Chronic Postsurgical Pain After Minimally Invasive Adrenalectomy: Prevalence and Impact on Quality of Life

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Abstract

Background.

Minimally invasive adrenalectomy is the standard of care for small adrenal tumours. Both the transperitoneal lateral approach and posterior retroperitoneal approach are widely used and have been proven to be safe and effective. However, the prevalence of chronic postsurgical pain has not been specifically investigated in previous studies. The primary goal of this study was to identify the prevalence of chronic postsurgical pain after minimally invasive adrenalectomy.

Methods.

A cross-sectional study was performed among all consecutive patients who had undergone minimally invasive adrenalectomy in a single university medical centre. The primary outcome was the prevalence of chronic postsurgical pain. Secondary outcomes were the prevalence of localized hypoesthesia, risk factors for the development of chronic postsurgical pain, and the Health-Related Quality of Life. Three questionnaires were used to measure the prevalence and severity of chronic postsurgical pain, hypoesthesia, and Health-Related Quality of Life. Logistic regression analysis was performed to determine risk factors for development of chronic postsurgical pain.

Results.

Six hundred two patients underwent minimally invasive adrenalectomy between January 2007 and September 2019, of whom 328 signed informed consent. The prevalence of chronic postsurgical pain was 14.9%. Young age was a significant predictor for developing chronic postsurgical pain. The prevalence of localized hypoesthesia was 15.2%. In patients with chronic postsurgical pain, Health-Related Quality of Life was significantly lower, compared to patients without pain.

Conclusions.

The prevalence of chronic postsurgical pain following minimally invasive adrenalectomy is considerable. Furthermore, the presence of chronic postsurgical pain was correlated with a significant and clinically relevant lower Health-Related Quality of Life. These findings should be included in the preoperative counselling of the patient. In the absence of evidence for effective treatment in established chronic pain, prevention should be the key strategy and topic of future research.

Background

Since the introduction in 1992, minimally invasive adrenalectomy (MIA) has become the standard of care for the management of small (≤7 cm) benign adrenal tumours and, in selected cases, for the treatment

of small (≤6 cm) malignant tumours.[1] The transperitoneal lateral approach (TLA) and the posterior retroperitoneal approach (PRA) have both been proven to be safe and effective when compared with open adrenalectomy, with low morbidity and complication rates, decreased blood loss, less postoperative pain, shorter hospital stay, and improved cosmetic effects.[2,3] Nevertheless, patients regularly report chronic postsurgical pain (CPSP). CPSP is defined as chronic pain that develops or increases in intensity after a surgical procedure or tissue injury and persists beyond the healing process, i.e. at least 3 months after surgery.[4] Since MIA is frequently performed worldwide, it is important to report these functional outcomes, because CPSP can have significant impact on quality of life and health care demand.[5] Predisposing factors described in literature for development of CPSP are the presence of pre-existing pain, early postoperative pain, psychological factors, the surgical procedure itself and patient characteristics, such as age and sex.[6,7]

The primary outcome of this study was the prevalence of CPSP. Secondary outcomes were the prevalence of hypoesthesia, risk factors for CPSP and the impact of CPSP on Health-Related Quality of Life (HRQoL).

Methods

Study design and patient population

All adult patients who underwent MIA in our hospital were included in a cross-sectional study. PRA was introduced in our hospital in 2011. Patients with (presumably) benign tumours or pheochromocytomas ≤7 cm and a body mass index (BMI) <35 kg/m^2 were eligible for PRA. In all other patients TLA was indicated. Two surgeons performed the procedures, both with more than 15 years of laparoscopic experience. Living patients were approached by telephone, subsequently written information was sent after which informed consent was obtained. All patients were asked to complete three questionnaires at the time of study. The study was approved by the research ethics committee of the Radboud University Nijmegen Medical Centre (2019-5500).

Measures

The primary outcome of this study was the prevalence of CPSP. The presence of CPSP was scored when patients replied “yes” to the question if they currently had pain which could be related back to their adrenalectomy. Secondary outcomes were the prevalence of localized hypoesthesia, possible risk factors for development of CPSP and the impact on HRQoL. To investigate this, patients were asked to complete three questionnaires: the Dutch version of the McGill Pain Questionnaire (MPQ),[8] a questionnaire concerning hypoesthesia and the RAND Short Form-36 Health Status Inventory (RAND SF-36) regarding their HRQoL.[9] The MPQ is a validated multidimensional pain questionnaire designed to measure the quality and intensity of chronic pain.[10] The main section of this questionnaire includes a list of 63 words, divided into three major classes: the sensory class, the affective class and the evaluative class. Pain intensity is measured quantitatively by the Number of Words Chosen (NWC), and qualitatively by the Pain

Rating Index (PRI). The questionnaire includes a Visual Analogue Scale (VAS), to determine pain severity at the time of analysis. Lastly, the MPQ includes a section for localization, duration, and course of pain.

For hypoesthesia, we used the MPQ format, to determine its localization, duration, and course (Appendix 1).

The RAND SF-36 is a validated questionnaire on HRQoL, separated into eight multi-item scales; physical functioning, role limitations due to physical health problems, role limitations due to emotional problems, general mental health, social functioning, energy/fatigue, bodily pain, and general health perceptions.[9]

Perioperative patient data were collected from a prospectively maintained database and included: medical history, age at the time of surgery, BMI, ASA-score, medication and indication for surgery, side of adrenalectomy, duration of surgery, operating technique, and conversion to open surgery.

Statistical analysis

The data were assessed for normality using the Shapiro-Wilk Test. To compare normally distributed continuous variables Student *t*-test was used. Chi-square and ANOVA were used for categorical variables. Correlation between variables that were normally distributed was calculated with the Pearson correlation coefficient and with the Spearman rank correlation method for non-normally distributed variables.

Binary logistic regression was performed to identify possible predictive factors for CPSP. Variables with a significance level of $p < .05$ in the univariate model were included in the multivariate model. Statistical significance was defined as a *p*-value <.05. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS IBM Statistics 24; Armonk, NY).

Results

Patient enrolment

A total of 602 patients underwent MIA between February 2007 and September 2019. Five hundred forty-four patients were approached by phone between October 2019 and January 2020. Fifty-eight patients were lost to follow-up because of death or missing contact information. We received response from 358 (65.8%) patients, of which 328 patients signed informed consent. Of these patients, 172 underwent TLA and 156 PRA. Patient enrolment is depicted in Figure 1.

Patient characteristics

The mean age of patients at time of adrenalectomy was 54 years and 52% was male. The mean follow-up time was 4.6 years. The most common indications for surgery were primary aldosteronism (PA) (50%), pheochromocytoma (23%), and Cushing's syndrome (13%), consecutively. Forty-nine patients preoperatively reported pain, and 52 patients preoperatively used pain medication. Patient characteristics are presented in Table 1.

Prevalence of chronic postsurgical pain

Forty-nine out of 328 patients (14.9%) reported the presence of CPSP, of which 34 received TLA (19.8%) and 15 PRA (9.6%). Sixteen patients reported both CPSP and hypoesthesia.

Table 1
Patient characteristics

	All patients **n = 328**	**Patients with CPSP** **n = 49**	**Patients with hypoesthesia n = 52**
Age during surgery (y)	54.1 ± 12.3	50.6 ± 11.9	50.5 ± 9.5
Sex (male)	172 (52.4%)	20 (40.8%)	22 (42.3%)
BMI (kg m^{-2})	27.8 ± 4.7	29.1 ± 5.9	27.3 ± 5.5
ASA-score, n (%)	13 (4.0)	1 (2.0)	3 (5.8)
ASA 1	242 (73.8)	31 (63.3)	33 (63.5)
ASA 2	73 (22.3)	17 (34.7)	16 (30.8)
ASA 3			
Diabetes Mellitus, n (%)	51 (15.5)	6 (12.2)	10 (19.2)
Preoperative pain, n (%)	49 (14.9)	12 (24.5)	11 (21.2)
Preoperative pain medication, n (%)	276 (84,1)	38 (77.6)	42 (80.8)
None	12 (3.7)	4 (8.2)	3 (5.8)
Paracetamol	8 (2.4)	3 (6.1)	2 (3.8)
NSAID	16 (4.9)	3 (6.1)	4 (7.7)
Opioid	16 (4.9)	1 (2)	1 (1.9)
Other			
History of neurological disease, n (%)	89 (27.1)	13 (26.5)	18 (34.6)
History of abdominal surgery, n (%)	101 (30.8)	19 (38.8)	23 (44.2)
Indication of adrenalectomy, n (%)	164 (50)	18 (36.7)	23 (44.2)
Primary aldosteronism	75 (23)	16 (32.7)	22 (42.3)
Pheochromocytoma	43 (13)	8 (16.3)	3 (5.8)
Cushing's syndrome	46 (14)	7 (14.3)	4 (7.7)
Other			

Categorical variables are presented as n (%); continuous variables are presented as mean ± SD. *BMI body mass index; NSAID non-steroidal anti-inflammatory drug; y years*

	All patients n = 328	Patients with CPSP n = 49	Patients with hypoesthesia n = 52
Side of adrenalectomy (left / right / both), n (%)	169 (51.5) / 139 (42.4) / 20 (6.1)	30 (61.2) / 16 (32.7) / 3 (6.1)	24 (46.2) / 28 (53.8) / 0
Type of procedure, n (%)	172 (52.4)	34 (19.8)	19 (11.0)
Transperitoneal	156 (47.6)	15 (9.6)	33 (21.2)
Retroperitoneoscopic			
Duration of surgery (min)	93.7 ± 44.3	99.0 ± 44.1	92.2 ± 45.5
Blood loss (mL)	47.7 ± 134.1	62.0 ± 164.7	80.5 ± 23.9
Tumor diameter (mm)	2.8 ± 2.3	3.5 ± 2.6	3.3 ± 2.9
Duration of admission (days)	3.8 ± 1.7	4.3 ± 2.1	4.1 ± 2.2
Conversion to transperitoneal /	16 (4.9) / 2 (0.6)	1 (2) / 1 (2)	5 (9.6) / 1 (1.9)
open procedure, n (%)			
Follow-up time since surgery, n (%)	60 (18.3)	11 (22.4)	11 (21.2)
<2 y	78 (23.8)	19 (38.8)	17 (32.7)
2-3 y	73 (22.3)	9 (18.4)	10 (19.2)
4-5 y	61 (18.6)	4 (8.2)	9 (17.3)
6-7 y	28 (8.5)	2 (4.1)	0
8-9 y	25 (7.6)	4 (8.2)	5 (9.6)
10-11 y	3 (0.9)	0	0
>11 y			

Categorical variables are presented as n (%); continuous variables are presented as mean ± SD. *BMI body mass index; NSAID non-steroidal anti-inflammatory drug; y years*

McGill Pain Questionnaire

Pain onset was slow in 28 patients (57.1%), and most patients (44.9%) experienced continuous pain with fluctuating severity. The mean general pain intensity measured by VAS was 34 (± 25). The reported localizations were the ipsilateral flank (67.3%), the contralateral flank (16.3%) and other more diverse localizations such as groin, shoulders or arms (16.3%).

The mean Number of Words Chosen (NWC) was 7.9 of 20 words. Sensory descriptors were chosen more frequently than affective or evaluative terms. The most frequently selected words were nagging (n = 21; 42.9%) and stabbing (n = 20; 40.8%) in the sensory class; tiring (n = 25; 51%) in the affective class; and annoying (n = 26; 53.1%) in the evaluative class. The mean pain intensity measured by the total score of the PRI (PRI-Total; PRI-T) was 40.8 (SD 26.7; maximum score 63); shown in Table 2. Twenty patients (40.8%) were using analgesics for the reported pain, mostly acetaminophen or nonsteroidal anti-inflammatory drugs (34.7%); four patients reported the use of opioids (8.2%).

Risk factors of CPSP

When looking at the univariate binary logistic regression, age, BMI, ASA-score, preexisting pain, TLA, and primary aldosteronism as indication for surgery were significant individual predictors of CPSP (Table 3). When performing multivariate binary logistic regression with these individual predictors, only young age remained a significant predictor for the development of CPSP.

Prevalence of hypoesthesia

Fifty-two patients (15.8%) reported hypoesthesia, of which 19 patients received TLA (11.0%) and 33 PRA (21.2%). Onset of hypoesthesia was acute in 28 (53.8%) patients and slow in 18 patients (34.6%). Twenty-one patients (40.4%) experienced a continuous feeling of hypoesthesia. The reported localizations were the ipsilateral flank (78.8%), leg or arms (11.5%) or unknown (9.6%). Further characteristics are presented in Table 2.

Table 2
Characteristics CPSP and hypoesthesia

Questionnaire components	**Patients with CPSP**	**Patients with hypoesthesia**
	n = 49	**n = 52**
Start of pain, n (%)	18 (36.7)	28 (53.8)
Acute	28 (57.1)	18 (34.6)
Slow	3 (6.1)	6 (11.5)
Unknown		
Both hypoesthesia and CPSP present, n (%)	16 (32.7%)	16 (30.8%)
Course of symptom experience, n (%)	14 (28.6)	-
Attacks, with pain-free moments	22 (44.9)	-
Continuous, differing in severity	11 (22.4)	21 (40.4)
Continuous, stable severity	2 (4.1)	31 (59.6)
Unknown		
VAS, general (0-100)	33.9 ± 24.5	-
VAS, least pain (0-100)	13.3 ± 18.0	-
VAS, worst pain (0-100)	56.7 ± 23.0	-
Localization of pain, n (%)	33 (67.3)	41 (78.8)
Ipsilateral flank	8 (16.3)	-
Contralateral flank	8 (16.3)	11 (21.2)
Other / unknown		
Referred pain or hypoesthesia *resp.*, n (%)	20 (40.8%)	7 (13.5%)
Tingling present, n (%)	-	23 (44.2%)

Categorical variables are presented as n (%); continuous variables are presented as mean ± SD. CPSP chronic postsurgical pain; NWC-S Number of Words Chosen of the sensory scale; NWC-A, NWC of the affective scale; NWC-E, NWC of the evaluative scale; NWC-T, total NWC; PRI-S, Pain-Rating Index of the sensory scale; PRI-A, PRI of the affective scale; PRI-E, PRI of the evaluative scale; PRI-T, total PRI; VAS visual analogue scale

Questionnaire components	Patients with CPSP n = 49	Patients with hypoesthesia n = 52
Pain intensity	3.9 ± 2.8	-
NWC-S (0 to 12 words)	1.8 ± 1.7	-
NWC-A (0 to 5 words)	2.1 ± 1.1	-
NWC-E (0 to 3 words)	7.9 ± 5.0	-
NWC-T (0 to 20 words)	21.9 ± 15.6	-
PRI-S (0 to 36 words)	9.1 ± 8.7	-
PRI-A (0 to 15 words)	9.9 ± 6.2	-
PRI-E (0 to 12 words)	40.8 ± 26.7	-
PRI-T (0 to 63 words)		
Hypoesthesia feels annoying, n (%)	-	33 (63.5)
No	-	9 (17.3)
Little	-	6 (11.5)
Fairly	-	3 (5.8)
Very	-	1 (1.9)
Unknown		

Categorical variables are presented as n (%); continuous variables are presented as mean ± SD. CPSP chronic postsurgical pain; NWC-S Number of Words Chosen of the sensory scale; NWC-A, NWC of the affective scale; NWC-E, NWC of the evaluative scale; NWC-T, total NWC; PRI-S, Pain-Rating Index of the sensory scale; PRI-A, PRI of the affective scale; PRI-E, PRI of the evaluative scale; PRI-T, total PRI; VAS visual analogue scale

Table 3
CPSP following MIA

Parameters	Univariate analysis OR (95% CI)	*p*-value	Multivariate analysis OR (95% CI)	*p*-value
Age at time of surgery	**0.973 (0.950 – 0.998)**	**.033**	**0.954 (0.928 – 0.981)**	**.001**
Gender (male)	0.576 (0.311 – 1.067)	.080	-	-
BMI (kg m^{-2})	**1.069 (1.006 – 1.137)**	**.031**	1.055 (0.989 – 1.125)	.104
ASA-score	**2.031 (1.099 – 3.751)**	**.024**	1.821 (0.910 – 3.641)	.090
Diabetes	0.726 (0.292 – 1.806)	.490		
Preoperative pain	**2.121 (1.015 – 4.434**	**.046**	1.799 (0.776 – 4.173)	.171
Preoperative neurological disease	0.965 (0.485 – 1.917)	.918		
History of abdominal surgery	1.522 (0.811 – 2.856)	.191		
Side of adrenalectomy (left)	1.659 (0.863 – 3.189)	.129	-	**-**
Type of procedure (retroperitoneal)	**0.432 (0.225 – 0.828)**	**.011**	1.924 (0.965 – 3.835)	.063
Indication of adrenalectomy	**0.529 (0.283 – 0.990)**	**.046**	0.584 (0.295 – 1.155)	.122
Primary aldosteronism	1.808 (0.932 – 3.507)	.080		
Pheochromocytoma	1.360 (0.589 – 3.139)	.471		
Cushing syndrome	1.026 (0.430 – 2.445)	.954		
Other				
Duration of surgery (d)	1.003 (0.997 – 1.010)	.363	-	**-**

Significant p-values are in bold. d days; MIA minimally invasive adrenalectomy; OR odds ratio; PA primary aldosteronism; y years; 95% CI 95% confidence interval

Health related quality of life

The HRQoL of patients with CPSP after MIA was significantly lower in all subscales compared with patients without pain (Table 4). Major differences were seen in role limitations due to physical health problems between patients without CPSP (mean 76.1 ± SD 38.7) and patients with CPSP (mean 40.6 ± SD 43.3) ($p < .001$) and on the scale of bodily pain between patients without pain (mean 86.1 ± SD 21.9) and patients with CPSP (mean 59.1 ± SD 20.1) ($p < .001$). When analyzing pain intensity, a higher mean VAS-score was significantly correlated with a lower score on the following subscales of the RAND-SF36

questionnaire: role limitations due to physical health problems (R^2 = 0.13, p = 0.012), role limitations due to emotional problems (R^2 = 0.11, p = 0.024), general mental health (R^2 = 0.18, p = 0.003) and bodily pain (R^2 = 0.30, p = 0.000). The presence of hypoesthesia did not have a negative influence on the HRQoL in any of the subscales (Table 4).

Table 4
HRQoL after adrenalectomy (RAND SF-36)

RAND SF-36 subscales (%)	**Whole group n = 328**	**Patients with pain n = 49**	**Patients without pain n = 279**	***p*-value**	**Patients with hypoesthesia n = 52**	**Patients without hypoesthesia n = 276**	***p*-value**
Physical functioning	78.3 ± 25.1	59.1 ± 26.2	81.5 ± 23.5	**.000**	72.1 ± 30.9	79.4 ± 23.8	.056
Role limitations due to physical health problems	70.8 ± 41.3	40.6 ± 43.3	76.1 ± 38.7	**.000**	72.1 ± 42.2	70.6 ± 41.2	.813
Role limitations due to emotional problems	83.1 ± 33.7	61.1 ± 43.1	86.9 ± 30.2	**.000**	79.5 ± 36.8	83.6 ± 33.2	.417
Energy/fatigue	61.1 ± 20.8	44.9 ± 19.1	63.8 ± 19.9	**.000**	59.9 ± 20.1	61.4 ± 21.0	.650
General mental health	76.4 ± 17.3	62.5 ± 20.6	78.9 ± 15.5	**.000**	73.8 ± 15.6	77.0 ± 17.7	.235
Social functioning	83.6 ± 23.7	68.1 ± 27.4	86.2 ± 22.0	**.000**	81.1 ± 24.4	84.0 ± 23.6	.430
Bodily pain	82.2 ± 23.6	59.1 ± 20.1	86.1 ± 21.9	**.000**	78.6 ± 26.0	82.8 ± 23.2	.250
General health perceptions	58.5 ± 22.7	44.0 ± 20.2	61.0 ± 22.2	**.000**	56.4 ± 21.7	58.9 ± 23.0	.469

Significant p-values are in bold. Variables are presented as mean ± SD. HRQoL health-related quality of life.

Discussion

Although MIA was proven to be safe and effective for a heterogeneous group of patients with adrenal disorders, the prevalence of CPSP has not been reported widely. In this cohort study the prevalence of CPSP following MIA was 14.9%. The presence of CPSP was correlated with a significantly lower HRQoL.

Acosta et al. found a prevalence of 8% chronic back pain in twelve open and 6% in seventeen laparoscopic bilateral adrenalectomies for hypercortisolism.[11] *Walz et al.* observed an incidence of 8.5% of temporary hypoesthesia and/or relaxation of the abdominal wall after PRA.[12] A study by *Bruintjes et al*. showed a prevalence of CPSP of 5.7% following laparoscopic donor nephrectomy in relatively healthy live kidney donors. They also showed a significantly lower HRQoL in patients with CPSP on all subscales of the RAND-SF36, except role limitation due to emotional problems.[13]

Perioperative nerve injury seems to play an important role in the development of neuropathic pain, but nociceptive and inflammatory processes are also involved.[14] We found sixteen patients (33%) with a combination of CPSP and symptoms of hypoesthesia. This is in accordance with the study by *Johansen et al*., who reported a strong association between sensory abnormalities and persistent pain, increasing with higher pain intensities.[15] These findings may indicate that direct neuronal injury is a potential factor for developing CPSP, since nerve damage can result in central sensitization, which is linked to the development of CPSP.[16] Preventing central sensitization may provide a mechanism-based approach by blocking nociceptive input using regional anesthesia or through direct antihyperalgesic medical therapy, subsequently reducing the chance to develop CPSP.

After multivariable regression analysis young age was a significant predictor of CPSP. This predictor has been described for other surgical procedures than adrenalectomy, such as video-assisted thoracoscopy or thoracotomy,[17] breast cancer surgery,[18] and hysterectomy.[19] The etiology is not well-understood, but may be the result of a reduction in peripheral nerve functioning that occurs with increased age.[20]

When looking at pain severity, patients with a higher VAS-score had significantly lower scores on several domains of the RAND-SF36. This means that the presence of more severe pain results in a significantly lower HRQoL. CPSP can lead to functional limitations and psychological distress in patients. Therefore, identifying the risk factors and applying a preventive strategy may help to decrease the incidence of CPSP and the resulting lower HRQoL. Possible preventive strategies include modification of the surgical technique, adequate pain control throughout the perioperative period, and preoperative psychological intervention focusing on psychosocial and cognitive risk factors.[21]

The main strength of this study is that we specifically investigated the prevalence of CPSP after MIA as a primary outcome, which was not done before. Furthermore, this study includes a large patient number from an expert centre, with a relatively high response rate compared with other small-scale phone or e-mail surveys.[22] This allowed us to perform multivariate logistic regression analyses to identify independent predictors of CPSP.

We acknowledge a few limitations in our study. First, patients with a variety of indications for surgery, disease-related symptoms and differences in comorbidity were compared. This could have an influence on preoperative and postoperative HRQoL between patients and may influence their recovery after surgery, with or without the presence of CPSP. Second, our data could be subject to a certain degree of recall bias, which can cause an overestimation of the true prevalence of CPSP, since patients with pain

are more likely to respond. Third, the prevalence of preoperative pain was 24.5% in patients that subsequently reported CPSP. Although the questionnaire regarding CPSP was specific to only answer “yes” if the pain could be related back to their adrenalectomy, it is possible that patients with pre-existing pain reported “yes” as well. This could have resulted in an overestimation of the true prevalence of CPSP. Finally, no structured preoperative HRQoL data were present in our population.

In conclusion, in this study we have shown a substantial prevalence of CPSP following MIA. The presence of CPSP was significantly correlated with a lower HRQoL. When present, CPSP should be identified in a timely manner, since adequate management by pharmacotherapy, appropriate pain interventions, surgery and/or psychological management, can improve the pain and the physical and social functionality of patients. Furthermore, in the absence of evidence for effective treatment in established chronic pain, prevention should be the key strategy. Future trials should focus on etiology and prevention of CPSP after MIA.

List Of Abbreviations

MIA	Minimally invasive adrenalectomy
TLA	Transperitoneal lateral approach
PRA	Posterior retroperitoneal approach
CPSP	Chronic postsurgical pain
HRQoL	Health-Related Quality of Life
BMI	Body mass index
MPQ	McGill Pain Questionnaire
RAND SF-36	RAND Short Form-36 Health Status Inventory
NWC	Number of Words Chosen
PRI	Pain Rating Index
VAS	Visual Analogue Scale

Declarations

Ethics approval and consent to participate

The study was approved by the research ethics committee of the Radboud University Nijmegen Medical Centre (2019-5500), on the basis of the Dutch Code of conduct for health research, the Dutch Code of

conduct for responsible use, the Dutch Personal Data Protection Act and the Medical Treatment Agreement Act. We confirm that all methods were performed in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

By request to the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors read and approved the final manuscript. Conception and design: EvH, AvU, MCW, JFL. Acquisition of data: EvH, AvU, MCW, JFL. Analysis and interpretation of data: EvH, AvU, MCW, JFL, GJS, CK. Drafting of manuscript: EvH, MCW. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: EvH, MCW, JFL. Obtaining funding: no funding applicable. Administrative, technical or material support: EvH, MCW, AvU, JFL. Supervision: MCW, JFL.

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Figures

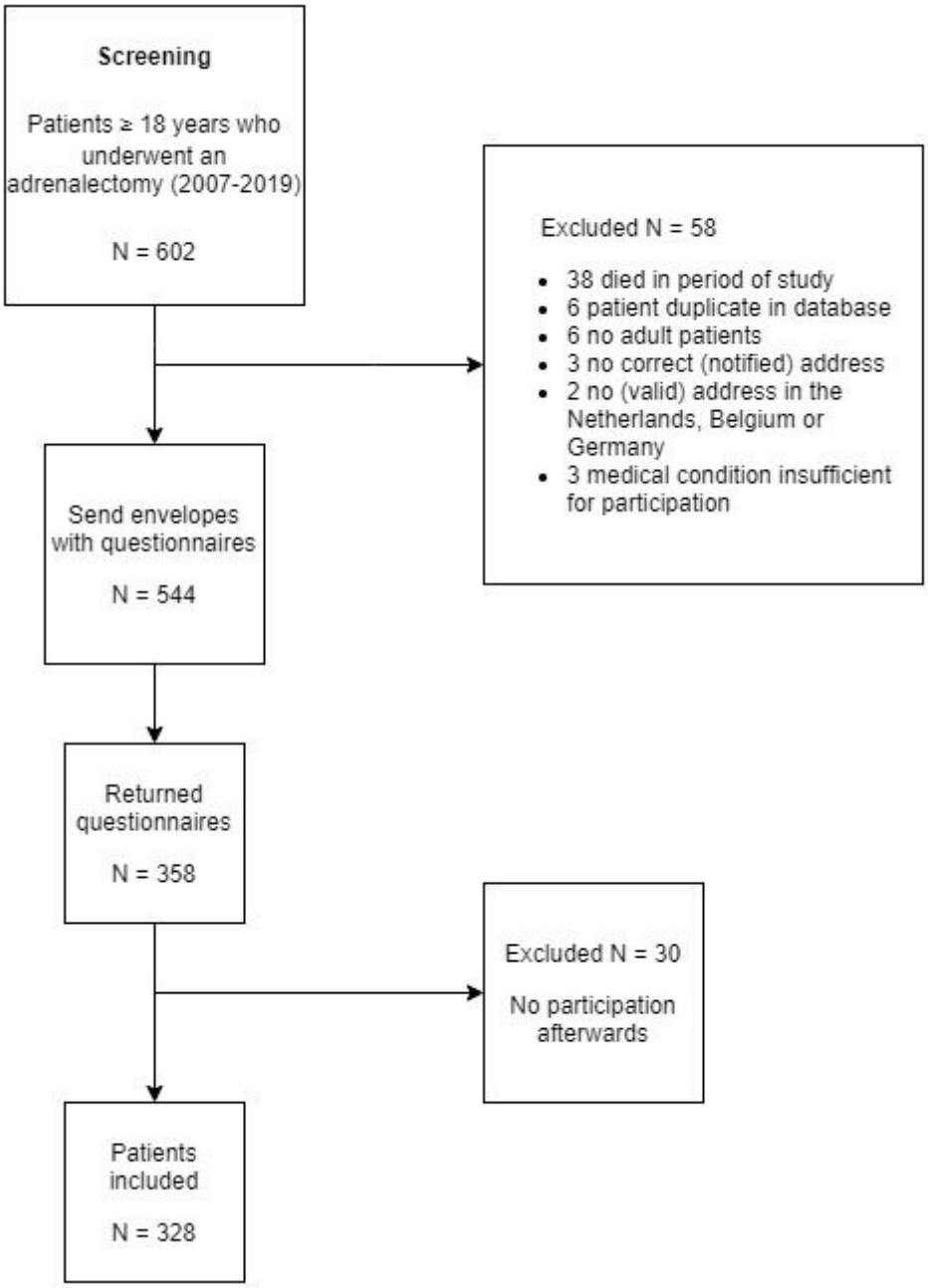

Figure 1

Patient enrolment

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