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Adrenal Insufficiency among Older People: An Insight from Qatar

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Abstract

Background: Adrenal Insufficiency (AI), a medical emergency disorder, usually starts with symptoms such as tiredness, fever, gastrointestinal discomfort which may progress to adrenal crisis combined with severe electrolyte imbalance. The current study results are important to provide insights since it was conducted among a seldom-studied population, i.e., elderly gulf arabs and compared with a broad variety of possible clinical correlates in statistical testing.

Methods: A retrospective review of electronic Cerner data was used to identify the cases reported on the prevalence of adrenal insufficiency in cohorts of at least 117 individuals aged 65 years and above living in Qatar, together with criteria used to define AI. The patient population included both males and females. The purpose of the current study is to measure the point prevalence of adrenal insufficiency based on the analysis conducted among hospitalized elderly people (age >65 years) in Qatar. The data was collected for a number of comorbidities including dyslipidemia, renal failure, dementia, congestive heart failure, coronary artery disease, cerebrovascular disease, chronic Obstructive pulmonary disorder (COPD), type 2 diabetes, and hypertension.

Results: Of the 117 people in the sample, 51 (43.59%) were diagnosed with adrenal insufficiency. The point estimate of the prevalence of AI was 0.436 as noted. The prevalence of AI among the Qatari population aged above 65 was between 34.470% and 52.71%.

Conclusion: It was found that the women were 1.98 times more likely to be adrenally insufficient than men. The type 2 diabetes is a significant predictor of AI (p=0.037) i.e., if someone has type 2 Diabetes, then they are 2.36 times likely to have adrenal insufficiency than those without Type 2 Diabetes. Finally, Cerebrovascular disease (CVA) is a significant predictor of adrenal insufficiency (p=0.051), as someone with CVA is 2.19 times more likely than without CVA to suffer from adrenal insufficiency. The study also showed that the cortisol level of individuals with adrenal insufficiency was statistically very low (p<.001) among elderly, than the baseline cortisol level of individuals without adrenal insufficiency.

Keywords: Adrenal insufficiency; Older people; Prevalence; Comorbidities

Abbreviations: AI: Adrenal Insufficiency; ACTH: Adreno Cortico Trophic Hormone; OR: Odd's Ratio; HGH: Hamad General Hospital; RH: Rumailah Hospital; COPD: Chronic Obstructive Airway Disease; DM: Diabetes Mellitus; IRB: Institutional Research Board.

Introduction

Adrenal insufficiency, also known as Addison's disease, can occur due to both primary and secondary means [1-3]. In primary adrenal insufficiency, the damage to the adrenal glands results in the inadequate production of adrenocortical hormones [1,4-7]. In secondary adrenal insufficiency, the pituitary gland diseases decrease the production of adrenocorticotropic hormone which signals the adrenal cortex to begin hormonal production [8-10]. The symptoms of adrenal insufficiency, whether primary or secondary, include fatigue, weight loss, reduced appetite, hyperpigmentation, hypoglycemia, salt cravings, nausea, muscle and joint pain, depression and irritability; if untreated, adrenal insufficiency leads to death [1-14].

The prevalence of adrenal insufficiency has been estimated in a number of studies by numerous public health authorities [11,13,14]. According to Arlt and Allolio's systematic literature review, the prevalence of primary adrenal insufficiency is between 93-140 per million, while it is between 150 and 280 per million in case of secondary adrenal insufficiency. Thus, combining these estimates, the prevalence of adrenal insufficiency could be calculated somewhere between 243 and 420 per million. According to a systematic review conducted by Løvås and Husebye [13], the incidence of adrenal inusfficiency among all caucasians is between 39 and 117 per million; the authors carried out a prevalence study in western Norway and found that the prevalence was 140 per million.

However, adrenal insufficiency is far more common among the elderly humans across the globe [12]. The purposes of the current study are to (a) measure the prevalence of adrenal insufficiency based on the retrospective analysis of data of 117 hospitalized elderly people (age >65 years) patient from 500 random sample during study period in tertiary hospital in Qatar; (b) identify the clinical correlates of adrenal insufficiency; and (c) measure the relationships among cortisol levels, cortisol responses, and adrenal insufficiency. These analyses were, as noted, conducted among 117 patients whose mean age was 81.25 (*SD*=7.256), of whom 60 were females and 57 were males, and who were presented to the hospital under a variety of admitting conditions, predominantly, pneumonia (*n*=27 or around 23% of the sample).

The statistical part has been divided into empirical analysis and discussion sections. The empirical analysis section contains the results of the various statistical procedures performed to achieve the purpose of the study which were reframed as the following research questions:

RQ1: What is the point prevalence of adrenal insufficiency among a sample of hospitalized elderly people (age >65 years)

RQ2: What are the correlates of adrenal insufficiency among a sample of hospitalized elderly people (age >65 years)

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RQ3 • What are the relationships exist among cortisol levels, cortisol responses, and adrenal insufficiency among a sample of hospitalized elderly people (age >65 years)

The results are unique to provide insights since it is being conducted among a seldom-studied population, i.e., elderly Gulf Arabs, and for the inclusion of a broad variety of possible clinical correlates in statistical testing.

Methods

The research materials included patient chart reviews, electronic data and evidence-based research papers that were collated between Jan 2004 to Dec 2013 provided that they fulfill the inclusion and exclusion criteria. The research team members extracted further relevant data from the medical records of the included patients using a standardized data extraction sheet. Geriatric patients, who are 65-years-old and above in HGH, admitted during this period, were considered as the test group in this study. The data was analyzed and the results were compared, in the order of diagnosed AI.

Statistical analysis

The data is presented as proportions, medians or mean ±SD wherever applicable. The continuous variables were analysed using student's tests or one-way ANOVA. Further, a non-parametric Mann–Whitney test was used for skewed continuous data. All the p-values presented were two-tailed and the p-values <0.05 were considered statistically significant. All the statistical analyses were performed using statistical packages SPSS 19.0 (SPSS Inc. Chicago, IL). The primary outcome variable i.e., the prevalence of adrenal insufficiency in elderly (aged >65 years) Qatari patients was estimated and tested using appropriate Z-test and corresponding 95% CI was computed to measure the precision of the estimate. Chi-square test or Fisher exact test was used to examine and assess the association of serum cortisol response to standard ACTH stimulation test (Synacthene test) in elderly aged >65years. Secondary endpoints were included to determine any difference in the basal serum cortisol levels at 8 am in the test group (aged >65 years) and to identify the clinical correlates for primary adrenal insufficiency. The results were presented with associated 95% confidence interval. The associations between two or more categorical variables were assessed using chi-square test and fisher exact test as appropriate. The chi-square test for trend analysis was used to study the trend in the prevalence of adrenal insufficiency in elderly patients (aged >65 years). The relationship between two quantitative variables was examined using Pearson's correlation coefficients.

Aim of the study

To study the point prevalence of adrenal insufficiency in elderly (aged >65 years) Qatari patients attending Hamad General Hospital.

Specific objective

To assess the serum cortisol response to standard ACTH stimulation test (Synacthene test) in elderly patients aged >65years.

Secondary objectives

- To assess the basal serum cortisol levels at 8 am in elderly Qatari (aged >65years).

- To identify the clinical correlates for primary adrenal insufficiency among elderly Qatari patients.

AI definition

Adrenal Insufficiency can be diagnosed by low cortisol levels at 8 am which can be assessed through ACTH stimulation test. Low cortisol levels after a dose of ACTH confirms that the patient has primary adrenal insufficiency or Delta rise of serum cortisol >9 after ACTH stimulation test.

ACTH stimulation test: To perform this test, a blood sample is taken at any time of the day to measure baseline cortisol level. A high dose 250 microgram ACTH (co-syntropin) is intravenously injected and blood sample is taken at intervals of 30 minutes and 60 minutes respectively to measure cortisol level. Low cortisol, after a dose of ACTH, confirms the diagnosis.

Study design: Retrospective, descriptive.

Sample size: 117 patients who underwent ACTH stimulation test between Jan 2004 to Dec 2013.

Inclusion criteria

- Elderly aged >65years admitted to Hamad General Hospital between January 2004 to December 2013.

- Both genders.

Exclusion criteria

- Non-Qatari patients.

- Patients on drugs which suppress HPA axis like ketoconazole, Metyrapone, Aminoglutethimide.
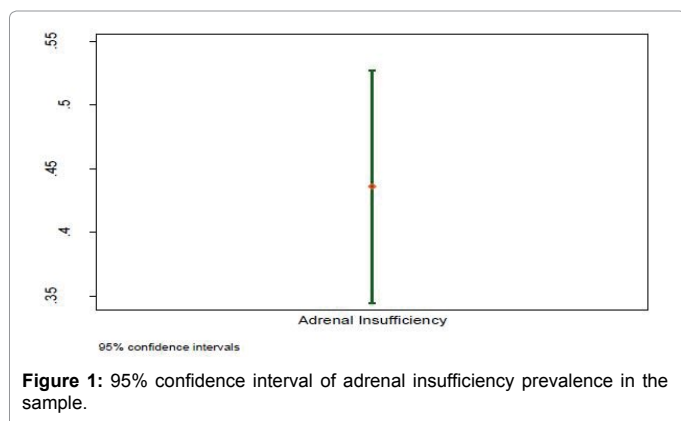
Procedure for research data collection

The research team identified the medical records with the help of HIS. All the patients who underwent ACTH stimulation test in HGH between January 2004 and December 2013 were recruited provided they fulfill the inclusion and exclusion criteria. Trained nursing staff were recruited to extract further relevant data from the Medical records of the included patients using a standardized data extraction sheet. Inter-rater reliability was calculated from a small sub-sample of five clinical records.

Results

Of the 117 suspected cases in the total sample, 51 (43.59%) were diagnosed with adrenal insufficiency by co-syntropin test according to diagnostic criteria. In order to rule out the possibility that adrenal insufficiency is a factor of age, age was regressed on the dichotomous outcome variable of adrenal insufficiency and was found not to be a significant predictor, $\chi^2=0.49$, $p=0.48$ ($b=-0.02$, $OR=0.98$). As the b coefficient was close to 0, and the Odds Ratio (OR) to 1, it is clear that there is an essentially undetectable influence of age on adrenal insufficiency exists.

The Medical Research Center at Hamad Medical Corporation, Qatar provided the ethics approval to conduct the study (IRB# 14501/14). The point estimate of the prevalence of adrenal insufficiency was 0.44 as noted above. The 95% Confidence Interval of the point estimate for the prevalence of adrenal insufficiency was calculated binomially and found to be between 0.35 and 0.54 (Figure 1). Thus, it can be calculated that the prevalence of adrenal insufficiency among the Qatari population aged above 65 is between 34.47% and 52.71%.

Figure 1: 95% confidence interval of adrenal insufficiency prevalence in the sample.

Figure 2: 95% confidence interval of adrenal insufficiency prevalence in the sample, sorted by gender.

Figure 3: Boxplot of baseline cortisol sorted by of adrenal sufficiency and insufficiency.

Gender and adrenal insufficiency

There is an interesting perspective on whether the prevalence of adrenal insufficiency varies by gender. A tabulation indicated that, out of the 60 women studied, 31 were adrenally insufficient, whereas, it was only 20 men who were adrenally insufficient out of the 57 men in the sample. Using an OR calculation within a logistic regression model, it was found that the women were 1.977 times more likely than men (*OR* 95% confidence interval=0.940 to 4.158) to be adrenally insufficient and at α value of 0.10, this difference is statistically significant, *p=0.070*.

Segmenting the sample by gender, it was found that the point estimate for the prevalence of adrenal sufficiency among men was 0.3509 (95% Confidence Interval=0.223 to 0.479), whereas the point estimate for the prevalence of adrenal sufficiency among women was 0.517 (95% Confidence Interval=0.387 to 0.647). The difference between male and female prevalence of adrenal insufficiency is illustrated in the Figure 2. Thus, gender is a significant predictor of adrenal insufficiency in the sample with women found to be more likely to suffer from adrenal insufficiency than men (Figure 2).

Thus, gender was a significant predictor of adrenal insufficiency in the sample with women found to be more likely to suffer from adrenal insufficiency than men.

Baseline cortisol

One predictor of adrenal insufficiency was baseline cortisol. The baseline cortisol level of individuals with adrenal insufficiency was 259.078 (*SD*=153.672), whereas the baseline cortisol level of individuals without adrenal insufficiency was 428.905 (*SD*=26.06). This difference is statistically significant, t (112)=4.87, $p<.001$, and illustrated in the Figure 3. The baseline cortisol for all subjects was 352.93 (*SD*=202.77). The baseline cortisol was not distributed normally, Shapiro-Wilk W=0.974, p=.023. The baseline cortisol values ranged from 12 to 921 in which 915 and 921 were outliers in the dataset and both values were over 2.75 standard deviations from the mean (Figure 3).

Comorbidities and adrenal insufficiency

The data was collected for a number of comorbidities, including dyslipidemia, renal failure, dementia, congestive heart failure, Coronary Artery Disease, cerebrovascular disease, Chronic Obstructive Pulmonary Disorder (COPD), type II diabetes, and hypertension. Each of these comorbidities was examined with respect to its predictive power over adrenal insufficiency.

A logistic regression indicated that hypertension is not a significant predictor of adrenal insufficiency based on the values χ^2=0.610,
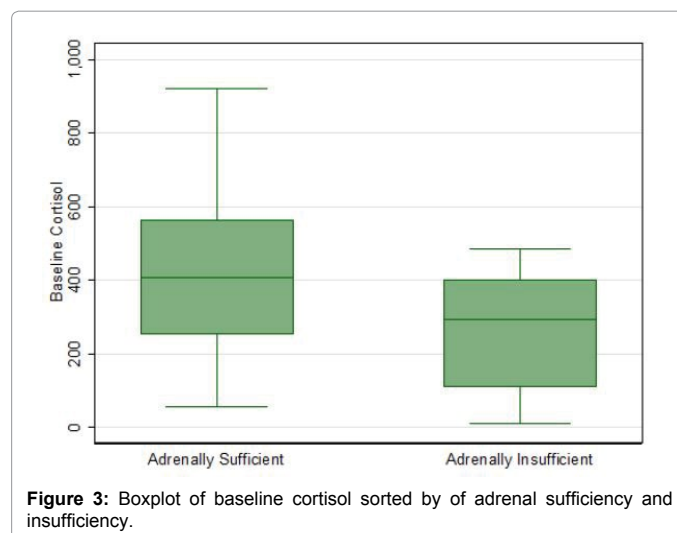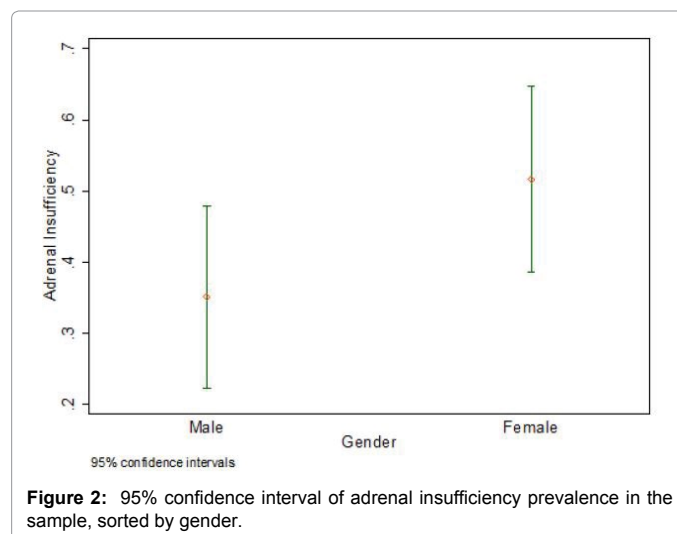
p=0.434, OR=0.712 (95% confidence interval of OR=0.303 to 1.669). As the OR included 1 in its Confidence Interval, and as the *p-value* for the logistic regression was >.10, it can be concluded that hypertension did not significantly increase the odds of getting affected by adrenal insufficiency.

A logistic regression indicated that type II diabetes is a significant predictor of adrenal insufficiency based on the values, χ^2=4.330, p=0.037, OR=2.364 (95% confidence interval of OR=1.030 to 5.421). As the OR did not include 1 in its Confidence Interval, and as the *p-value* for the logistic regression was<.10, it can be concluded that type II diabetes significantly increase the odds of getting affected by adrenal insufficiency. Someone with type II diabetes is 2.364 times as likely as someone without diabetes to have adrenal insufficiency.

A logistic regression indicated that asthma is not a significant predictor of adrenal insufficiency based on the values, χ^2=0.110, p=0.739, OR=0.830 (95% Confidence Interval of OR=0.275 to 2.504). As the OR included 1 in its confidence interval, and as the *p-value* for the logistic regression was >0.10, it is concluded that asthma did not significantly increase the odds of getting affected by adrenal insufficiency.

A logistic regression indicated that COPD is not a significant predictor of adrenal insufficiency based on the values, χ^2=2.070,

Variables	OR	SE	z	p	95% Confidence Interval	
					Lower	Upper
Hypertension	0.734046	0.374962	-0.61	0.545	0.269722	1.997699
Type 2 DM	0.911741	0.456774	-0.18	0.854	0.341529	2.433971
Asthma	1.097248	0.712619	0.14	0.886	0.307244	3.918558
COPD	0.21276	0.24314	-1.35	0.176	0.022654	1.998187
Cerebrovascular Disease	1.105708	0.516378	0.22	0.83	0.442711	2.761603
Coronary Artery Disease	1.271965	0.573738	0.53	0.594	0.525447	3.079086
Congestive Heart Failure	0.771128	0.658106	-0.3	0.761	0.144771	4.107428
Dementia	0.648057	0.365059	-0.77	0.441	0.214842	1.95482
Dyslipidemia	1.329501	0.838666	0.45	0.652	0.386136	4.577594
Renal Failure	1.07048	0.467564	0.16	0.876	0.454769	2.5198
Gender	1.818387	0.761375	1.43	0.153	0.800351	4.13135
Constant	0.739604	0.429364	-0.52	0.603	0.237055	2.307543

Table 1: Logistic regression model, comorbidities, gender, and adrenal insufficiency.

$p=0.150$, $OR=0.240$ (95% confidence interval of $OR=0.027$ to 2.157). As the OR included 1 in its confidence interval, and as the *p-value* for the logistic regression was >.10, it can be concluded that COPD did not significantly increase the odds of getting affected by adrenal insufficiency.

A logistic regression indicated that cerebrovascular disease is a significant predictor of adrenal insufficiency based on the values, $\chi^2=3.800$, $p=0.051$, $OR=2.188$ (95% confidence interval of $OR=0.990$ to 4.831). As the OR did not include 1 in its Confidence Interval, and as the *p-value* for the logistic regression was<.10, it can be concluded that cerebrovascular disease significantly increases the odds of getting affected by adrenal insufficiency. Someone with cerebrovascular disease is 2.188 times more likely to suffer from adrenal insufficiency than someone without cerebrovascular disease.

A logistic regression indicated that congestive heart failure is not a significant predictor of adrenal insufficiency based on the values, $\chi^2=0.130$, $p=0.717$, $OR=0.762$ (95% confidence interval of $OR=0.173$ to 3.351). As the OR included 1 in its confidence interval, and as the *p-value* for the logistic regression was >.10, it can be concluded that congestive heart failure did not significantly increase the odds of getting affected by adrenal insufficiency.

A logistic regression indicated that coronary artery disease is not a significant predictor of adrenal insufficiency based on the values, $\chi^2=0.300$, $p=0.581$, $OR=1.232$ (95% confidence interval of $OR=0.587$ to 2.587). As the OR included 1 in its confidence interval, and as the *p-value* for the logistic regression was >.10, it can be concluded that coronary artery disease did not significantly increase the odds of getting affected by adrenal insufficiency.

A logistic regression indicated that renal failure is not a significant predictor of adrenal insufficiency based on the values, $\chi^2<0.001$, $p=0.959$, $OR=0.980$ (95% confidence interval of $OR=0.447$ to 2.150). As the OR included 1 in its confidence interval, and as the *p-value* for the logistic regression was >.10, it can be concluded that renal failure did not significantly increase the odds of getting affected by adrenal insufficiency.

A logistic regression indicated that dyslipidemia is not a significant predictor of adrenal insufficiency, $\chi^2=0.260$, $p=0.608$, $OR=1.341$ (95% confidence interval of $OR=0.438$ to 4.1501). As the OR included 1 in its confidence interval, and as the *p-value* for the logistic regression was >.10, it can be concluded that dyslipidemia did not significantly increase the odds of getting affected by adrenal insufficiency.

A logistic regression indicated that dementia is not a significant predictor of adrenal insufficiency based on the values, $\chi^2=0.190$, $p=0.661$, $OR=0.795$ (95% confidence interval of $OR=0.285$ to 2.22). As the OR included 1 in its confidence interval, and as the *p-value* for the logistic regression was >0.10, it is concluded that dementia did not significantly increase the odds of getting affected by adrenal insufficiency.

Therefore, mentioned logistic regressions were performed in a univariate manner. In order to test the possible impact of covariates, all the ten comorbid conditions were regressed on the dependent value of adrenal insufficiency. In addition, gender was included as an explanatory variable. The logistic regression model results are presented in Table 1.

Age and adrenal insufficiency

One of the unexpected findings in the study is the statistically insignificant relationship between age and adrenal insufficiency. The age range of individuals with and without adrenal insufficiency overlapped each other. Using an independent samples *t*-test, it was found that the mean age of individuals with adrenal insufficiency ($M=80.72$, $SD=7.95$) is not significantly different from the mean age of individuals without adrenal insufficiency ($M=81.66$, $SD=6.70$). This finding is different from the findings obtained by Chen et al., in which the prevalence rates of adrenal insufficiency were observed to increase in a roughly linear fashion as the age of individuals in the sample increased. Based on Chen empirical findings and for theoretical reasons as well, it is of special interest that the findings of the current study did not disclose a statistically significant effect of age on adrenal insufficiency.

Discussion

The main findings of the study are discussed in the order of research questions. The first research question is as follows; What is the prevalence of adrenal insufficiency among a sample of hospitalized elderly people (age >65 years) . The point estimate of the prevalence of adrenal insufficiency was 0.44. The 95% Confidence Interval of the point estimate for the prevalence of adrenal insufficiency was between 34.47% and 52.71%.

The second research question is as follows: What are the correlates of adrenal insufficiency among a sample of hospitalized elderly people (age >65 years). Using an OR calculation within a logistic regression model, it was found that the women were 1.98 times more likely than men (*OR* 95% confidence interval=0.94 to 4.16) to be adrenally insufficient, and at α value of .10, this difference is statistically

significant, $p=0.07$. Additionally, a logistic regression indicated that type 2 diabetes is a significant predictor of adrenal insufficiency based on the values, $\chi^2=4.33$, $p=0.04$, $OR=2.36$ (95% confidence interval of $OR=1.03$ to 5.42). Someone with type 2 Diabetes is 2.36 times as likely as someone without Type 2 Diabetes to have adrenal insufficiency. Finally, a logistic regression indicated that cerebrovascular disease is a significant predictor of adrenal insufficiency based on the values, $\chi^2=3.80$, $p=0.05$, $OR=2.19$ (95% confidence interval of $OR=0.99$ to 4.83). Someone with cerebrovascular disease is 2.19 times more likely than someone without cerebrovascular disease to suffer from adrenal insufficiency.

The third research question is as follows: What are the relationships among the cortisol levels, cortisol responses, and adrenal insufficiency among a sample of hospitalized elderly people (age >65 years. The baseline cortisol level of individuals with adrenal insufficiency was 259.078 ($SD=153.672$), whereas the baseline cortisol level of individuals without adrenal insufficiency was 428.905 ($SD=26.060$). This difference is statistically significant with the values, $t(112)=4.873$, $p<0.001$.

The prevalence findings of the study are highly dissimilar to previous findings and therefore deserve a more extensive discussion. For example, Chen et al. (2010) discovered that adrenal insufficiency in an elderly (age >60) population in Taiwan was at a rate of 2,080 per million, or 0.002, whereas the overall adrenal insufficiency prevalence identified in the current study is 0.436, or 218,000 times higher than Chen et al.'s point estimate.

The study has some limitations. This finding is likely to be due to the fact that the suspected AI of 117 individuals in the sample did not represent real representation of random cross-section of elderly hospitalized elderly patients. The point prevalence was underestimated because those patients who are hospitalized only were included in the study. This study did not analyze the severity of AI among elderly and out come with medication. Three of the 117 individuals in the sample were already diagnosed with adrenal insufficiency, and a number of remaining individuals reported to the hospital for complaints that could have been related to, or somehow comorbid with, adrenal insufficiency. There is no cut off value for cortisol level to diagnose AI among older people which can lead to underestimation of many cases suffering from disease. So further prospective, the study is required to define AI with respect to cortisol level in older people. A better point estimate for adrenal insufficiency in the sample is that of 3 / 117, or 0.026. The 95% Confidence Interval of the point estimate of 0.026 is from 0.005 to 0.073. These figures are much closer to Chen [12] point estimate for the prevalence of adrenal insufficiency among an elderly (age >60) sample in the country of Taiwan. Although Chen et al. did not reported the Confidence Interval for their point estimate of 0.002, it is possible that the point estimate of 0.026 made in the current study might fall within the 95% Confidence Interval identified by Chen et al.

The revised prevalence estimate is even quite high, not only in comparison to Chen [12] point estimate, but to the general point estimates discussed in the introduction section. The magnitude of the point estimate, if it is indeed a valid reflection of the true prevalence of adrenal insufficiency, in an elderly population, has several important implications. First, it is possible that adrenal sufficiency increases radically after 65. Chen et al.'s analysis was carried out on the basis of a sample that included numerous individuals aged 60-64; indeed, Chen's tabulation [12] identified a pattern of rising adrenal insufficiency incidence in age bands. For example, the female adrenal insufficiency prevalence in the 60-64 age band of Chen et al.'s study was 365 per million, whereas the adrenal insufficiency prevalence in the 85-89+

age band was 1,860.800. The higher prevalence estimate in the current study could be due to the exclusion of individuals aged 60-64, who were included in Chen et al.'s study [12].

Conclusion

The point estimate of the prevalence of adrenal insufficiency was 0.44. It was found that the women were 1.98 times more likely to be adrenally insufficient than men. Type 2 diabetes is a significant predictor of AI (p=0.037) i.e., if someone has type 2 Diabetes, they are 2.36 times likely to have adrenal insufficiency than those without Type 2 Diabetes. Finally, Cerebrovascular disease (CVA) is a significant predictor of adrenal insufficiency (p=0.051), as someone with CVA is 2.19 times more likely to suffer from adrenal insufficiency than without CVA. The study also showed that the cortisol level of individuals with adrenal insufficiency was statistically very low (p<.001) among elderly than the baseline cortisol level of individuals without adrenal insufficiency.

Ethics Approval and Consent to Participate

The Medical Research Center at Hamad Medical Corporation, Qatar provided the ethics approval to conduct the study (IRB# 14501/14). Waiver consent was taken by principal investigator from all file review.

Consent for Publication

We declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. We know of no conflicts of interest associated with this publication, and there has been no significant financial support for this work that could have influenced the outcome.

Availability of data and materials

Available on request

Competing interests

None declared

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Authors Contributions

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