | *0.50* | *0.13 – 1.92* | | *27* |

***Supplementary Table 9.*** *Curative interventions in Cushing's Disease compared to acromegaly and prolactinomas. * Pituitary surgery or radiation as compared to primary medical treatment*

| | *Curative intervention ab initio** | *Additional curative treatments in case of postoperative persistence* | *Second-tier approaches following medical treatment failure* |
|---|---|---|---|
| ***Cushing's Disease*** | *113/120 (93%)* | *32/38 (84%)* | *4/7 (57%)* |
| ***Acromegaly and prolactinomas*** | *65/189 (34%)* | *17/44 (39%)* | *6/124 (5%)* |
| ***p*** | ***<0.01*** | ***<0.01*** | ***<0.01*** |