Low serum iodine is associated with iodine deficiency and thyroid dysfunctions: a cross-sectional study

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Research Article

Keywords: serum iodine, thyroid dysfunctions, iodine deficiency, adults

Posted Date: June 13th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1730748/v1

Abstract

Background The relationship between low serum iodine and thyroid dysfunctions in adults is not well understood. This study aimed to explore the relationship between serum and urinary iodine and thyroid dysfunctions in the adult population.

Methods: A total of 1320 participants were included in the final analysis. We collected basic demographic information, as well as blood and spot urine samples, to determine serological indices and iodine nutritional status of subjects.

Results: The median (IQR) serum iodine (SI) level was 70.5μg/L (59.6–83.6μg/L). Compared to those with 59.6μg/L ≤ SI < 83.6μg/L, subjects with SI ≤ 59.6μg/L had a higher risk of thyroid dysfunctions (OR = 1.72, 95%CI: 1.08–2.75), clinical hypothyroidism (OR = 16.4, 95%CI: 3.72–72.2) and sUIC < 100μg/L (OR = 1.41, 95%CI: 1.05–2.00). The areas under the ROC curve of SI (0.554, *P* = 0.02) was significantly higher than that of sUIC/UCr (0.446, *P* = 0.005).

Conclusions: Serum iodine is more sensitive than urine iodine in the diagnosis of thyroid dysfunctions. Low serum iodine concentration is associated with an increased risk of thyroid dysfunctions, especially hypothyroidism.

Background

Thyroid hormone is vital for maintaining normal basic metabolism and body growth. Both insufficient and excessive iodine levels can lead to thyroid diseases. Severe iodine deficiency can manifest in the occurrence of goitre and hypothyroidism[1 2], and long-term mild to moderate iodine deficiency can lead to an increased incidence of toxic nodular goiter and hyperthyroidism. Furthermore, excessive serum iodine (SI) levels have been associated with an increased risk of goiter, thyroid nodules, and subclinical hypothyroidism[3 4]. Because of these clinical manifestations, more attention has recently been paid to iodine nutrition in individuals, and an accurate evaluation method for individualized iodine nutrition has been sought[5 6].

Serum iodine is an important biomarker for iodine metabolism. Normally, excess iodine is excreted in the urine[7]. However, long-term excess iodine or iodine deficiency will misalign the body's delicate iodine balance, resulting in abnormal serum iodine levels and eventually thyroid dysfunctions, causing thyroid disease[8].

At present, limited population studies have explored the relationship of serum iodine and iodine nutritional status or thyroid dysfunctions[9–11]. And lacked data on the association between low serum iodine levels and thyroid dysfunctions in adults[9 12]. To further improve the correlation data between low serum iodine and urinary iodine, thyroid dysfunctions, we conducted the cross-sectional study in non-high water iodine areas of Tianjin. This enabled us to explore whether serum iodine can be used as an

indicator to reflect iodine nutritional status and thyroid function to help prevent the occurrence of thyroid disorders.

Methods

Subjects

A cross-sectional survey was undertaken for this study. Areas without high water iodine levels in Tianjin were selected as the survey sites, including the urban areas of Hedong District and the suburban areas of Hangu District. The subjects of this study were individuals with insufficient iodine, adequate iodine, and above requirements iodine levels. The classification of iodine nutritional status is shown in supplemental material[12]. The study population was selected by random cluster sampling[13]. Participants included in the study had lived l ocally for at least five years. Pregnant women, breastfeeding women, and participants who took drugs containing iodine in the last three months were excluded.

PASS (version 15) was used for sample-size calculations. As this study was a cross-over research design, we used the confidence interval (CI) for one proportion for sample size calculation. According to Flores-Rebollar's study[14], the prevalence of clinical hypothyroidism, subclinical hypothyroidism and subclinical hyperthyroidism in healthy adults was 1.8%, 5%, 2.8% and the 1.8% was selected for calculation. the allowable error was set at 1% and the α error was set at 0.05. The calculation revealed a minimum sample size of 789.

Sample collection

Baseline demographic information (gender, age, height, weight) was obtained through questionnaires. Body mass index (BMI) was calculated according to the following formula: BMI = weight (kg)/height ^{2}(m^2) and body surface area (BSA) was calculated according to the following formula: BSA=weight (kg)$^{0.425}$ × height (cm)$^{0.725}$ × 0.007184[15]. Trained professionals collect blood and urine samples on-site. Serum and urine samples were sealed and stored at −80°C until analysis.

Laboratory analysis

sUIC and UCr

Urinary iodine concentration (sUIC) was detected and analyzed by inductively coupled plasma mass spectrometry ICP-MS (iCAP Q, Thermo Fisher Scientific, Germany) using Te for mass bias correction. A calibration curve was obtained using nine solutions with iodine concentrations within the range of 0–1200 μg/L. The R^2 of the standard curve was not less than 0.999. The quality of each batch of urine samples was compared with standard human urine material (Ref. 1403081, Seronorm, Norway). The average concentration of iodine in the standard urine was 292.5±10.3μg/L, which was consistent with the certified value (297 μg/L).

Urinary creatinine (UCr) was measured by a national standard spectrophotometric method. Using this method, the CV for UCr concentration was 0.2 - 3.2% in the laboratory. Two concentrations of urinary creatinine standard were used to correct the urinary creatinine concentration: 0.649g/l (95% CI: 0.489-0.808g/L) and 1.469g/l (95% CI: 1.050-1.887g/L). The relative standard deviation was 3.8% ~ 4.2%.

Thyroid function tests

Serum free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH) were measured by chemiluminescence immunoassays (Bayer Healthcare, Siemens, Germany). The detection range of FT3, FT4 and TSH were 0.8-30pg/ mL, 4.5-60pg/ mL and 0.2-50mIU/L, respectively. The intra assay coefficients of variation were TSH: 2.1-4.9%, FT4: 1.7-4.2%, FT3: 2.4-3.1%. The coefficients of variation between batches were FT3: 2.8-4.1%, FT4: 1.4-3.5%, TSH: 1.5-4.4%. Thyroid disorders include clinical hyperthyroidism, subclinical hyperthyroidism, clinical hypothyroidism, and subclinical hypothyroidism. Detailed diagnostic criteria are provided in Table 1, which includes the suggested reference ranges as suggested by the Laboratory Department of the General Hospital of Tianjin Medical University.

Serum iodine concentration

Serum iodine concentration was analyzed by inductively coupled plasma mass spectrometry ICP-MS (iCAP Q, Thermo Fisher Scientific, Germany) using tellurium for mass bias correction. Serum samples were diluted with 1.5% isopropyl alcohol and 7 mmol aqueous ammonium before ICP-MS analysis to determine serum iodine (SI)[16]. Protein was precipitated with acetonitrile (acetonitrile: serum = 50μL: 25μL). The quality of each batch of serum samples was compared with standard human serum material (Ref. 201405, Seronorm, Norway). The average concentration of iodine in the standard serum was 71.7±2.2μg/L, which was consistent with the certified value (71.8μg/L). The detection range of serum iodine was 0-1000μg/L.

Statistical analysis

Microsoft Excel (Win10, 2019) and SPSS (version 22, NCSS Statistical Software) were used for data processing and statistical analyses. The statistical power (1-β error probability) was set at 0.8, the significance level α was set at $P < 0.05$, The normal distribution variables, including age, height, weight, BMI, BSA, were expressed as mean ± standard deviation. sUIC, UCr, sUIC/UCr, SI and TSH were non-normal distribution variables and were therefore expressed using the median (25th percentile, 75th percentile). Categorical variables, such as the prevalence of thyroid disorders, are expressed as percentages. Comparative analysis of the different groups was performed using a one-way ANOVA or Kruskal-Wallis tests. The trend test was performed to assess the relationship between trends in iodine nutrition indicators and the prevalence of thyroid dysfunctions by SI quartile groups. The relationship between SI and LnTSH was analyzed by local polynomial regression, with fitting on a scatter diagram. Binary and multivariate logistic regression was used to assess the relationship between SI and iodine deficiency, iodine excess, and thyroid dysfunctions.

Results

Participants

Of the 1598 participants recruited in this study, 278 adults were excluded due to incomplete data. There was no significant difference in age, height, weight, BMI and BSA between the included and excluded subjects (Supplementary table 2). 1320 adults were included in the final analyses, including 610 males and 710 females (Figure 1). The mean age, height, weight, BMI and BSA of subjects were 42.9 ± 16.2years, 42.9 ± 16.2cm, 69.2 ± 29.0kg, 24.9 ± 9.70kg/m^2 and 1.74 ± 0.40m^2, respectively. Table 2 shows the baseline characteristics of subjects grouped by their SI quartile. There were no significant differences in age, height, weight, BMI or BSA in the SI quartile groups.

Thyroid function and iodine nutrient levels

The median sUIC, sUIC/UCr, SI, TSH in subjects were 155.8 (94.5, 211.3)μg/L, 138.2 (91.7, 206.9)μg/g, 70.5 (59.6, 83.6)μg/L, 25.6 (1.00, 32.4)μg/L, 30.0 (1.00, 39.6)μg/L and 2.02 (1.41, 2.95) mIU/L, respectively. Grouped by SI quartile, the differences in sUIC, sUIC/UCr and TSH between the different groups were statistically significant ($P = 0.033$, $P = 0.007$, $P < 0.001$, $P < 0.001$ and $P = 0.04$, respectively), and an increasing trend was identified in sUIC and sUIC/UCr from low SI quantiles to high quantiles ($P_{trend} = 0.003$, $P_{trend} = 0.011$, $P_{trend} < 0.001$), whereas serum TSH decreased with increasing SI quartile ($P_{trend} < 0.001$) (Table 3).

Thyroid dysfunctions prevalence grouped by serum iodine quartile

There was a significant difference identified when analyzing the prevalence of thyroid dysfunctions and clinical hypothyroidism ($P < 0.001$) in the different SI quartile groups, and a decreasing trend was observed from the 1st SI quartile to the 4th ($P_{trend} < 0.001$). The prevalence of subclinical hypothyroidism showed also a downward trend ($P_{trend} = 0.017$), but the difference between groups was not statistically significant ($P = 0.115$) (Table 4).

The association between serum iodine and urine iodine and thyroid dysfunctions

Compared with the 59.6μg/L ≤ SI < 83.6μg/L group, subjects with SI ≤ 59.6μg/L had a higher risk of TSH > 5mIU/L (OR = 2.15, 95% CI: 1.36, 3.39), thyroid dysfunctions (OR = 1.72, 95% CI: 1.08, 2.75), clinical hypothyroidism (OR = 16.4, 95% CI: 3.72 - 72.2), sUIC < 100μg/L (OR = 1.41, 95%CI: 1.05 - 2.00) and sUIC/UCr < 91.1μg/g (OR = 1.49, 95% CI: 1.09 - 2.06). Besides, those with SI > 138.5μg/L were more at risk of having sUIC ≥ 300μg/L (OR = 1.55, 95% CI: 1.03 - 2.33) and sUIC/UCr > 209.0 μg/g (OR = 1.41, 95% CI: 1.03 - 1.94) than those with lower SI values (Table 5).

The ROC curves for SIC, sUIC and sUIC/UCr

Taking thyroid dysfunctions as the gold standard, the AUC (area under the curve) of SIC, sUIC and sUIC/UCr was 0.554 ($P = 0.02$), 0.446 ($P = 0.005$) and 0.450 ($P = 0.007$), respectively. the AUC of SI was

significantly higher than that of sUIC/UCr (0.446, *P*=0.005). (Figure 2). Taking clinical hypothyroidism as the gold standard, the AUC (area under the curve) of SI, sUIC and sUIC/UCr was 0.763 (*P* = 0.012), 0.684 (*P* = 0.026) and 0.678 (*P* = 0.049), respectively (Figure 3).

Discussion

At present, the most widely implemented indicator utilized to assess the iodine status of a population is Urinary Iodine Concentration (sUIC)[17]. sUIC can reflect recent iodine intake but varies with dietary iodine content, fluid intake and the time of collection[15 18]. Iodine levels in urine are highly variable, requiring 10 spot samples to determine accurately the status of an individual[19]. To correct deficiencies in the use of sUIC to evaluate iodine nutrition, UI/Cr ratio has increasingly been used to describe iodine status. However, UI/Cr can be affected by the daily protein intake of individuals[20 21] and cannot address daily variation in intake, or circadian variation. In addition, thyroid dysfunctions can be used to assess iodine nutritional status, since iodine deficiency can result in hypothyroidism, and hypothyroidism or hyperthyroidism can manifest when iodine levels are excessive[22]. Thyroid dysfunctions analysis can reflect abnormal iodine intake but does not prevent disease.

Dietary iodine is mainly absorbed into the bloodstream via the small intestine. The majority of iodine in systemic circulation is enriched in the thyroid gland for the synthesis of thyroid hormones before being transported to the periphery. In addition, after thyroxine and triiodothyronine in peripheral tissue are decomposed by deiodinase, iodine will be released into the blood circulation. Serum iodine is another potential biomarker for iodine status.

In 1949, researchers used radioactive iodine to explore systemic changes in blood iodine levels and distribution; in doing so they identified that serum iodine was eliminated faster in hypothyroidism than in hyperthyroidism, suggesting that serum iodine levels could reflect thyroid function[23]. In this study, individuals with SI levels of less than 59.6μg/L had a higher risk of clinical hypothyroidism than those with SI in the 59.6–83.6μg/L range. TSH of patients with clinical hypothyroidism is higher than that of normal adults, and FT4 is lower than that of normal people. The possible reason is that serum iodine was positively correlated with total triiodothyronine (TT3), total thyroxine (TT4), and FT4[24], whilst TSH promoted the synthesis and secretion of thyroid hormone, which is contrary to the usual effect of low levels of TT3, TT4 and FT4.

An ROC (Receiver Operating Characteristic) curve can be used to compare the sensitivity of two or more different diagnostic methods. The diagnostic test with an area under the ROC curve that is closest to 1.0 has the best discriminatory power. In the present study we found that taking thyroid dysfunctions as the gold standard, the AUC of SI was greater than that of sUIC/UCr, and sUIC. Therefore, serum iodine can not only reflect the iodine nutritional status of the body, but can also represent thyroid function status more sensitively[9 10 25]. Serum iodine can be combined with urinary iodine and used to screen a population for those at high risk of thyroid disease. individuals with low serum iodine should pay special attention to their diet to prevent them from developing thyroid dysfunctions.

The main drawback of the present study is to collect spot urine and not collect 24-hour urine samples, so 24-hour urinary iodine data was lacking. However, we corrected random urinary iodine data using creatinine measurements. Creatinine measurement removes the influence of hydration status but does not address daily variation in intake, or circadian variation. In future study, we plan to collect 24h urine to reduce the impact of random urine on research results. Conversely, the clear benefit of this study is that it supplemented the relationship between low serum iodine and thyroid dysfunction, and revealed that low serum iodine increased the risk of clinical hypothyroidism. These will provide a good basis for future assessment of iodine status.

Conclusion

Overall, serum iodine can be combined with urinary iodine and used to screen a population for those at high risk of thyroid dysfunctions. individuals with low serum iodine should pay special attention to their diet to prevent them from developing thyroid dysfunctions, especially clinical hypothyroidism.

Abbreviations

sUIC
Spot urinary iodine concentration
UCr
Urinary creatinine
SI
Serum iodine
TSH
Thyroid stimulating hormone
SIC
Serum iodine concentration
TT3
Total triiodothyronine
TT4
Total thyroxine.

Declarations

Funding

This work was supported by grants from National Natural Science Foundation of China (grant number 81703218, grant number 82073549).

Competing interests

The authors have no relevant financial interests to disclose.

Ethics approval

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the Medical Ethics Committee of Tianjin Medical University (serial number: IRB[2013]115). Informed consent was obtained from all individual participants included in the study.

Availability of data and materials

All the data regarding the findings are available within the manuscript. Anyone who is interested in the information should contact the corresponding author.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Tingting Xu, Wenxing Guo, Ren zhiyuan and Hongyan Wei. The first draft of the manuscript was written by Tingting Xu and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Thanks to School of Public Health, Tianjin Medical University and Tianjin Key Laboratory of Environmental Nutrition and Human Health for providing a good environment for sample testing and paper writing; Thanks to Tianjin Medical University General Hospital for providing the study population and sample collection.

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Tables

Tables 1 to 5 are available in the Supplementary Files section.

Figures

Figure 1

The flow chart of the study. The flow chart of the study. Of the 1598 adults recruited in this study, 13 adults were excluded due to miss characteristic data, 142 adults were excluded due to miss urinary iodine data and 123 adults were excluded due to miss serum iodine data. A total of 1320 adults were included in the final analyses, including 610 males and 710 females.

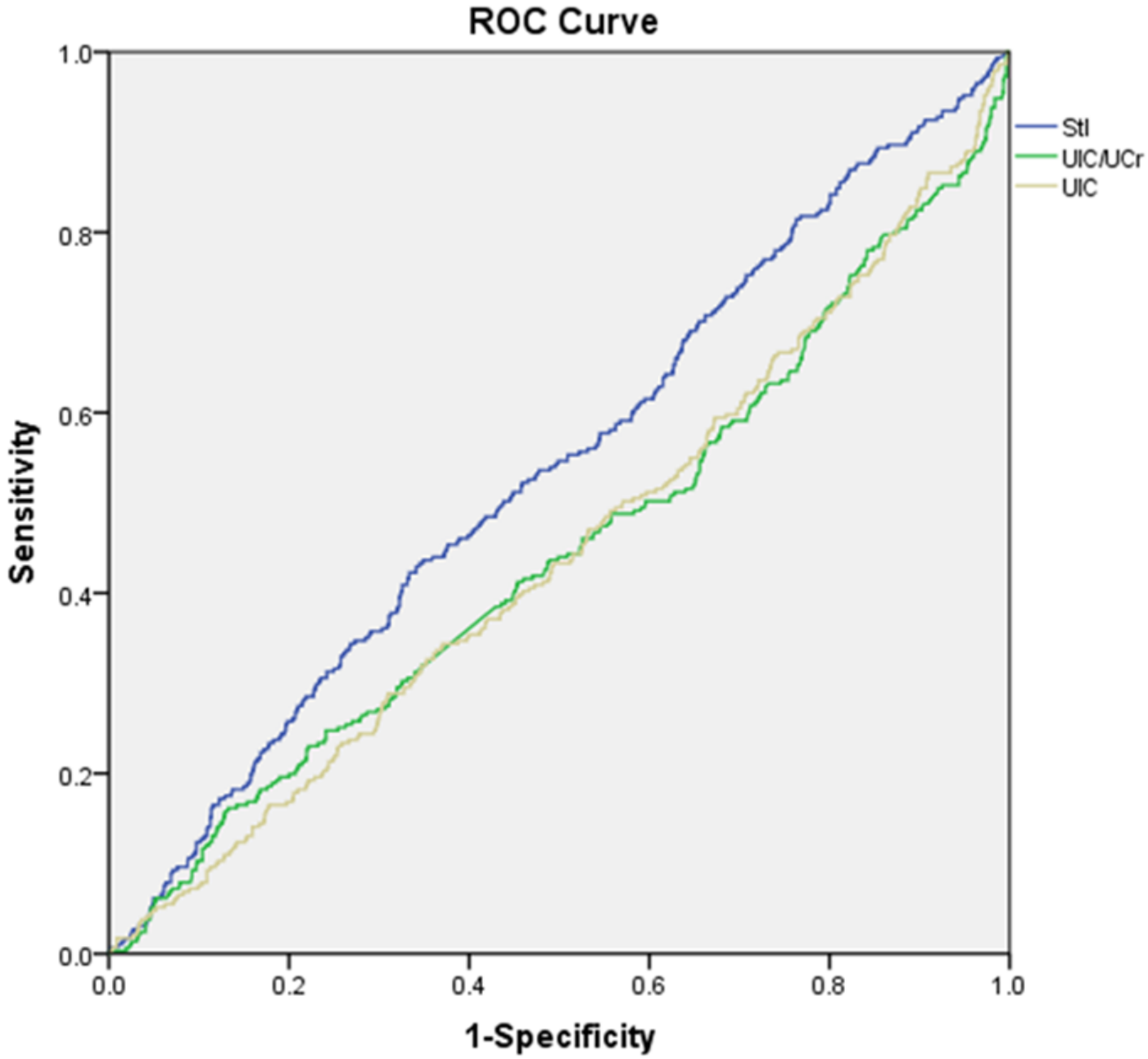

Figure 2

The ROC curves for SIC, sUIC and sUIC/UCr. The diagnostic test with an area under the ROC curve that is closest to 1.0 has the best discriminatory power. the area under the ROC curve for SIC was 0.554, UIC was 0.446 and UIC/UCr was 0.450. SIC: Serum iodine concentration; UIC: urinary iodine concentration; UCr: urinary creatinine.

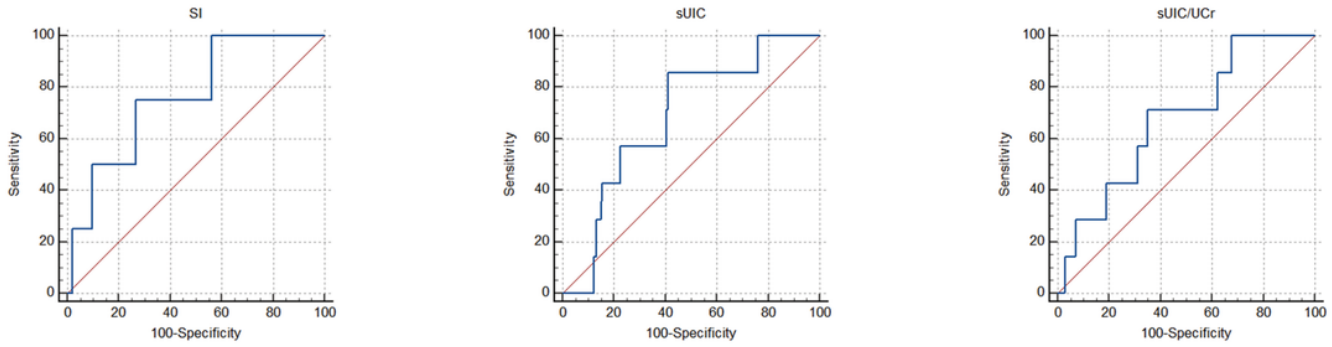

Figure 3

The ROC curves for lower SIC, sUIC and sUIC/UCr. The diagnostic test with an area under the ROC curve that is closest to 1.0 has the best discriminatory power. the area under the ROC curve for SIC was 0.763, UIC was 0.684 and UIC/UCr was 0.678. SIC: Serum iodine concentration; UIC: urinary iodine concentration; UCr: urinary creatinine.

Supplementary Files

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- Table2.pdf
- Table3.pdf
- Table4.pdf
- Table5.pdf
- SupplementalTable1.pdf
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