Quality of life in primary aldosteronism: A prospective observational study

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1   **QUALITY OF LIFE IN PRIMARY ALDOSTERONISM: A PROSPECTIVE OBSERVATIONAL STUDY**

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Abstract

Background Previous studies suggested that patients affected by primary aldosteronism (PA) have impaired quality of life (QOL) compared to the general population, but a direct comparison with patients affected by essential hypertension (EH) has never been performed. The aim of the study was to compare the QOL of patients affected by PA to the QOL of patients affected by EH.

Material and methods

We designed a prospective observational study comparing the QOL of patients with PA and carefully matched patients with EH before and after treatment. We recruited 70 patients with PA and 70 patients with EH, matched for age, sex, blood pressure levels and intensity of anti-hypertensive treatment. We assessed QOL at baseline and after specific treatment for PA or after optimization of medical therapy for patients with EH.

Results

Patients with PA displayed impaired QOL compared with the general healthy population, but similar to patients with EH. Both laparoscopic adrenalectomy and treatment with mineralocorticoid receptor antagonist allowed an improvement of QOL in patients with PA, that was more pronounced after surgical treatment. Optimization of blood pressure control by implementation of antihypertensive treatment (without MR antagonists) allowed a minimal improvement in only one of eight domains in patients with EH.

Conclusions

Patients with PA have impaired QOL, which is likely caused by uncontrolled hypertension and the effects of intensive anti-hypertensive treatment. Surgical and medical treatment of PA

47 allows a significant improvement of QOL, by amelioration of blood pressure control and,

48 after surgical treatment, by reduction of anti-hypertensive treatment.

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Introduction

The World Health Organization considers quality of life (QOL) a key component of "health" status and recommends to consider the effects of medical treatments by assessing patients' well-being with health related QOL evaluation.[1] The QOL of patients with primary aldosteronism (PA) has been neglected until 2010, when a significant reduction of QOL in patients with aldosterone producing adenoma (APA), compared with the Australian general population, was reported for the first time.[2] In the following years, these findings were confirmed in larger cohorts of patients with unilateral PA,[3–6] and similar findings were obtained in patients with bilateral or idiopathic hyperaldosteronism (IHA).[4,7]

Beyond QOL, primary aldosteronism has been associated with anxiety, depressive disorders and somatization.[8–11] Recent findings suggested that aldosterone levels might correlate with depressive symptoms in women with PA[12] and, more broadly, previous studies indicated a correlation between serum aldosterone levels and the prevalence of depressive disorders in patients without PA.[13,14]

Well-being is an essential component of QOL and a previous study reported lower psychological well-being in patients with PA, compared with normotensive control.[9] A following study reported contrasting results, with no differences in well-being of patients with PA compared to Dutch normative data.[11] Several explanations may be offered for the conflicting results, including the use of different questionnaires, a predominantly male cohort and the lack of an appropriate control group in one study.

PA is the most common cause of endocrine hypertension and affects about 4-6% of patients with arterial hypertension in the general population.[15,16] Beyond the strict criteria for PA, recent studies identified an autonomous aldosterone secretion in up to 20% of individuals with hypertension and up to one fifth of patients with normotension.[17,18] Specific PA treatments, both unilateral adrenalectomy and medical treatment with mineralocorticoid receptor (MR)

86 antagonists, resulted in significant QOL improvement, that occurred earlier and was more

87 pronounced in surgically treated patients compared with those medically treated.[4,7]

88 Some authors proposed that the impaired QOL of patients with PA could be attributed to the

89 direct effects of aldosterone excess on central nervous system. However, uncontrolled and

90 resistant hypertension could themselves account for a significant impairment of QOL.[19] No

91 study directly compared the quality of life of patients with PA versus patients with essential

92 hypertension with similar clinical characteristics. At the same time, in most of the former

93 studies, QOL was assessed after PA diagnosis,[2,4] making the awareness of the disease a relevant

94 component in QOL evaluation. Finally, no study compared the effect of specific treatment for

95 PA versus optimization of medical treatment.

96 In this context, we designed a prospective observational study comparing, for the first time, the

97 QOL of patients affected by PA (before diagnosis) with patients affected by essential

98 hypertension (EH), matched for age, sex, blood pressure levels and intensity of drug treatment.

99 We evaluated the modification of QOL after specific treatment in patients with PA and

100 compared with QOL modification after optimization of anti-hypertensive therapy in the control

101 cohort. In order to compare our study with previous findings[2-7], we adopted RAND SF-36 as

102 tool to investigate QOL in our cohort.

103 **Materials and methods**

104 *Study Design*

105 The protocol was approved by the ethical committee of the hospital A.O.U. Città della Salute

106 e della Scienza di Torino and written informed consent was obtained from all recruited patients.

107 Reporting of the study conforms to broad EQUATOR guidelines.[20]

108 In the QUALIty of Life of patients with PA in TOrino (QUALITO) study we prospectively

109 enrolled 140 patients (70 patients with PA and 70 matched controls with EH) from 03/2017 to

110 09/2019 in Torino, Italy. Patients with PA and EH were matched for sex, age, systolic blood

111   pressure (SBP) and intensity of antihypertensive drug treatment (quantified by daily defined

112   dose,   calculated   with   the   online   tool   available   at

113   https://github.com/ABurrello/PASOPredictor/raw/master/00 - PASO Predictor.xlsm).[21]

114   All the included patients were affected by arterial hypertension, diagnosed according with the

115   European Society of Cardiology/European Society of Hypertension (ESC/ESH) guideline [22,23];

116   diagnosis of EH was made after the exclusion of all the main secondary forms of arterial

117   hypertension (including hypercortisolism, pheochromocytoma, hyperthyroidism and reno-

118   vascular hypertension), while patients with PA were included following a confirmed diagnosis

119   according to the Endocrine Society guideline and the recent ESH consensus.[24–26] The only

120   exclusion criterion for EH cohort was treatment with MR antagonists at recruitment or at follow

121   up. For PA cohort, exclusion criteria were I) patients under MR antagonist or II) previous

122   adrenalectomy for unilateral PA at recruitment.

Diagnosis of primary aldosteronism

124   Before screening test, all interfering antihypertensive drugs were stopped (at least 2 weeks for

125   ACE-I, ARBs and beta blockers and 4 weeks for diuretics). When complete discontinuation of

126   antihypertensive treatment was not feasible, non-interfering drugs were administered. The

127   screening test was considered positive in case of serum aldosterone $\geq$ 10 ng/dl and aldosterone

128   to renin ratio (ARR) $\geq$ 30 ng/dl/ng/ml/h or aldosterone to active renin ratio (AARR) $\geq$ 2.7

129   ng/dl/mU/l. Seated saline infusion test (SSIT) or, in case of contraindication, captopril

130   challenge test (CCT), were used as confirmatory tests. PA was considered confirmed in case

131   of serum aldosterone post-SSIT $\geq$ 5 ng/dl or ARR $\geq$ 30 ng/dl/ng/ml/h after CCT.

132   Subtype diagnosis was performed by computed tomography of the adrenal glands and

133   unstimulated and/or cosyntropin-stimulated adrenal venous sampling (AVS). A selectivity

134   index $\geq$ 3 for unstimulated and $\geq$ 5 for stimulated AVS was used to define successful

135   cannulation of adrenal veins. A lateralization index ≥ 4 or ≥ 3 with contralateral suppression

136   (contralateral ratio < 1) was used to define unilateral PA.

137   *Quality of life data collection*

138   36-Item Short Form Health Survey (RAND SF-36) is a self-administered questionnaire used

139   to assess health-related QOL and validated in the Italian population.[27] RAND SF-36 includes

140   35 items and 8 different subscales: physical functioning, role limitations due to physical

141   problems, role limitations due to emotional problems, vitality, general mental health, social

142   functioning, bodily pain, and general health perceptions.

143   At baseline, RAND SF-36 was self-administered in patients with PA before confirmatory test

144   and in patients with EH before optimization of antihypertensive medical treatment.

145   In the PA cohort, RAND SF-36 was also collected 2 and 6 months after laparoscopic surgical

146   adrenalectomy or initiation of MR antagonist. RAND SF-36 was collected 6 months after

147   optimization of medical treatment in patients with EH.

148   Data of the PA cohort, at baseline and at 6 months, have been compared to the Italian normative

149   data from "healthy subjects".[27]

150   *Statistical methods*

151   IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, New York) was used for statistical

152   analyses. PRISM software (GraphPad, San Diego, CA) was used for charts and graphs

153   preparation. Data are expressed as mean ± SD for continuous variables with a normal

154   distribution. Data with non-normal distributions are expressed as median (interquartile range).

155   Charlson Comorbidy index was used to estimate burden of comorbidity and considered as

156   categorical variable.[28] Statistical significance between groups was calculated in normally

157   distributed data by paired t test for groups of matched patients and Student t test for independent

158   samples in other cases. Mann-Whitney U test was used for non-normally distributed data and

159   Kruskal-Wallis test for paired samples for non-normally distributed data of matched samples.

160   Chi-square test was used for qualitative variables. Repeated measure ANOVA was used for

161   comparison of daily defined dose (DDD) and blood pressure levels during follow up.

162   Linear mixed model is a statistical approach that can be applied in prospective studies for the

163   analysis of repeated measures. In contrast to repeated measure ANOVA, usually used for

164   repeated measures analysis, mixed models consider both fixed and random effects, allowing a

165   more accurate analysis of prospective data. Moreover, using random effects for baseline values,

166   mixed models take into account differences in starting point for each subject.

167   Linear mixed models, with unstructured correlation and maximum likelihood method, were

168   used for longitudinal comparison of QOL changes and performed with R version 3.6.1. Scores

169   of the 8 subscales of RAND SF-36 were used as dependent variables. Time, treatment, sex,

170   diabetes and CCI were considered as fixed factors and potassium, creatinine, age, BMI and

171   duration of hypertension as covariates. 20 different models were evaluated for each subscale

172   and minimum Akaike information criterion (AIC) was used for model selection (Supplemental

173   Methods).

174   **Results**

175   *PA and EH cohort*

176   A total of 140 patients were recruited for the QUALITO study in Torino: 70 patients with PA

177   and 70 patients with EH matched for age, sex, systolic blood pressure and intensity of anti-

178   hypertensive drug treatment (DDD). Of the 70 patients with PA, 43 were diagnosed as affected

179   by unilateral PA, 37 of whom underwent laparoscopic adrenalectomy (Figure S1). All the

180   patients that underwent unilateral adrenalectomy displayed complete biochemical outcome at

181   6 months follow-up according to PASO criteria.[29] Twenty out of 70 patients with PA were

182   classified as IHA and 7 patients with undetermined subtype, because unwilling to undergo AVS

183   or unsuccessful procedure. Thirty patients were treated with MR antagonist (14 with

184   spironolactone, 16 with potassium canrenoate), including 6 patients with unilateral PA, 19

185 patients with IHA and 5 with undetermined subtype. One of 37 patients after surgical

186 adrenalectomy and one of 30 patients under MR antagonist were lost at follow up (Figure S1).

187 Principal clinical and biochemical characteristics of patients with EH and PA are summarized

188 in Table 1. No significant differences were present between the two cohorts for the evaluated

189 parameters, except for lower serum potassium in PA cohort.

190 *Baseline comparison*

191 At baseline, patients with PA had non-significant differences in either of the 8 subscales

192 compared with matched individuals with EH (Figure 1, Table S1). No differences were present

193 even after stratification for subtype diagnosis, in patients with unilateral PA and IHA (Table

194 S2-S3), compared with the respective matched patients with EH.

195 Compared to Italian normative data of "healthy subjects",[27] patients with PA displayed lower

196 score in 5 of 8 domains: physical functioning, role limitations due to physical health problems,

197 vitality, social functioning and general health perceptions (Figure 1, Table S1), with similar

198 results in patients with unilateral PA and IHA, with the exception of social functioning, that

199 did not differ significantly between patients affected by IHA and healthy subjects (Table S2-

200 S3). At baseline, independently of PA or EH diagnosis, patients with DDD≥3 displayed lower

201 QOL in two physical subscales than patients with DDD<3 (Tables S4).

202 *Follow up*

203 After surgical adrenalectomy, patient with APA displayed a significant reduction, at 2 and 6

204 months of follow up, of SBP (149±13 *vs* 124±11 *vs* 121±11 mmHg), diastolic blood pressure

205 (DBP) (92±9 *vs* 80±11 *vs* 78±8 mmHg) and anti-hypertensive treatment (DDD 3.05±1.68 *vs*

206 1.31±1.53 *vs* 0.94±1.26). Patients under MR antagonist showed a reduction of SBP (145±15

207 *vs* 134±14 *vs* 131±13 mmHg) and DBP (88±9 *vs* 83±9 *vs* 83±8 mmHg) with a non-significant

208 increase of anti-hypertensive treatment (DDD 3.07±1.24 *vs* 3.43±1.42 *vs* 3.44±1.44).

209   Similarly, patients treated with general anti-hypertensive treatment showed SBP and DBP

210   reduction at 6 months, with increased DDD (Table S5).

211   We used linear mixed models to compare baseline values with follow up scores at 2 and 6

212   months after treatment, selecting the best of 20 tested models, for each of the 8 subscales

213   (Supplemental Methods and Table S6). Effect and statistical significance of fixed factors,

214   covariates and interactions in each of the 8 subscales are showed in Table S7.

215   During follow up, patients undergoing unilateral surgical adrenalectomy displayed a significant

216   improvement in 4 of 8 domains: physical functioning, vitality, general health perceptions and

217   general mental health, with the latter significant at 2 but not at 6 months. Patients with PA

218   treated with MR antagonist, had a significant improvement in 2 domains: physical functioning

219   and general health perceptions. Patients with EH undergoing optimization of anti-hypertensive

220   treatment without MR antagonist displayed a significant improvement in only one domain

221   (general mental health) at 6 months of follow up (Figure 2A-B-C, Table S8).

222   *Six months comparison*

223   At 6 months, adrenalectomized patients displayed higher scores in physical activity and general

224   health perceptions, compared to patients under general anti-hypertensive treatment, and higher

225   score in social functioning, compared to patients under MR antagonist. Patients with PA under

226   MR antagonist had higher score of physical functioning compared to patients under general

227   anti-hypertensive treatment (Figure 2D, Table S9).

228   Six months after surgery, adrenalectomized patients displayed similar score in 7 of 8 domains,

229   compared to Italian normative data of healthy subjects,[27] with lower score in only general

230   health perception. Instead, after 6 months of medical treatment, patients with MR antagonist

231   had lower scores in 4 of 8 domains compared to healthy subjects (Figure 3, Table S10).

232   **Discussion**

233   QOL is a well-recognized component of health and QOL assessment has an important role in

234   the evaluation of the impact of diseases on affected patients. Whether the impaired QOL of

235   patients affected by PA is the result of aldosterone effect on the central nervous system or the

236   consequence of uncontrolled blood pressure is still an open question.[30]

237   In the QUALITO study we compared, for the first time, the QOL of patients affected by PA to

238   the QOL of carefully matched patients affected by EH, as control group. The scores of patients

239   affected by PA were lower than healthy subjects, but not different from those of patients

240   affected by EH, suggesting that the impairment of QOL in PA could be attributable to

241   uncontrolled blood pressure and anti-hypertensive treatment, more than a direct effect of

242   aldosterone excess.

243   Female sex, obesity and metabolic syndrome have been related to reduced QOL in previous

244   studies.[3,31] Supporting these findings, in our study, sex female had a significant negative impact

245   on 6 of 8 domains, including both physical and emotional subscales; similarly, high BMI had

246   a significant negative impact in role limitations due to physical health problems and general

247   health perception. Considering the known relationship between primary aldosteronism, obesity

248   and metabolic syndrome, it is possible that the coexistence of these conditions may

249   synergistically contribute to the reduction of QOL in patients with PA.[32]

250   In agreement with previous studies,[2–4,7] we observed that both surgical and medical treatments

251   for PA induced a significant improvement in QOL, that was remarkably more pronounced in

252   the surgery group compared with the MR antagonist group. The optimization of anti-

253   hypertensive treatment, without MR blockade, in patients affected by EH, resulted into a

254   minimal increase in only one of 8 domains of QOL. This result suggests that reduction of blood

255   pressure levels *per se*, is probably not sufficient for a significant improvement of QOL and that

256   a specific role for MR antagonists, beyond its anti-mineralocorticoid activity, can be

257   hypothesized.

258   Multiple factors are likely working synergistically, reducing QOL in patients with hypertension

259   and PA, including disease awareness, medical treatment and uncontrolled blood pressure.

260   Knowledge of the disease is a key component of impaired QOL in many conditions. Patients

261   aware of the diagnosis of arterial hypertension have lower QOL than patients unaware of the

262   disease, independently of blood pressure levels.[33] Therefore, patients' perception of PA-related

263   cardiovascular risk, the need of invasive procedure for subtype diagnosis (such as adrenal

264   venous sampling) and lifestyle recommendations (such as dietary modification) can further

265   impact their QOL. In our study, the questionnaire was administered before PA diagnosis, thus

266   eliminating the potential bias of disease-awareness.

267   Another important factor affecting the QOL is represented by anti-hypertensive treatment. In a

268   previous study, the QOL in physical and mental components was higher in patients taking < 4

269   anti-hypertensive medications than in patients taking a higher number of drugs. The association

270   between number of drugs and mental component was significant even after correction for the

271   main confounding factors including blood pressure levels.[34] We confirmed this finding,

272   reporting lower QOL in patients with DDD≥3 than patients with DDD<3 at baseline evaluation,

273   independently from the final diagnosis (PA or EH).

274   In our study, patients treated with MR antagonist or optimization of anti-hypertensive treatment

275   achieved blood pressure control by increase of drug treatment. On the counterpart, six months

276   after surgery, the mean DDD dropped to less than 1 in patients adrenalectomized. This

277   difference probably contributes to the significant improvement in QOL observed in patients

278   undergoing surgical treatment for unilateral PA, allowing a normalization of QOL scores in 7

279   of 8 domains, compared to healthy subjects.

280   Among patients with hypertension under anti-hypertensive treatment, the highest QOL in

281   physical component is encountered in those with SBP around 125 mmHg and DBP around 75

282   mmHg.[34] After surgery, adrenalectomized patients displayed lower blood pressure levels than

283 patients under MR antagonist or general anti-hypertensive treatment, with values close to the

284 figures reported above. Therefore, beyond reduction of anti-hypertensive treatment, the

285 achievement of lowest blood pressure could probably contribute to the better quality of life in

286 adrenalectomized patients.

287 The importance of psychosocial stress in arterial hypertension has been largely evaluated in

288 the last decade. A recent study expanded this concept, introducing and highlighting the

289 importance of allostatic load in arterial hypertension.[35] Allostatic load is the reflection of

290 cumulative effects of daily life experiences, including ordinary and extra-ordinary events.[36]

291 Allostatic load is significantly more prevalent in patients with arterial hypertension than

292 individuals with normotension and patients with hypertension and allostatic load display

293 significantly decreased quality of life.[35] The role of allostatic load in PA has never been

294 evaluated. This aspect should probably be investigated in future studies to better elucidate the

295 development of impaired QOL in PA.

296 Patients with PA treated with MR antagonist displayed a significant increase in the score

297 related to physical functioning and general health perceptions. In particular, the physical

298 functioning score was significantly higher after 6 months, compared to patients with EH treated

299 with medical treatment, without MR blockade. This finding may suggest a direct role of MR

300 antagonist in the improvement of physical functioning, beyond blood pressure control *per se*.

301 High aldosterone levels have been associated with significantly lower exercise capacity in

302 patients with chronic heart failure,[37] and spironolactone significantly improved exercise

303 tolerance.[38] Spironolactone may act by reduction of myocyte apoptosis and enhancing of

304 skeletal muscle contractility.[39]

305 The limits of our study are the absence of a control group of patients with PA treated with

306 optimization of medical treatment without MR blockade, the absence of a control group of

307 patients with EH treated with MR antagonist, the absence of a control group of normotensive

308 subjects collected in the same setting and the lack of anxiety and depression symptoms

309 evaluation. The strengths and novelties of this study are the comparison of QOL of patients

310 with PA with matched patients with EH, the comparison of specific treatments for PA

311 (adrenalectomy and MR antagonist) *versus* optimization of medical treatment in a similar

312 group of patients, the diagnosis and subtype diagnosis of PA according to guidelines, and the

313 administration of the first questionnaire for QOL assessment before PA diagnosis.

314 In conclusion, patients with PA displayed lower QOL than healthy subjects, but not different

315 from matched patients with EH. Treating patients affected by APA with surgical adrenalectomy

316 allows a better control of blood pressure levels, with lower anti-hypertensive treatments,

317 reaching a significantly higher QOL at medium term follow up than medical therapy alone.

318 Treatment with MR antagonist allows a significant improvement in physical aspects of QOL

319 compared to optimization of medical therapy without MR blockade.

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324 and M.T. collected data; F.B., M.A., J.B. analyzed data; S.M., P.M. and F.V. supervised the

325 entire study; F.B., G.C., S.M., P.M. wrote the original draft; all authors reviewed and edited

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441 **Figure Legends**

442 **Figure 1.** Baseline QOL: PA vs. EH-matched controls and healthy subjects. Comparisons were

443 performed by paired t-test for PA vs. EH and unpaired t-test for PA vs. healthy subjects.

444 QOL=quality of life, PA=primary aldosteronism, EH=essential hypertension, PF=physical

445 functioning, RLP=role limitations due to physical problems, RLE=role limitations due to

446 emotional problems, V=vitality, GMH=general mental health, SF=social functioning,

447 BP=bodily pain, GHP=general health perceptions. * = significant at p<0.05 PA vs. healthy

448 subjects.

450 **Figure 2.** Longitudinal comparison of QOL and cross-sectional comparison at 6 months in

451 patients with different treatments. Comparisons are considered significant at at p<0.05. Figure

452 2A-2B-2C: * = 6 months vs. Time 0, † = 2 months vs. Time 0. Figure 2D: * = adrenalectomy

453 vs. general anti-HT treatment, † = MR antagonist vs. general anti-HT treatment, ‡ =

454 adrenalectomy vs. MR antagonist. Estimated mean scores comparison have been performed by

455 linear mixed models (details in Supplemental Methods).

457 PF=physical functioning, RLP=role limitations due to physical problems, RLE=role limitations

458 due to emotional problems, V=vitality, GMH=general mental health, SF=social functioning,

459 BP=bodily pain, GHP=general health perceptions, MR=mineralocorticoid receptor, anti-

460 HT=anti-hypertensive.

462 **Figure 3.** Six months QOL: patients treated with ADX and MRA vs. healthy subjects. * =

463 significant at p<0.05 adrenalectomy vs. healthy subjects, † = MR antagonist vs. healthy

464 subjects. Comparisons were performed by unpaired t-test.

465 PF=physical functioning, RLP=role limitations due to physical problems, RLE=role limitations

466 due to emotional problems, V=vitality, GMH=general mental health, SF=social functioning,

467 BP=bodily pain, GHP=general health perceptions, MR=mineralocorticoid receptor.

471 **Table 1.** Descriptive Statistics

	PA (n = 70)	EH (n=70)	p-value
Age (years)	52±9	54±10	0.199

Sex
    Male
    Female
	
	45 (64.3)
	25 (35.7)
		
		45 (64.3)
		25 (35.7)
			1.000

SBP (mmHg)	146±14	143±13	0.118
DBP (mmHg)	90±10	90±9	0.806
DDD	3.02±1.46	2.83±1.35	0.427
Duration of hypertension (years)	5 (1-10)	7 (1-16)	0.233
Creatinine (mg/dl)	0.87±0.21	0.91±0.19	0.385
Sodium (mmol/l)	141±2	142±2	0.103
Potassium (mmol/l)	3.6±0.5	4.1±0.4	<0.001
BMI (kg/m^2)	25.9±4.1	26.9±5.4	0.196

Type 2 diabetes mellitus
    No
    IFG
    Diabetes
	
	67 (95.7)
	3 (4.3)
	-
		
		66 (94.3)
		4 (5.7)
		-
			0.698

Presence of comorbidity by CCI	9 (12.8)	20 (28.6)	0.152

472 PA=primary aldosteronism, EH=essential hypertension, SBP=systolic blood pressure, DBP=diastolic
473 blood pressure, DDD=daily defined dose, BMI=body mass index, IFG=impaired fasting glucose,
474 CCI=Charlson Comorbidity Index. Comparisons were performed by unpaired *t*-test for continuous
475 variables and $\chi 2$ test for categorical variables.

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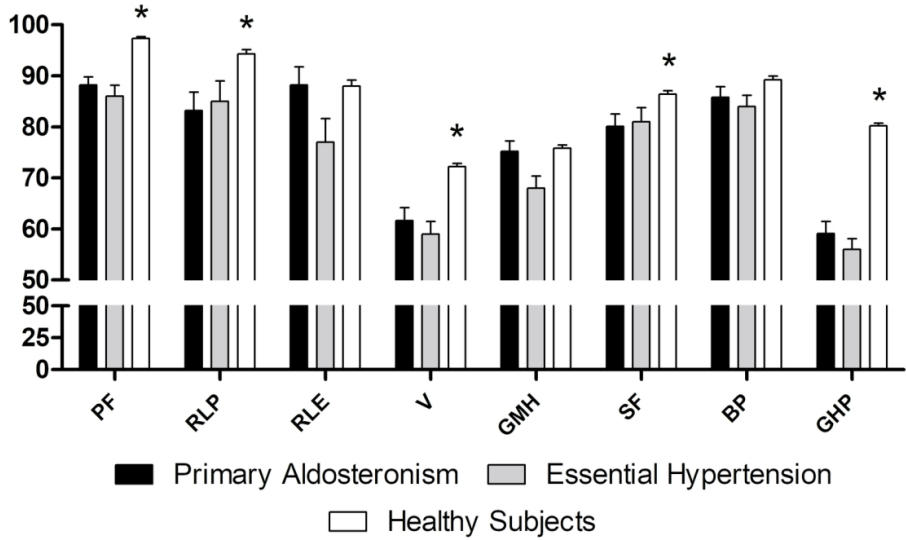43
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Figure 1. Baseline QOL: PA vs. EH-matched controls and healthy subjects.
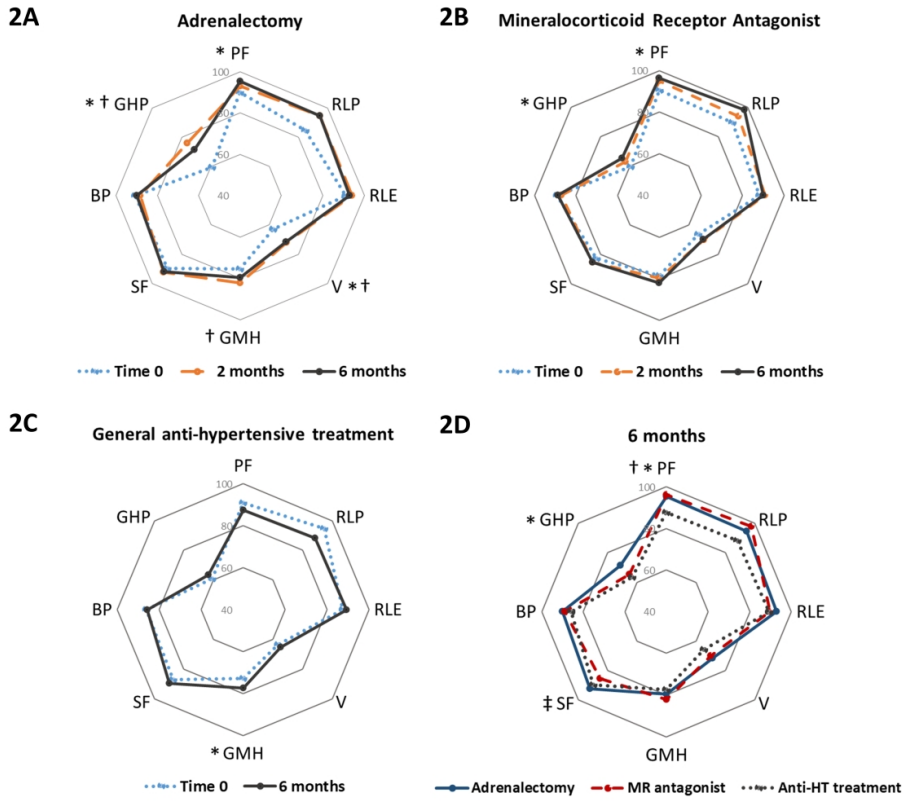
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Figure 2. Longitudinal comparison of QOL and cross-sectional comparison at 6 months in patients with different treatments.

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