**Table 1. Characteristics of the patients in the case group**

|  |  |
| --- | --- |
| **Characteristics** | **Case Group (n = 93)** |
| **Dichotomous variables, No. (%)** |  |
| Fever | 2 (2.15) |
| Weight loss | 1 (1.08) |
| Large lymph node | 2 (2.15) |
| Swelling parotid/lacrimal/submaxillary glands | 2 (2.15) |
| Joint pain | 6 (6.45) |
| Synovitis | 1 (1.08) |
| Erythema | 3 (3.23) |
| Interstitial lung changes | 2 (2.15) |
| Proteinuria > 0.5g/24h | 2 (2.15) |
| Active myositis | 0 (0.00) |
| Abnormal peripheral sensation | 0 (0.00) |
| Central neuropathy | 0 (0.00) |
| NE < 1 (10×9) /L | 1 (1.08) |
| HB < 120 g/L | 3 (3.23) |
| PLT <100 (10×9) /L | 4 (4.30) |
| **Continuous variables** |  |
| C3, g/L | 1.02 ± 0.24 |
| C4, g/L | 0.22 ± 0.07 |
| IgG, g/L | 13.20 (10.75, 15.85) |
| ESSDAI | 0 (0, 2) |

Dichotomous variables date are presented as n (%), normal variables are presented as mean ± standard deviation, and non-normal variables are presented as median (interquartile).

NE: neutrophilic granulocyte; HB: hemoglobin; PLT: platelet; C3: Complement 3; C4: Complement 4; IgG: immunoglobulin G.

Normal Range: C3 (0.80-1.60) g/L; C4 (0.20-0.40) g/L; IgG (8.00-16.00) g/L.

**Table 2. Descriptive Statistics of the Study Variables in Controls and Cases**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **Cases (n=93)** | **Controls (n =90)** | ***p* value** |
| **Dichotomous variables, No. (%)** | | | |
| Smoker | 1 (1.08) | 2 (2.22) | 0.541 |
| Tea/Coffee addiction | 3 (3.23) | 4 (4.44) | 0.667 |
| Alcohol addiction | 2 (2.15) | 3 (3.33) | 0.624 |
| Hypertension | 15 (16.13) | 14 (15.56) | 0.865 |
| Diabetes | 10 (10.75) | 9 (10.00) | 0.828 |
| E2 < 89.76 (poml/L) | 58 (62.37) | 42 (46.67) | 0.033 |
| **Continuous variables** | | | |
| Age (years) | 56.00 (53.00, 63.00) | 57.00 (55.00, 63.25) | 0.230 |
| Age at menopause (years) | 47.00 (43.50, 52.00) | 48.50 (44.75, 52.25) | 0.188 |
| BMI | 22.22 ± 2.64 | 21.68 ± 2.24 | 0.133 |
| FBG (mmol/L) | 4.65 (4.27, 5.27) | 5.08 (4.12, 6.12) | 0.260 |
| FT4 (pmol/L) | 17.17 ± 3.36 | 16.58 ± 3.43 | 0.247 |
| FT3 (pmol/L) | 5.05 ± 1.19 | 5.04 ± 1.17 | 0.924 |
| TSH (mIU/L) | 2.30 ± 1.24 | 2.13 ± 1.17 | 0.349 |
| E2 (pmol/L) | 84.41 ± 25.25 | 91.57 ± 22.62 | 0.045 |
| Testosterone (nmol/L) | 0.88 (0.70, 1.17) | 0.91 (0.73, 1.20) | 0.741 |
| SHBG (nmol/L) | 96.42 ± 4.61 | 93.55 ± 4.74 | 0.678 |
| FSH (mIU/mL) | 39.67 ± 34.99 | 39.98 ± 24.95 | 0.946 |
| LH (mIU/mL) | 22.18 ± 17.58 | 19.16 ± 13.18 | 0.191 |
| PRL (ug/L) | 14.61 (8.91, 50.99) | 13.10 (6.78, 133.00) | 0.205 |

Dichotomous variables date are presented as n (%), normal variables are presented as mean ± standard deviation, and non-normal variables are presented as median (interquartile).

BMI: body mass index; FBG: fasting blood-glucose; FT3: free triiodothyronine; FT4: free (unbound) thyroxine; TSH: thyroid stimulating hormone; E2: estradiol; SHBG: sex hormone-binding globulin; FSH: follicle stimulating hormone; LH, luteinizing hormone; PRL: prolactin.

**Table 3. Crude and Adjusted OR Values for the Association Between SS and Each Hormone**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables** | **Crude Estimates** | | **Adjusted Estimates** | |
| cOR (95%CI) | *p-*value | aORa (95%CI) | *p-*value |
| **OR values for E2 levels and SS** | | | | |
| E2 | 0.988 (0.975-1.000) | 0.047 | 0.984 (0.971, 0.997) | 0.018 |
| E2 < 89.76 (poml/L) | 1.894 (1.050,3.415) | 0.034 | 2.195 (1.156, 4.165) | 0.016 |
| **OR values for the remaining hormone levels** | | | | |
| SHBG (nmol/L) | 1.001 (0.995, 1.008) | 0.676 | 1.000 (0.994, 1.007) | 0.965 |
| FSH (mIU/mL) | 1.000 (0.990, 1.009) | 0.946 | 1.001 (0.991, 1.011) | 0.887 |
| LH (mIU/mL) | 1.013 (0.994, 1.032) | 0.192 | 1.013 (0.993, 1.034) | 0.200 |
| Testosterone (nmol/L) | 0.952 (0.437, 2.075) | 0.901 | 0.867 (0.379, 1.983) | 0.736 |
| PRL (ug/L) | 1.000 (0.998, 1.002) | 0.807 | 1.000 (0.998, 1.002) | 0.847 |
| TSH (mIU/L) | 1.123 (0.882, 1.431) | 0.347 | 1.105 (0.859, 1.421) | 0.436 |

OR: odds ratio; SS: Sjögren's Syndrome; aOR: adjusted odds ratio; CI: confidence interval; cOR: crude odds ratio; SHBG: sex hormone-binding globulin; FSH: follicle stimulating hormone; LH: luteinizing hormone; E2: estradiol; PRL: prolactin; TSH: thyroid stimulating hormone.

a The following variables were also included in each model: age, menopausal age, body mass index (BMI), smoking, tea/coffee addiction, medical history of hypertension and diabetes and thyroxine levels.

**Table 4. Sensitivity analysis of the causal relationship between** **sex hormones and Sjögren's Syndrome**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Sex hormones** | **Heterogeneity** | | | **Horizontal pleiotropy** | | | **Outlier examination by MR-PRESSO (*p*-value)** | |
|  | IVW Q | IVW Q df | IVW  *p*-value | Intercept | SE | *p*-value | Before correction | After correction |
| **Sjögren's Syndrome as outcome** | | | | | | | | |
| Testosterone in females | 257.460 | 132.000 | 0.000 | 0.004 | 0.007 | 0.586 | 0.206 | 0.392 |
| Testosterone in males | 161.410 | 129.000 | 0.028 | 0.007 | 0.006 | 0.240 | 0.346 | NA |
| E2 in females | 5.785 | 6.000 | 0.448 | 0.013 | 0.035 | 0.726 | 0.103 | NA |
| E2 in males | 13.867 | 10.000 | 0.179 | 0.046 | 0.035 | 0.222 | 0.932 | NA |
| SHBG in females | 202.199 | 149.000 | 0.002 | -0.003 | 0.006 | 0.674 | 0.651 | 0.521 |
| SHBG in males | 187.104 | 162.000 | 0.086 | -0.009 | 0.005 | 0.098 | 0.674 | NA |
| **Sjögren's Syndrome as exposure** | | | | | | | | |
| Testosterone in females | 16.201 | 5.000 | 0.006 | 0.004 | 0.003 | 0.165 | 0.128 | NA |
| Testosterone in males | 16.849 | 5.000 | 0.005 | 0.011 | 0.006 | 0.112 | 0.314 | NA |
| E2 in females | 1.235 | 3.000 | 0.745 | -0.007 | 0.020 | 0.747 | 0.035 | NA |
| E2 in males | 7.992 | 3.000 | 0.046 | 0.028 | 0.037 | 0.525 | 0.923 | NA |
| SHBG in females | 0.595 | 4.000 | 2.783 | 0.000 | 0.005 | 0.953 | 0.149 | NA |
| SHBG in males | 2.121 | 4.000 | 0.714 | -0.002 | 0.005 | 0.714 | 0.513 | NA |

IVW: inverse-variance weighted; E2: estradiol; SHBG: sex hormone-binding globulin; NA: not applicable