UNIVERSITÀ
DEGLI STUDI
DI PADOVA

**Università degli Studi di Padova**

**Dipartimento di Medicina - DIMED**

**CORSO DI DOTTORATO DI RICERCA INTERNAZIONALE IN**

**IPERTENSIONE ARTERIOSA E BIOLOGIA VASCOLARE**

**XXIX° CICLO**

# EFFECT OF UNILATERAL ADRENALECTOMY ON THE QUALITY OF LIFE OF PATIENTS WITH LATERALIZED PRIMARY ALDOSTERONISM

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**ABSTRACT**

***Background.*** Previous studies reported that primary aldosteronism (PA) is associated with an increased prevalence of anxiety, depression and subnormal quality of life (QoL) scores that may be improved after surgical treatment.

***Aim of the Study.*** The aim of the study was to assess the impact of surgery on health-related QoL and depression status of patients suffering from PA, comparing the results with a control group of patients undergoing surgery for a non-secreting adrenal tumor.

***Materials and Methods.*** Data on QoL and depression status were prospectively collected, from January 2014 to October 2016, before, early after surgery (at 1 month) and at long term (at least 6 months) in patients with unilateral PA and in a control group of patients with non-secreting adrenal tumor submitted to unilateral transperitoneal laparoscopic adrenalectomy. QoL was assessed using the Short Form 36 (SF-36) Health Survey for Physical (PCS) and Mental Component (MCS); the depression status by a 20-item depression scale (DS) questionnaire.

***Results.*** Twenty-six PA patients and 15 controls were recruited. Biochemical cure of the disease was achieved following surgery in all PA patients; hypertension was cured in 31% of cases and improved in the remaining 69% of cases. No morbidity occurred in both groups. There were no significant differences between PA patients and controls concerning demographics, preoperative PCS, MCS and DS values. In patients with PA, MCS values improved at early (42.72±13.68 vs 51.56±9.03, $p=0.0005$) and long term follow up (42.72±13.68 vs 51.81±7.04, $p<0.0001$); also DS values improved at early (15.92±11.98 vs 8.3±8.8, $p=0.0002$) and long term follow up (15.92±11.98 vs 4.57± 6.11, $p<0.0001$). In PA patients PCS values

significantly improved at long term follow up (51.02±8.04 vs 55.85±5.1, p=0.013). Also in controls an improvement of MCS and DS scores was found at early and long term follow up compared to preoperative values, while no significant differences in PCS were found.

***Conclusions.*** Both PA and non-secreting adrenal tumors affect health-related QoL, worsening MCS and DS scores. Adrenalectomy is effective in curing PA, and improving MCS and DS scores at early and long-term follow-up, in patients with PA and non-secreting adrenal tumors. In PA patient surgery also significantly improves PCS at long term follow up.

**RIASSUNTO**

***Presupposti dello studio.*** Studi precedenti hanno descritto che l'iperaldosteronismo primario (PA) è associato ad un aumento della prevalenza di ansia, depressione e peggioramento della qualità di vita (QoL), con miglioramento significativo dopo il trattamento chirurgico.

***Scopo dello studio.*** Lo scopo dello studio è quello di indagare l'impatto della chirurgia sulla qualità di vita dei pazienti con PA, comparando i risultati con un gruppo di controllo costituito da pazienti sottoposti a surrenectomia per tumori surrenalici non secernenti.

***Materiali e Metodi.*** I dati sulla qualità di vita e lo stato di depressione sono stati raccolti prospetticamente, da Gennaio 2014 a Ottobre 2016, preoperatoriamente, dopo 1 mese e dopo almeno 6 mesi dall'intervento chirurgico di surrenectomia laparoscopica transperitoneale in pazienti con PA lateralizzato e in un gruppo di controllo costituito da pazienti con tumori non-secernenti del surrene. La QoL è stata valutata utilizzando il questionario SF-36, per valutazione della componente

fisica (PCS) e mentale (MCS); lo stato depressivo è stato quantificato utilizzando un questionario di valutazione della depressione (DS) costituito da 20 domande.

***Risultati.*** Sono stati reclutati 26 pazienti con PA e 15 controlli. La cura biochimica della malattia è stata ottenuta in tutti i pazienti con PA; l'ipertensione è stata curata nel 31% dei casi ed è migliorata nel 69% dei casi. Non si sono verificate complicanze chirurgiche in entrambi i gruppi. Non sono state rilevate differenze statisticamente significative tra i pazienti con PA e i controlli per quanto riguarda i dati demografici e i valori preoperatori di PCS, MCS e DS. Nei pazienti con PA, i valori di MCS sono migliorati sia a 1 mese dall'intervento (42.72 ± 13.68 vs 51.56 ± 9.03, p = 0,0005) che a distanza (42,72 ± 13.68 vs 51.81 ± 7.04, p <0,0001). Nei pazienti affetti da PA anche i valori di DS sono migliorati sia a breve (15.92 ± 11.98 vs 8.3 ± 8.8, p = 0,0002) che a lungo termine (15,92 ± 11.98 vs 4.57 ± 6.11, p <0,0001); i valori di PCS sono migliorati significativamente solo a distanza dall'intervento (51.02 ± 8.04 vs 55.85 ± 5.1, p = 0,013). Anche nel gruppo di controllo i valori di MCS e DS sono migliorati sia a breve dopo l'intervento che a distanza; in questi pazienti non sono state rilevate variazioni significative nei valori di PCS dopo l'intervento.

***Conclusioni.*** I pazienti affetti da PA e tumori surrenalici non-secernenti sono caratterizzati da una QoL peggiore rispetto alla popolazione normale. La surrenectomia è efficace nella cura del PA, e nel migliorare i punteggi di MCS e DS sia a 1 mese dall'intervento che a lungo termine, sia nei pazienti con PA che nel gruppo di controllo. Nei pazienti con PA, i valor di PCS migliorano significativamente solo a lungo termine.

# 1.INTRODUCTION

## 1.1 THE ADRENAL GLAND

The adrenal glands were first described in 1552 by the anatomist Bartolomeo Eustachi as ‘‘glandulae renis incumbentes’’ (glands lying on the kidney) (1).

In 1586, Piccolomineus and Baunin named them the suprarenal glands and nearly two-and-a-half centuries later, Cuvier described the anatomical division of each gland into the cortex and medulla.

The adrenal are located in the lateral retroperitoneal area and surrounded by perirenal fascia, in close contact with the superior pole of the kidney (2).

Pararenal fat and perirenal fascia separate the adrenals from the pleural reflection, ribs, and the subcostal, sacrospinalis, and latissimus dorsi muscles (2). Posteriorly, the glands are near the diaphragmatic crus and arcuate ligament; Laterally, the right adrenal resides in front of the $12^{th}$ rib and the left gland is in front of the 11th and $12^{th}$ ribs (2).

The right adrenal gland is triangular or pyramidal in shape, sometimes called the “witch’s hat,” instead the left adrenal gland is semilunar.

Each adrenal gland weighs approximately 3–6 g and measures roughly 5\2.5\0.5 cm (3).

The adrenal gland combines the outer cortex of mesodermal origin, and the central medulla that has a neuroectodermal origin.

The adrenal cortex has a characteristic bright chrome yellow with a granular surface and firm consistency (3,4). The cortex is divided into three zones (4): the *zona glomerulosa,* secretes the mineralocorticoid aldosterone, which regulates salt and water homeostasis; the *zona fasciculate* secretes the glucocorticoid cortisol, which regulates carbohydrate metabolism; the *zona reticularis* secretes sex steroids

(estrogen precursors, progesterone, and androgens). The central medulla is dark red or pearly gray, depending on the blood content, and is rather friable. It secretes catecholamines which modulate the fightor-flight response to stress**.**

## 1.2 PRIMARY ALDOSTERONISM

In 1952, Simpson and Tait isolated aldosterone from the adrenal glands of animals and a year later, its structure was described for the first time (5).

Primary aldosteronism (PA) was first described by Litynski in Poland and Conn in the USA (6,7). It is an adrenal disease which causes sodium and water retention, potassium excretion, with ensuing hypertension and hypokalemia.

Aldosterone is the main mineralocorticoid hormone, produced by the zona glomerulosa of the adrenal cortex and its production is regulated mainly by angiotensin II, resulting from the action of renin secreted by the juxtaglomerular apparatus in the kidney on its substrate (angiotensinogen) made by the liver.

Angiotensin II is the most powerful stimulus for adrenal aldosterone secretion, mediated via angiotensin II type 1 receptor (AT1R) in the adrenal cortex (8). In addition to circulating angiotensin II, local production of angiotensin II occurs in the adrenal gland and contributes to aldosterone release (9). Both adrenocorticotropic hormone (ACTH) and potassium also stimulate aldosterone secretion.

Aldosterone binds to the mineralocorticoid receptor in various tissues, inducing pleiotropic effects. Its main action is in the kidney, where it increases the expression of epithelial sodium channels in the distal tubule, resulting in sodium and water reabsorption and potassium secretion. These renal actions contribute to extracellular fluid volume expansion, increased blood pressure, decreased serum

potassium. The hypokalemia results from aldosterone increasing potassium excretion in urine, feces, sweat, and saliva (10).

Recent guidelines have defined PA as "a group of disorders in which aldosterone production is inappropriately high, relatively autonomous from the renin-angiotensin system, and non-suppressible by sodium loading" (11). The guidelines recommend case detection of PA by using the aldosterone-renin ratio measured under standard conditions, followed by one of the commonly used confirmatory tests (oral sodium loading, saline infusion, fludrocortisone suppression, and captopril challenge) (11), although the accuracy of these tests is debated (12).

PA is the most common cause of endocrine hypertension, and it has been reported in more than 11 % of referred hypertensive patients (13-16).

It is important to search for PA in a systematic way at least in some categories of patients, because of its prevalence, and also because patients with PA have higher cardiovascular morbidity and mortality than age-, BP- and sex-matched patients with essential hypertension (17,18). These categories include patients with Joint National Commission stage 2 (>160-179/100-109 mm Hg), stage 3 (>180/110 mmHg), or drug-resistant hypertension; hypertension and spontaneous or diuretic-induced hypokalemia; hypertension with adrenal incidentaloma; or hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 years). Case detection is also recommended for all hypertensive first-degree relatives of patients with PA (11).

PA may be caused by unilateral or bilateral adrenal involvement: the unilateral form (aldosterone producing adenoma, APA) (**Figure 1A**) is considered surgical curable; for the bilateral adrenal involvement (idiopathic adrenal hyperplasia), which is considered non-surgically curable, the medical treatment is indicated. APA and

idiopathic adrenal hyperplasia were claimed to account for more than 95% of all cases (19). In recent years, several studies have reported novel variants of surgically treatable PA, including diffuse or nodular unilateral adrenal hyperplasia (UAH) (**Figure 1B**). It was previously considered to be very rare (0.1%) (19), but is actually described to involve from 8% to 70% of cases of surgically treated PA (20-24). The normalization of aldosterone is the goal of treatment, because chronical hyperaldosteronism concurs with high blood pressure in causing cardiovascular complications, including, left ventricular hypertrophy, arterial wall stiffening, metabolic syndrome, renal damage, myocardial infarction and atrial fibrillation (25,26).

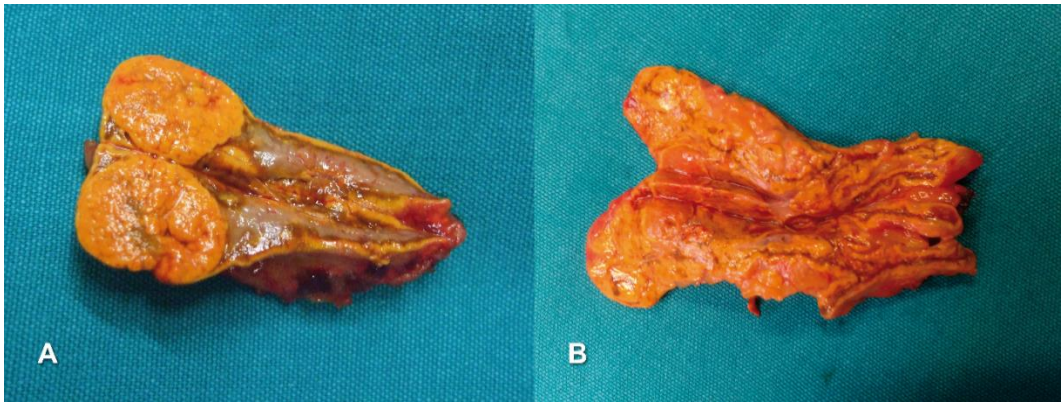


**Figure 1.** Surgical specimens. (A) Aldosterone producing adenoma; (B) micronodular diffuse hyperplasia.

### ***1.2.1 Lateralizing techniques***

Only patients with unilateral adrenal hypersecretion may be cured by unilateral adrenalectomy, thus the distinction between unilateral and bilateral aldosterone hypersecretion is crucial. To this aim adrenal venous sampling (AVS), computerized tomography (CT), magnetic resonance imaging (MRI) and adrenocortical scintigraphy have been used.

AVS was introduced in the late 1960s and became the first test to distinguish unilateral from bilateral primary aldosteronism (27). Adrenocortical scintigraphy, CT and MRI developed later and they are the primary procedures used to differentiate unilateral from bilateral adrenal abnormalities, because they are less invasive than AVS.

**Image-based techniques.** CT is the most widely used imaging test; MRI performs in a similar way (28) (**Figure 2**). Most aldosterone-producing adenomas are less than 20 mm in diameter (29,30). The finding of a small adrenal nodule in patients with PA suggests the presence of an APA; however, it does not exclude the coexistence of a non-secreting adenoma and idiopathic PA (11,31).

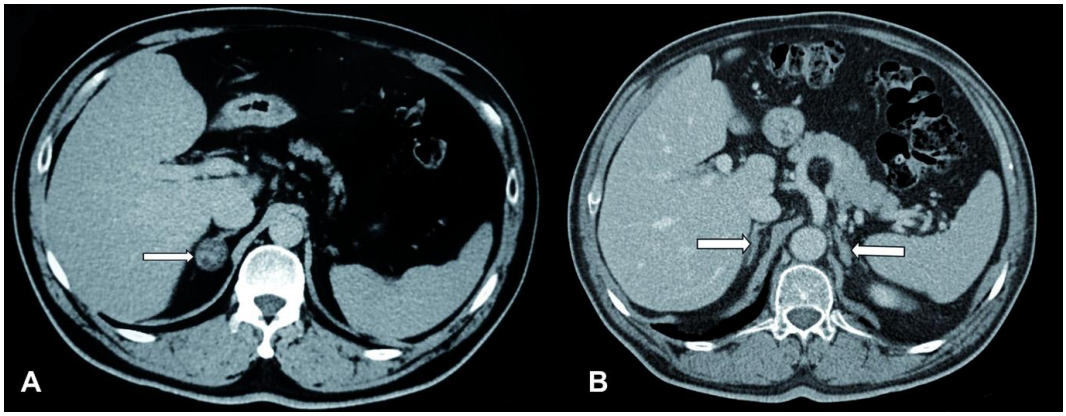


**Figure 2.** Computed tomography. (A) Right aldosterone producing adenoma (arrow); (B) bilateral adrenal hyperplasia (arrow).

A recent meta-analysis (14) demonstrated that the proportion of patients with an unilateral nodule on CT or MRI imaging, and a bilateral or contralateral secretion documented by AVS, was about 20%.

Since the prevalence of non-secreting adenoma increase with age, their presence is less likely in young patients with PA.

Thus, the presence of an isolated characteristic adrenal adenoma > 1 cm in PA patients aged less than 40 is considered by some experts as a surrogate for diagnosing unilateral aldosterone hypersecretion (16,21), although results from recent series do not support use of this strategy (32).

The guidelines recommend the use of CT in all patients with confirmed PA to detect an adrenal carcinoma, even if surgery is not otherwise considered (11). However, adrenal carcinomas presenting as isolated PA are rare, 2.5% of patients with adrenocortical carcinoma, which represents 0.05-0.2 % of all malignancies (33).

Moreover, CT and MRI results were found to disagree with AVS in a considerable proportion of patients. CT/MRI would show a unilateral abnormal adrenal gland and AVS would describe a contralateral or bilateral aldosterone hypersecretion, or image-based techniques would show bilateral normal or abnormal adrenal glands when aldosterone hypersecretion is lateralized in only one gland (34,35-38).

A prospective study of 203 patients (21) showed that operative planning based on anatomical imaging alone would have inappropriately excluded 21.7% of patients from adrenalectomy and would have led to unnecessary surgery in 24.7%; this situation led to a "renaissance" of AVS.

**Adrenal vein sampling.** AVS involves the measurement of aldosterone and cortisol levels in the infra-adrenal inferior vena cava and in the adrenal veins of both sides (**Figure 3**). Considering the variability of aldosterone secretion, some experts advocate AVS during exogenous ACTH infusion to maximize cortisol secretion, enhancing the assessment of selectivity of catheterization and to maximize differences of aldosterone between sides (21). Other experts suggest AVS in the early morning, when peaks ACTH secretion (11). While comparative study reported that exogenous ACTH infusion does not improve the detection of

unilateral aldosterone hypersecretion if the two adrenal veins are catheterized simultaneously (39), most experts agree that ACTH does facilitate the assessment of selectivity, but may confound the ascertainment of lateralization.

There is not agreement regarding the definition of successful selectivity and lateralization in AVS (11). Catheter insertion is considered successful under unstimulated conditions, if cortisol concentrations are 1.1 to 3 times higher in the adrenal veins than in the inferior vena cava or in a peripheral vein. Aldosterone concentrations in both adrenal veins are then divided by the corresponding cortisol concentrations. Aldosterone secretion is considered to be lateralized if the aldosterone to cortisol ratio is 2 to 5 times higher on the dominant side than contra-laterally.

AVS has a rate of failure between 3 (40) and 22% (34). It is an invasive procedure but it carries a very tiny risk of complications, when performed by skilled radiologist (41,42). The only clinically relevant complication is the adrenal veins rupture (0.6%), usually managed with conservative treatment (41).

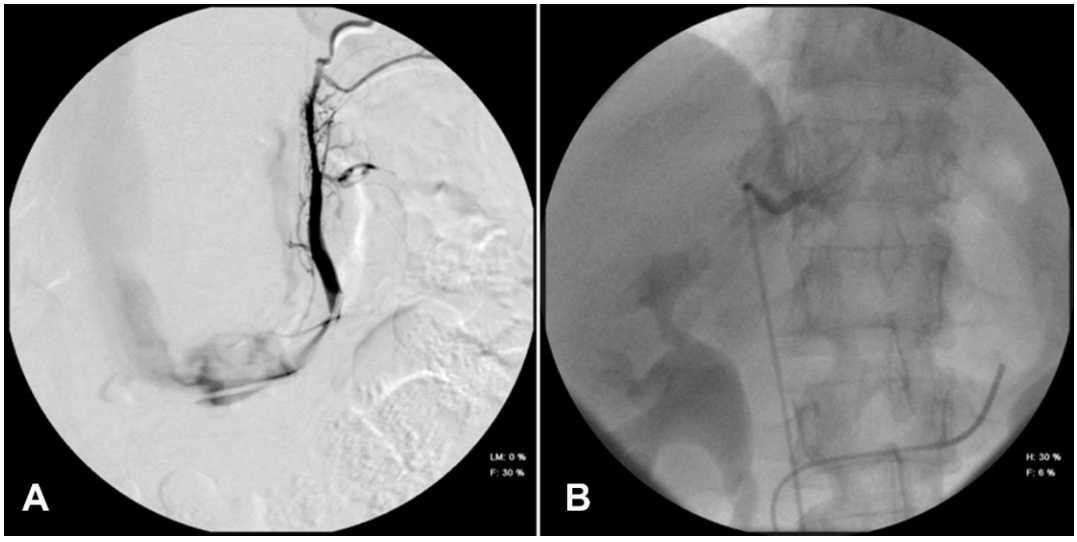


**Figure 3.** Adrenal venous sampling (angiographic images). (A) Identification of left adrenal vein; (B) simultaneous catheterization of both adrenal veins.

The objective of surgery is to resolve the aldosterone hypersecretion, and not just to remove a nodule. Since aldosterone hypersecretion can occur even with no adrenal enlargement (as detected by CT and MRI), AVS was found to be superior to image-based techniques for surgical decisions, as unilateral hypersecretion may be associated with UAH that can be undetectable on imaging (21,29,34).

Recently, some authors tried to develop a score to avoid the use of AVS. Kupers et al published data on a clinical prediction score (CPS), developed to diagnose unilateral PA, using a combination of biochemical and radiological characteristics (43). Applying this score, 30% of the cohort of patients they reported could potentially have avoided AVS and proceeded directly to surgery. Likewise, a prospective study by Sze et al. (44), suggested that the CPS has the potential to lead to occasional erroneous patient selection for adrenalectomy; therefore, it may be useful for clinical decisions only in cases of unsuccessful AVS or in centers where AVS is not available.

**Iodocholesterol scintigraphy.** [131I]19-Iodocholesterol scintigraphy was first used in the early 1970s (45). In 1977, the NP-59 scan [6-131I]iodomethyl-19-norcholesterol (NP-59) performed with dexamethasone suppression was introduced and had the advantage of correlating anatomical abnormalities with function (46). However, its sensitivity depends heavily on the size and the degree of hyperfunction of the adenoma (47,48). The introduction of the multiple head gamma camera and SPECT technique improved imaging resolution and enhanced the ability of NP-59 scintigraphy to detect smaller adrenal lesions (49).

However, this technique is often not helpful in interpreting micronodular findings obtained with high-resolution CT, because of a poor tracer uptake in adenomas smaller than 1.5 cm in diameter (50).

In 2014 Lu et al evaluated the ability of NP-59 scintigraphy to predict outcome in PA after adrenalectomy; they concluded that semiquantification of NP-59 scintigraphy shows ability similar to AVS in differentiating APA from bilateral idiopathic adrenal hyperplasia and has excellent ability to predict postsurgical outcomes of adrenalectomy (51).

However, other series have found misleading results in establishing lateralization with NP-59 (32). Moreover, NP-59 is an expensive and time-consuming procedure and its use is limited by the poor availability of the radiotracer (52).

Thus, most experts now agree that the referral diagnostic test for lateralization of aldosterone hypersecretion is AVS, because the interpretation of other imaging techniques (CT, MRI, adrenocortical scintigraphy) may lead to inappropriate treatment of PA patients (11,14,20,21).

### ***1.2.2 Medical treatment vs surgery***

Adrenalectomy represents the elective treatment in APA and other unilateral PA variants, while the administration of mineralcorticoid receptor antagonists (MRAs) is the choice for patients with bilateral disease and non-surgically correctable PA. The two main MRAs currently available are spironolactone and eplerenone (53) and the guidelines recommend the first as the primary agent for the management of PA, and eplerenone as an alternative (11).

MRAs or potassium chloride are commonly prescribed also to hypokalemic patients with APAs to correct hypokalemia before surgery, in order to avoid the risk of

hypokalemia-related arrhythmia during anesthesia (54). After surgery, the incidence of hypoaldosteronism or hyperkalemia is not increased by the preoperative treatment (55).

Some studies that compared spironolactone to surgery also in patients with APA reported no differences between treatments for the control of either BP or serum potassium concentrations (56).

Few follow-up echocardiographic studies have been conducted in PA patients treated with either adrenalectomy or MRAs. Whereas adrenalectomy was almost consistently found to rapidly decrease left ventricular mass (LVM), the effects of MRAs were more controversial (57-60). According to a recent meta-analysis, no significant difference in LVM change between patients with PA who underwent to adrenalectomy or treatment with MRAs were found, despite a greater effect of surgery over medical treatment in reducing blood pressure (61).

However, spironolactone has adverse effects such as gynaecomastia, mastodynia, menstrual abnormalities and erectile disfunction (62); otherwise the newest eplerenone is more expensive and seems to be less effective but better tolerated (63).

According to some authors, it remains uncertain whether adrenalectomy for lateralized disease, should routinely be offered to PA patients (64).

Reimel et al. attempted to compare the cost-effectiveness of a guideline-based surgical strategy with universal pharmacologic management, using a Markov state transition model (65). They demonstrated that screening for PA and resecting an APA was the least costly strategy. Even though most APA patients can be managed medically, in order to make universal pharmacologic therapy the less costly strategy for patients with an approximately 40-year life expectancy, the probability of finding a unilateral APA should be less than 10%; the cost of adrenalectomy should

be more than double; the cost of AVS should be more than four-fold higher than current and the surgical failure rate should be more than sextuple.

### ***1.2.3 Surgical procedures in primary aldosteronism***

The first adrenalectomy for PA was performed in December of 1954, just two months after the description of its metabolic basis. A middle aged hypertensive female underwent adrenalectomy for a 4-cm unilateral adrenal adenoma, curing her symptoms.

***Open vs laparoscopic adrenalectomy.*** Open removal of the aldosterone secreting tumours, by either the transabdominal or the lumbar approach, was unchallenged until 1992, when Gagner, Suzuki and Higashihara were published and opened the option for laparoscopic excision, performed via a transperitoneal approach (66-68). The supine anterior approach was described in 1995 (69), whilst other authors have described the retroperitoneoscopic approach (70,71).

Laparoscopic adrenalectomy, has been proven to be a safe and effective treatment for PA (72); laparoscopically treated patients have fewer postoperative complications and are equally likely to improve in blood pressure and correct hypokalemia, if present preoperatively, when compared with patients treated with open adrenalectomy. Additional benefits of laparoscopy are smaller incisions, decreased postoperative pain, and shorter hospital stay (73,74). In a recent review, laparoscopic adrenalectomy showed a morbidity of 5-14%, a mortality below 1%, and a mean hospital stay around 3 days (75). Complications of laparoscopic adrenalectomy may include conversion to open surgery, hematoma due to intraoperative vascular injury, thromboembolism, pneumothorax or hemothorax.

***Transperitoneal vs retroperitoneal approach.*** Laparoscopic surgery using the transperitoneal or retroperitoneal approaches is currently the preferred strategy to

treat patients with unilateral PA (76,77) (**Figure 4**). In general, three recent meta-analyses compared the transperitoneal and retroperitoneal adrenalectomy: two concluded that the two techniques have equivalent outcomes (78,79) whereas the other claimed the retroperitoneal approach to be superior in short-term outcomes (80).

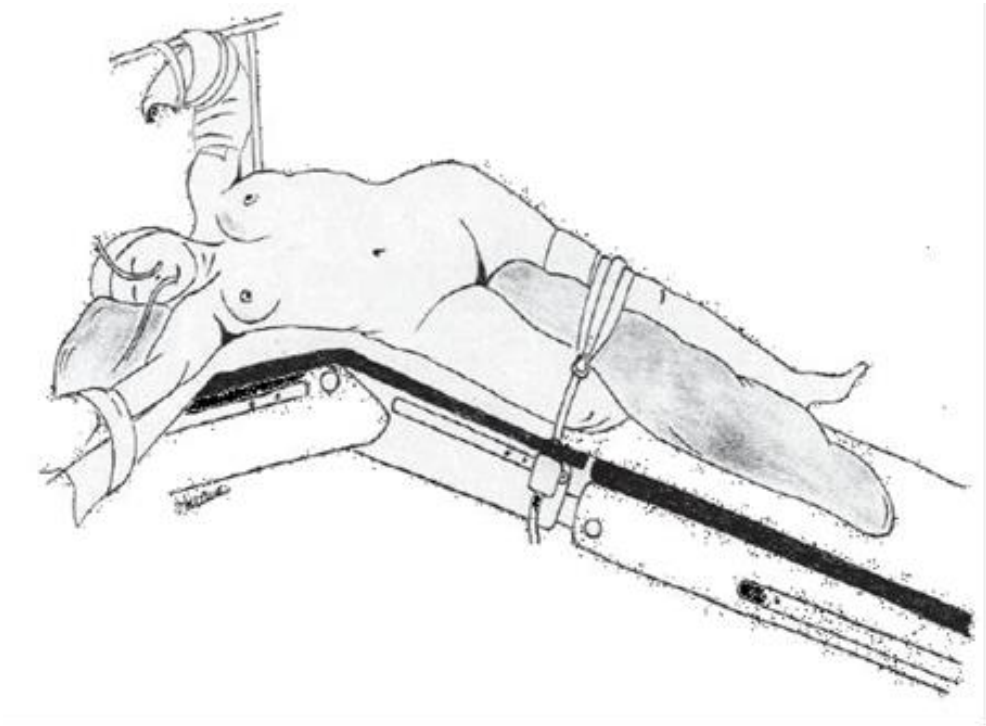

**Figure 4.** Position of patients for left transperitoneal laparoscopic adrenalectomy.

***Total vs partial "sparing"adrenalectomy.*** For a long time, unilateral total adrenal excision has been considered the technique of choice in patients with surgically correctable PA. However, the routine unilateral partial adrenalectomy in order to preserve the remnant adrenal function and avoid potential adrenal insufficiency has also been advocated (81).

This strategy may expose to increased risk of failures because of incomplete excision with subsequent persistent and recurrent PA, thus the risk-to-benefit ratio of partial adrenalectomy must be weighed. Partial adrenalectomy in cases of

unsuspected UAH may theoretically achieve an incomplete removal of abnormal adrenal tissue.

In fact, Shigematsu et al found that aldosterone hypersecretionis not localized exclusively in the adenoma cells but also in the adjacent hyperplastic or micronodular tissue (82). However, little is known about how the cells expressing the enzyme for aldosterone synthase are distributed in the adrenal glands; new findings in immunohistochemistry and immunofluorescence may provide useful tools for diagnosis and treatment of adrenocortical adenomas (83,84).

When an unilateral disease has been unequivocally established adrenalectomy results in the normalization of aldosterone secretion in close to 100% of the cases. It also achieved the correction of hypokalemia, if present before surgery, in virtually all patients (32). Furthermore, the cure of hypertension is reported in about 30-60% of cases, and in the remaining patients a marked improvement of BP values is described (58,75).

The wide variation of BP outcome after adrenalectomy could be explained by the different criteria used to define cure and improvement, and even more by the fact that BP is a highly complex phenotype, deriving from several factors. For example a patients with no cure of PA after adrenalectomy can became normotensive just for lifestyle measures and/or because of myocardial infarction. Conversely a patients with concomitant essential hypertension is unlikely to be cured even if the PA is fully corrected. Hence, we strongly advocate the need of considering the postoperative normalization of ARR as the main endpoint for determining outcomes of PA.

Several authors have suggested potential predictors of a postoperative hypertension cure in PA patients, including female sex, young age, no family history of

hypertension, short duration of hypertension, low preoperative BP, few prescribed antihypertensive drug classes, low body mass index, and high estimated glomerular filtration rate (29,75,85-88).

Zarnegar et al developed the Aldosteronoma Resolution Score, which was composed of 4 predictors (number of antihypertensive drugs, body mass index, duration of hypertension, sex) and roughly estimated postoperative hypertension cure according to 3 categories of likelihood (87).

Utsumi et al have recently proposed a more accurate nomogram that could predict hypertension cure in PA patients after laparoscopic adrenalectomy. Age, sex duration of hypertension, and number of antihypertensive drug classes are included in the nomogram (88). These score can help clinicians to calculate the probability of postoperative hypertension cure in PA patients and inform patients preoperatively.

### ***1.2.4 Primary aldosteronism and quality of life***

Besides leading to increased cardiovascular morbidity and mortality (26), PA has been claimed to be associated to higher prevalence of anxiety and depression, with potential impact on health-related quality of life (QoL), through mechanisms and pathways that remain to be clarified (89,90). Undoubtedly, both surgical and medical treatment of PA can control hypertension and severe cardiovascular damages in the long term (58). However, whether these two strategies, which show substantial differences (as surgery eliminates the source of aldosterone excess while mineralocorticoid receptor antagonists simply control it) have the same beneficial effects on QoL and depression remains uncertain (91,92).

Measurement of QoL investigates the functional status of the individual and the patient's appraisal of health, allowing assessment of the impact of a disease and/or treatment from the patient's perspective.

Therefore, health-related QoL has been investigated in patients suffering from PA by few studies that have reported subnormal scores compared to normal population (93,94); amelioration of health-related QoL as well as scores for depression and anxiety in patients with PA after surgery with respect to medical treatment has been reported (92,95).

However, in some studies, it could not be excluded that non-specific psychological effects secondary to surgery could be at least partly responsible for some improvement in QoL (91).

## 2. AIM OF THE STUDY

The aim of the present study was to assess the impact of surgery on health-related QoL (both in Mental and Physical components) and depression status of patients suffering from PA.

The purpose was to compare the results of PA patients with the best possible controls, to underline the role of hyperaldosteronism. Thus, patients with non-secreting adrenal tumor who underwent to the same intervention (laparoscopic transperitoneal adrenalectomy), but without hormone excess, were selected.

## 3. PATIENTS, MATERIAL AND METHODS

Data were prospectively collected from January 2014 to October 2016 at Minimally Invasive Endocrine Surgery Unit of Padua University. The study included patients with unilateral PA and a control group of patients with non-secreting adrenal tumor submitted to laparoscopic transperitoneal adrenalectomy by flank approach, performed by the same surgeon (M.I.). The institutional ethics committee approved the study and informed consent was obtained from all patients.

PA was diagnosed based on a plasma aldosterone concentration greater than 15 ng/dL and an aldosterone/renin ratio greater than 40 ng/dL:ng/mL/h, measured after washout of interfering drugs or after changes of the drug treatment as previously detailed (32). The diagnosis was confirmed by saline infusion and/or the captopril test (32).

Surgery was performed in patients with lateralized PA, according to the results of preoperative lateralizing techniques. Lateralizing techniques included CT scan and/or MRI and selective AVS.

AVS was performed with bilateral simultaneous catheterization, by using one catheter for each adrenal vein. Successful selective catheterization was usually

confirmed when the ratio between cortisol concentration in each adrenal vein and the inferior vena cava was greater than 1.1; unilateral aldosterone hypersecretion was usually confirmed when the ratio of adrenal vein aldosterone concentration to the homolateral cortisol concentration on the side with the higher ratio over the contralateral aldosterone to cortisol ratio (AVS ratio) was greater than 2.

The control group was composed of patients suffering from non-secreting adrenal tumor, defined as an asymptomatic adrenal mass, incidentally detected on imaging not performed for suspected adrenal disease, in patients without glucocorticoid, catecholamine or mineralcorticoid hypersecretion (assessed by plasmatic ACTH, 24-hour urinary free cortisol levels and 1 mg overnight dexamethasone suppression test, 24-hour urinary catecholamine or metanephrine levels and plasma renin and aldosterone levels, respectively).

In these patients, surgery was indicated by the presence of adrenal mass with suspicious radiological findings (even without evidence of local invasion or distant metastases), evidence of significant tumor growth during follow-up imaging and/or patient preference. Patients with adrenal or extra-adrenal malignancies or any psychiatric disorders were not included in the study.

The surgical procedure was performed with the patient in lateral decubitus flank position. Pneumoperitoneum (at 12-14 mmHg by $CO_2$) is usually made by Hasson cannula inserted by open technique. A subcostal port is placed for the laparoscope, and two/three other 5/10 mm ports sited. For right adrenalectomy the liver is mobilized and retracted and the right medium adrenal vein is identified by following the lateral edge of the vena cava. The main right adrenal vein is identified and divided early. Then the adrenal branches from the inferior phrenic artery, aorta, and the renal artery are divided.

On the left side the colonic flexure is mobilized and the splenorenal ligament dissected, allowing the fall of the spleen medially and the identification of the tail of the pancreas and the splenic vein and artery. The avascular plane separating adrenal gland from the tail of the pancreas and the splenic vein is opened, allowing the view of the inferior adrenal vein, going into the left renal vein. The inferior adrenal vein is divided and then the gland is dissected and removed. Small arterial vessel from superior, medium and inferior pedicle can be easily coagulated. In all cases, the adrenal gland is removed via a retrieval bag.

The biochemical cure of PA was defined by the normalization of aldosterone/renin ratio (<40 ng/dL:ng/mL/h) and serum potassium levels (≥3.5 mmol/L).

Patients were defined being hypokalemic if their serum potassium level was less than 3.5 mmol/L or if they needed potassium supplementation to maintain normokalemia. Hypokalemia was considered cured if serum potassium levels regained the normal range without potassium supplementation.

Arterial hypertension was defined by a systolic BP of 140 mm Hg or greater, diastolic BP of 90 mm Hg or greater, or both and/or the presence of antihypertensive medical treatment. Hypertension was considered cured if BP regained normal levels after discontinuing any medical treatment; it was considered improved when the hypertensive patients switched from a higher to a lower hypertension degree or the antihypertensive drugs were reduced.

Health-related QoL and depression status, were assessed preoperatively (at the time of hospital admission) and postoperatively at 1-month outpatient control and at long term, at least 6 months after surgery.

QoL was evaluated using the Italian version of Short Form 36 (SF-36) Health Survey for a Physical (PCS) and a Mental Component (MCS). The SF-36 is a 36 item self-administered questionnaire measuring QoL across eight domain obtaining

eight scaled scores, which are the weighted sums of the questions in their section. These domains are physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, vitality, bodily pain, general health perceptions, and general mental health. PCS and MCS are a summary of physical and emotional QoL respectively. Scores may range from 0 (poorest health status) to 100 (best health status). The depression status was evaluated using a 20-item depression scale (DS) questionnaire; the score may range from 0 (best status) to 60 (poorest status) (26).

Results were compared with published normative values for the Italian population (96).

Records of the patients were reviewed to gather relevant demographics, body mass index (BMI, defined as body weight (kg)/height ($m^2$), normal values 20 to 24.9), hormonal parameters (including glucocorticoid, mineralcorticoid and catecolamine assays), BP values, number of antihypertensive drugs, side and size of adrenal masses, intra and postoperative morbidity and definitive pathology.

Postoperative follow-up data (including hormonal, BP parameters, number of antihypertensive drugs), were assessed 1 month after surgery and at long-term.

Results were expressed as absolute numbers, ratio, percentage, mean (± standard deviation) or median (range).

Statistical analysis was performed using Fisher's exact test for categorical variables, Student's paired *t* test, Wilcoxon matched-paired test, Mann–Whitney *U* test, as appropriate. $P < .05$ was considered statistically significant.

## 4. RESULTS

Twenty-six PA patients and 15 patients with non-secreting adrenal tumor who also underwent laparoscopic transperitoneal adrenalectomy were recruited.

No significant differences were found between PA patients and controls concerning demographics, BMI, side and dimension at preoperative imaging of the mass (**Table 1**).

**Table 1.** Demographics, and general features in patients with Primary Aldosteronism and Controls (patients with non-secreting adrenal tumor) undergoing laparoscopic adrenalectomy.

| | **PA PATIENTS (n=26)** | **CONTROLS (n=15)** | **p value** |
|---|---|---|---|
| **Sex (female/male)** | 10/16 | 6/9 | 0.92 |
| **Age (years)** | 54±11 | 56±9 | 0.54 |
| **Body Mass Index ($kg/m^2$)** | 26.6±4 | 27.4±6 | 0.95 |
| **Side of the mass (left/right)** | 12/14 | 9/6 | 0.59 |
| **Size of the mass (mm)** median(range) | 15 (6-30) | 44 (25-60) | <0.0001 |

*PA: Primary aldosteronism*

The size of the adrenal mass at preoperative imaging was significantly higher in controls than in PA patients ($p<0.0001$) (**Table 1**).

Hypertension was present in all patients with PA and in five patients with non-secreting adrenal tumor ($p<0.0001$); hence, the mean systolic and diastolic BP were significantly higher in PA patients than in controls (154±19 vs 125±9 mmHg, $p<0.0001$ and 91±12 vs 75±8 mmHg, $p=0.0002$, respectively); likewise, the number

of antihypertensive drugs was significantly higher in PA patients than in controls (3.42±1.47 vs 0.60±0.99, p<0.0001).

Preoperative MCS and DS scores were impaired in PA patients compared to normal Italian reference population; similar finding were found also in the control patients. No significant differences were found between PA patients and controls concerning preoperative PCS (51.02±8.04 vs 51.16±9.63, p=0.75), MCS (42.72±13.68 vs 39.39±12.81, p=0.39), and DS values (15.92±11.98 vs16.26±12.56, p=0.91).

All patients underwent uneventful laparoscopic surgery; no conversion to open approach was performed, no blood transfusion was required and no intra- or post-operative morbidity occurred in both groups.

Pathological specimens revealed benign adrenal tumors in all cases in both groups.

<u>One month after surgery</u>

PA was biochemically cured in all patients, according to the normalization of the aldosterone/renin ratio and serum potassium levels; hypertension was cured in 10 cases (38%), and improved in the remaining 16 cases (62%). The systolic and diastolic BP were significantly reduced (from 154±19 to 130 ± 15 mmHg, p<0.0001 and from 91±12 to 78±9 mmHg, p<0.0001); also the mean number of antihypertensive drugs was significantly reduced (from 3.42±1.47 to 1.15±1.1, p<0,0001).

In patients with PA, MCS values significantly improved (42.72±13.68 vs 51.56±9.03, p=0.0005) (**Figure 5**), mainly due to an amelioration in the "mental health" (42.7±15.7 vs 53.17±7.33, p=0.001) and "emotional role" (45.5±11.83 vs 51.23±9.84, p=0.001) scores. Also DS values significantly improved (15.92±11.98 vs 8.3±8.8, p=0.0002). Conversely, no quite significant differences were found regarding PCS scores (51.02±8.04 vs 48.01±6.85, p=0.07) (**Figure 5**).

In controls, no significant changes in BP levels and number of antihypertensive drugs was found; also in the five hypertensive patients no changes in BP values and number of antihypertensive drugs were detected after adrenalectomy.

Also in controls MCS (39.39±12.81 vs 50.62±8.68, p=0.0005) and DS (16.26±12.56 vs 7.86±7.19, p=0.001) values improved after surgery, mainly due to a significant amelioration in the "mental health" (46.69±12.01 vs 53.79±6.36, p=0.006) and "emotional role" (33.19±13.69 vs 46.93±9.26, p=0.001) scores (**Figure 5**). No significant differences were found regarding PCS values (51.16±9.63 vs 48.60±6.99 p=0.26).

No significant differences were found between PA and control patients concerning postoperative MCS and PCS and DS (p= 0.69, p=0.81 and p= 0.93, respectively).

Long-term follow-up

The median time of follow-up was 231 days (range 184-391) for PA patients and 270 days (range 211-369) for controls.

At long term, all patients that underwent surgery for PA were still biochemically cured, but two patients that at one month had achieved the cure of hypertension, restarted antihypertensive therapy; thus, the hypertension cure was achieved in 8 patients (31%).

At long term follow up PA patients had systolic and diastolic BP values significantly reduced (from 154±19 to 129± 13 mmHg, p<0.0001 and from 91±12 to 79±8 mmHg, p<0.0001), compared with preoperative values; also the mean number of antihypertensive drugs was significantly reduced (from 3.42±1.47 to 1.28±1.2, p<0,0001).

These patients had no significant differences in BP values and number of antihypertensive drugs one month after surgery and at long term follow up.

In patients with PA, a significant improvement in PCS (51.02±8.04 vs 55.85±5.1, p=0.013), MCS (42.72±13.68 vs 51.81±7.04, p<0.0001) and DS (15.92±11.98 vs 4.57± 6.11, p<0.0001) values was described at long term, compared with preoperative period; at long term PCS values improved significantly, compared with values recorded one month after surgery (p=0.0002) (**Figure 5**).

At long term, also in controls MCS (39.39±12.81 vs 49.30±10.46, p=0.001) and DS (16.26±12.56 vs 6.80±5.64, p=0.002) values improved after surgery, mainly due to a significant amelioration in the "mental health" (46.69±12.01 vs 54.64±7.87, p=0.007) and "emotional role" (33.19±13.69 vs 51.62±9.87, p<0.0001) scores (**Figure 5**). No significant differences were found regarding PCS values (51.16±9.63 vs 53.91±4.30 p=0.25). However, compared with values recorded one month after surgery, at long term PCS values improved significantly (p=0.04).

Also at long term, no significant differences were found between PA and control patients concerning MCS and PCS and DS (p= 0.58, p=0.16 and p= 0.18, respectively).

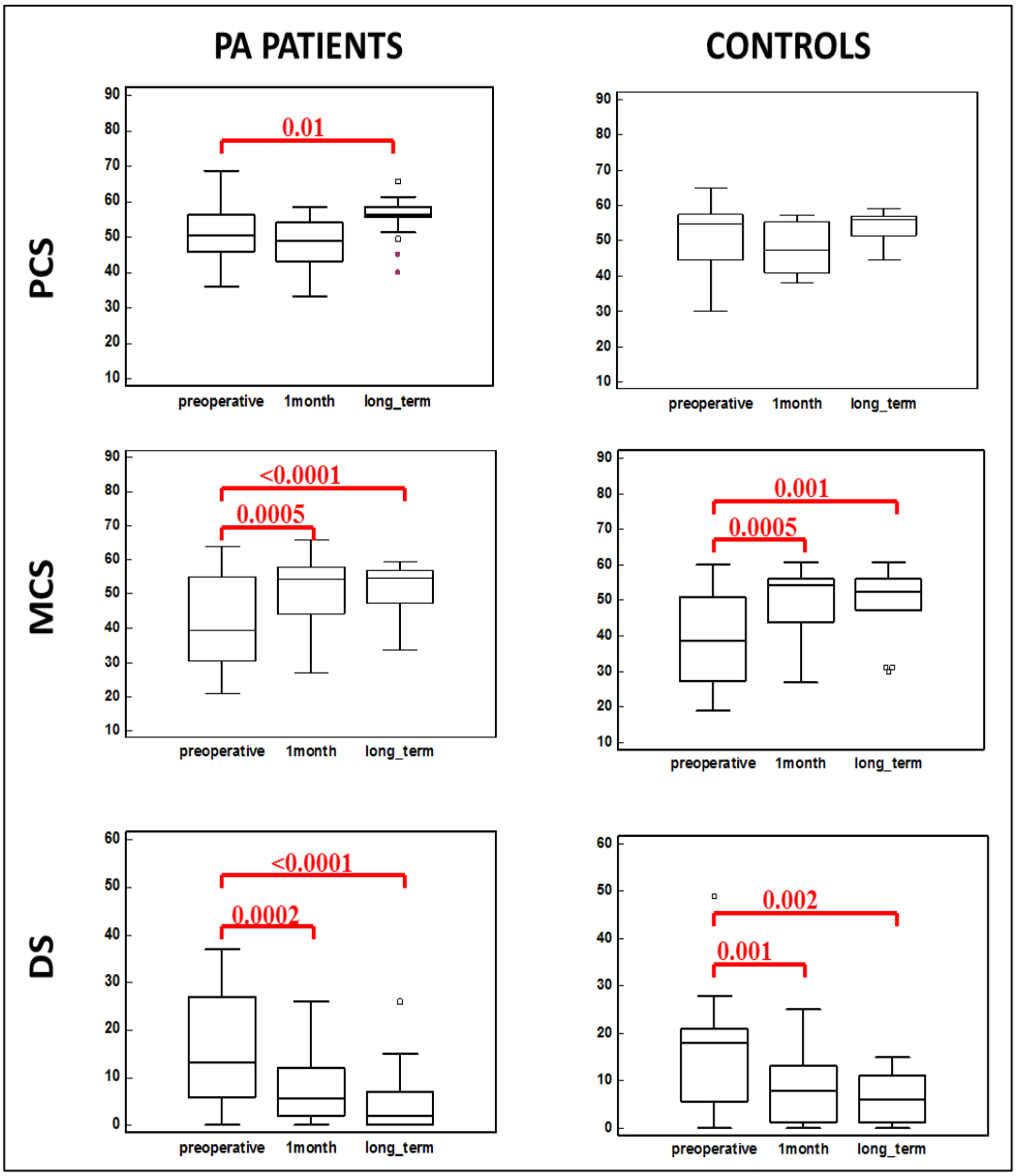


**Figure 5.** PCS, MCS and DS values in PA patients and controls, preoperatively, 1 month after surgery and at long term. *PA: primary aldosteronism; PCS: Physical Component Score; MCS: Mental Component Score; DS: depression scale.*

## 5. DISCUSSION

PA is a common, albeit often overlooked, cause of hypertension which is often severe and/or drug resistant and, therefore, associated with cardiovascular damage and a worse prognosis (17,97). Moreover, it implies clear cut alterations of the renin-angiotensin-aldosterone system, which suggests that it entails multiple reasons to imply a worsened QoL, given that the derangements of this important system can affect QoL (89,90).

Hypertension is an important factor for reduced QoL: an impairment of QoL has been reported in patients with essential hypertension compared to normal controls in the somatization and psychological distress (98).

Along with this hypothesis, health-related QoL in patients suffering from PA has been previously investigated only by 3 studies (93,94,99).

In 2010, Sukor et al (99) examined health-related QoL in 22 patients with unilateral PA before and after unilateral adrenalectomy at 3 and 6 months, using SF-36 questionnaire. They found a significant improvement in the QoL of these patients both in physical and mental component. However, they did not examine depression and anxiety.

In 2011 the same authors (93) compared the results of the previous study with those from 21 patients with bilateral PA, before or after commencing medical treatment, and with those of the normal Australian population. They confirmed that PA patients had subnormal QoL scores compared to normal population. Moreover, they described that QoL improved in all patients with bilateral PA undergoing medical treatment, but more slowly and to a lesser degree than in patients undergoing surgery for unilateral PA.

In 2012, Kunzel et al (94) published the results of a cross sectional study data from the German Conn Registry examining health-related QoL using SF12

questionnaire, in which they investigated acute impairment of QoL and long-term treatment effects in patients with PA. The study included 132 patients with PA, stratified according to the treatment status: 27 newly diagnosed, untreated; 52 in chronic medical treatment, 49 patients treated with adrenalectomy. The study confirmed that PA patients had a worse physical and mental condition than the normal German reference population; untreated and medically treated patients reported the lowest scores.

Our study differed substantially from these previous studies, in that we used the best possible controls, i.e. patients with a non-functioning adrenal mass treated with adrenalectomy.

This allowed adjustment for the potentially confounding effect of being harboring an adrenal tumor and of being submitted to adrenalectomy. Moreover, our study was aimed to clarify the impact of surgery on health-related QoL (both in Mental and Physical components) and for the first time on depression status, in patients suffering from PA.

In agreement with previous studies, we confirmed that patients with PA have an impaired QoL and depression status compared with normal population, as assessed by worse MCS and DS scores.

In PA patients, MCS (especially in the mental health and emotional role dimensions) and DS values significantly improved 1 month after surgery and at long term follow-up, confirming the beneficial effect of adrenalectomy previously reported (93). However, we failed to find significant differences with the controls, since also these patients (without aldosterone excess) showed an impaired preoperative MCS and DS scores, and a significant amelioration one month and at long term after surgery. Interestingly, also in controls MCS improvement was

mainly due to mental health and emotional role amelioration. However, the amelioration was more evident in PA patients.

Even if controls and PA patients were similar according to demographics and type of surgical procedure, the former had lower BP levels, larger adrenal masses and underwent surgery mainly because of a suspicion of malignancy, while there was not suspicion for the latter.

Thus, it remains unclear if it may be related to the reduction of BP levels or antihypertensive drug treatment (with a possible reduction of drug-related size effects), to the aldosterone/renin system normalization or a non-specific psychological effect of surgery.

We may argue that in control population the thought of impending surgery and the uncertain nature of the non-secreting adrenal mass might have affected the mental component and increased the depression status before surgery. Obviously, both factors might have been solved after surgery, since in all cases definitive pathology described a benign adrenal tumor; however other psychologic effects of adrenalectomy may not be excluded, as previously reported (91).

In the present study, no significant amelioration of PCS scores was detected in PA patients one month after surgery; this finding might be related to the sequelae of recent surgery. In fact, in PA patients the improvement in PCS values become evident at long term follow-up. This is in agreement with previous studies that demonstrated at 3 months a significant increase of physical condition, after disease cure and BP normalization or amelioration [99]. In the control group no significant variations were detected in PCS values at one month and at long term, compared with preoperative values. However, some limitations to the present study that might have biased the results should be underlined; the mental component of health–

related QoL is difficult to explore; moreover, the SF-36 and DS questionnaires are not disease specific.

Furthermore, the administration of the baseline questionnaire during hospitalization for surgery, when factors such as optimism or anxiety and fear of surgery could have some effects, might have affected the results in terms of worsening QoL and depression as compared to the normal population. However, if any, the effect was likely similar in both PA and controls.

## 6. CONCLUSIONS

PA affects the health-related QoL, worsening the mental component and the depression status. Adrenalectomy is effective in curing PA, and improves the mental component of health-related QoL and depression status at 1 month and at long term. At long term, surgery determines an improvement also in the physical component of health-related QoL of PA patients.

The role of hormonal cure of PA and the possible weight of the psychological effects of surgery itself in affecting QoL need to be further explored, since some relevant results may be observed also in patients undergoing surgery for non-secreting adrenal masses. Further studies are needed to confirm these results at a longer follow up and with a larger population.

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