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Serum Interleukin-6 and pro-B-type Natriuretic Peptide as Biomarkers of Cardiac Involvement in Thyroid Dysfunction: A Comparative Study of Hyperthyroid, Cardiac, and Combined Thyro-Cardiac Disease

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ABSTRACT

Thyroid hormones have profound effects on the cardiovascular system, but the signature of the changes is not known to distinguish thyroid-induced cardiac stress from primary cardiac disease. This study aimed to assess the role of interleukin-6 (IL-6) and pro-B-type natriuretic peptide (proBNP) in addition to thyroid, metabolic and renal parameters in four clinical groups. This study iniclude 140 participants, 50 healthy controls and 30 with hyperthyroidism treated with carbimazole, 30 with heart disease, and 30 with hyperthyroidism and heart disease. Roche cobas c111 for glucose, lipid profile and renal functions, Mindray CL-900i for thyroid hormones and by ELISA method were used to measure the IL6 and ProBNP. ANOVA or Kruskal–Wallis test was used to analyse the data, correlation analysis and receiver operating characteristic (ROC) curves. Results: The level of IL-6 increased in a step-wise fashion and proBNP was significantly increased in both cardiac groups. proBNP was nearly as good at discriminating against heart disease alone as against combined disease (AUC 1.000), while IL-6 separated heart disease from combined disease (AUC 0.706, p = 0.002). In conclusion, thyroid and cardiac biomarker profiling when performed together is helpful in the recognition of cardiac involvement in thyroid disease.

Keywords- hyperthyroidism; heart disease; interleukin-6; proBNP; thyroid hormones.

I. INTRODUCTION

The thyroid gland has a significant effect on the cardiovascular system. Synthesizes tri-iodothyronine (T3) and thyroxine (T4) which controls the metabolism of nearly all tissues. These hormones have two ways of affecting the heart. Genomic pathway changes the transcription of genes associated with cardiac contractile proteins and ion channels. The non-genomic route works quickly on the cell membrane and on the vascular tone. They both increase the heart rate and decrease the vascular resistance. This causes a sudden increase in cardiac output. This sensitivity makes thyroid status a big issue in the study of cardiology[1][2] and thyroid disease often presents as a cardiac symptom.[3]

With hyperthyroidism, the heart is chronically worked. It causes hyperdynamic circulation, tachycardia and a widened pulse pressure. Common symptoms are palpitations, dyspnoea and poor exercise tolerance. Eventually this overloading can cause injury to the myocardium and give rise to thyrotoxic cardiomyopathy, which may be partially reversible after obtaining a euthyroid state; atrial fibrillation is the frequent but not uncommon and dangerous complication, increasing the risk of stroke and embolism. A recent systematic review and meta-analysis identified heart failure in

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approximately eight percent of patients with hyperthyroidism, with other important risk factors identified including atrial fibrillation, chronic kidney disease, anaemia and hypertension. These results support the fact that hyperthyroidism does have a cardiovascular burden, and that it is measurable. They also make a case for further research on the biomarkers that measure this burden.

Thyroid disease affects the cardiovascular system regardless of how mild the symptoms are. In some cohorts, cardiac events have been associated with subclinical dysfunction (abnormal TSH and normal free hormones). Thyroid function has even been found to predict heart failure[16] and mortality in chronic heart failure patients[17]. treatment is directed toward achieving the euthyroid state, with antithyroid drugs being one of the most frequently used treatments. Many abnormalities respond to therapy and the treated hyperthyroid patient is a valuable comparison group for research. Carbimazole and its metabolite methimazole are the most commonly used agents, and long-term therapy has generally acceptable safety and efficacy.

Recently, inflammation has come to be recognized as a contributor to cardiac disease. Interleukin-6 is a crucial inflammatory cytokine secreted by immune cells, endothelium and stressed cardiomyocytes. Interleukin-6 is also important in thyroid disease, and it is also associated with a variety of cardiovascular disease outcomes beyond heart failure, such as infarction, stroke, and atherosclerosis. The majority of cases of hyperthyroidism are auto-immune with a deranged cytokine balance. Thus it is conceivable that IL-6 is a reflection of both cardiac stress and thyroid related inflammation. If so, it may contain data which a cardiac marker cannot give. This dual signal is one of the main motivations for studying IL-6 in the current study.

Natriuretic peptides are the main biomarkers used in the diagnosis of heart failure. When stressed, the heart secretes B-type natriuretic peptide (BNP) and its fragments. Although they are still very much a part of current guidelines for heart failure, thyroid hormone affects these peptides. This renders interpretation difficult as it has been shown that NT-proBNP is elevated in overt hyperthyroidism, even when there is no cardiac dysfunction, and this normalization is achieved, albeit in part, after treatment [11, 18]. Elevated level of proBNP could be a sign of true cardiac disease, hyperthyroidism or both. This study aims to address one of the questions that need to be answered to separate these contributions.

Thyroid disease also alters renal function and metabolism. It affects glucose metabolism and can impair glucose tolerance[12]; it increases turnover of lipids and cholesterol is likely to be decreased[13]; it changes the renal blood flow and glomerular filtration rate as well[14]. Receiver-operating-characteristic (ROC) analysis is applied to fairly assess each of the biomarkers. This approach presents a summary of the separation between two groups by the area under the curve (AUC) and serves as the analytical support for the present work.

Although there is a considerable amount of literature, there is a significant gap. Only a few studies make such comparisons within one design between the healthy state, isolated thyroid disease, isolated cardiac disease and combined disease. Even fewer studies look at whether a single biomarker can identify thyroid involvement in people with pre-existing heart disease. This is a real clinical dilemma as high proBNP may not uncover the presence of hidden hyperthyroidism. The present study therefore profiled the cytokines (IL-6), the natriuretic peptides (proBNP), the thyroid hormones (FT3 and FT4) and markers of metabolism and kidney function in four distinct groups. These objectives were to compare the parameters between groups, to describe their correlations, to evaluate their diagnostic value using ROC analysis and, most importantly, to determine if IL-6 has any value in identifying thyroid involvement in existing heart disease.

II. MATERIALS AND METHODS

Study Design

This cross sectional comparative study was conducted at Al-Sheikh Zayed Hospital, Baghdad, Iraq. Samples were taken from 23 March 2025 to 11 June 2025. Four groups of 140 adults were recruited. 50 people were included in the healthy control group. 30 patients with hyperthyroidism were given carbimazole 20 mg. There were 30 patients in the group of heart disease. There were 30 patients in the combined heart disease with hyperthyroidism group. All participants gave written informed consent. The study followed the principles of the Declaration of Helsinki and was approved by the local institutional ethics committee.

Sample Collection

Venous blood was drawn after an overnight fast (8 hours). Serum separation was done by collecting the sample in plain gel tubes and centrifuging for 10 minutes at 3000 rpm. Aliquots were taken for cytokine and peptide assays and frozen at −80 °C until analysis. Samples which were haemolysed or lipaemic were excluded.

Biochemical Analysis

Blood glucose level, the lipid profile and renal parameters were determined using the Roche cobas c111 analyser (Roche Diagnostics, Mannheim, Germany). Levels of Interleukin-6 and proBNP were measured using enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions, using absorbance read at 450 nm. Serum free tri-iodothyronine (FT3), free thyroxine (FT4) and thyroid-stimulating hormone (TSH) levels were determined using the Mindray CL-900i chemiluminescence immunoassay (CLIA) analyser (Shenzhen Mindray, China). Throughout study, all assays contained the manufacturer's calibrators and 2 levels of quality-control material that were within the acceptable range.

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Statistical Analysis

A numerical pipeline was developed for the purpose of analysing the data. Continuous variables were presented as mean ± SD and as median (IQR). Normality was tested in each group using the Shapiro-Wilk test. One way analysis of variance (ANOVA) was used for variables with a normal distribution, and the Kruskal–Wallis test was used for variables that were not normally distributed. Dunn's test (with Bonferroni correction) was used for post-hoc pairwise comparisons. The chi-square test was used to compare categorical variables. Spearman correlation was used to determine the associations between the markers. Key biomarkers were tested by receiver-operating-characteristic (ROC) curves, and the area under the curve (AUC), 95% confidence interval (CI) and the optimal cut-off with the sensitivity and specificity were reported. Two-sided p-value < 0.05 was deemed significant.

III. RESULTS

Baseline Characteristics

The four groups were comparable in age and sex. Mean age ranged from about 55 to 59 years, and the Kruskal–Wallis test showed no significant age difference ($p = 0.161$). The sex distribution did not differ between groups ($\chi^2 = 3.25$, $p = 0.354$). Body mass index differed significantly ($p < 0.001$), being lower in the hyperthyroid groups, consistent with the catabolic effect of thyroid hormone excess. These baseline data are summarised in **Table 1**.

Table 1. Baseline demographic characteristics of the four study groups. Values are mean ± SD for continuous variables and n (%) for sex.

Variable	Healthy Control (n=50)	Hyperthyroidism + Carbimazole (n=30)	Heart Disease (n=30)	Heart Disease + Hyperthyroidism (n=30)	p-value
Age (years)	55.26 ± 15.81	59.47 ± 14.84	51.60 ± 15.34	51.73 ± 15.36	0.161
Sex (M / F)	26 (52%) / 24 (48%)	13 (43%) / 17 (57%)	13 (43%) / 17 (57%)	19 (63%) / 11 (37%)	0.354
BMI (kg/m²)	24.61 ± 3.18	22.85 ± 2.88	30.10 ± 3.48	28.15 ± 3.69	<0.001

Metabolic and Renal Parameters

There was a significant difference between the groups in the biochemical profile (Table 2). Cardiac groups showed higher levels of fasting glucose compared to controls and hyperthyroid patients and the difference was highly significant (p < 0.001). There was no significant difference in the cardiac-dominant pattern for triglycerides. The total cholesterol and LDL-cholesterol values were also found to be lowest in hyperthyroid group, consistent with the increased lipid turnover in thyrotoxicosis. The cardiac groups showed increased levels of creatinine and urea, reflecting the cardio-renal overlap seen with cardiovascular disease.

Table 2. Metabolic and renal parameters across the four groups (mean ± SD). The omnibus test statistic (ANOVA F or Kruskal–Wallis H) and its p-value are shown.

Parameter	Healthy Control	Hyperthyroidism +Carbimazole	Heart Disease	Heart Disease +Hyperthyroidism	Test	p
Glucose	95.64 ± 10.01	101.03 ± 12.11	120.76 ± 16.01	119.60 ± 14.19	H = 62.36	<0.001
Total Cholesterol	175.82 ± 21.07	172.92 ± 25.73	222.08 ± 32.32	204.52 ± 27.99	F = 26.91	<0.001
Triglycerides	129.60 ± 22.71	117.09 ± 25.27	186.70 ± 39.33	164.69 ± 33.47	F = 36.91	<0.001
HDL	51.24 ± 6.88	51.46 ± 7.07	42.88 ± 5.96	48.76 ± 7.94	F = 10.66	<0.001
LDL	108.06 ± 17.83	104.02 ± 20.64	141.62 ± 34.78	130.99 ± 19.29	F = 19.89	<0.001
Creatinine	0.91 ± 0.16	1.01 ± 0.18	1.47 ± 0.40	1.31 ± 0.31	F = 33.88	<0.001
Urea	28.19 ± 5.15	33.59 ± 5.71	48.58 ± 10.87	45.11 ± 9.66	F = 55.24	<0.001

Thyroid Hormones and Cardiac Biomarkers

The clinical grouping was confirmed by the thyroid hormone profile (Table 3). The two hyperthyroid groups had approximately double the levels of FT3 and FT4, and very low levels of TSH. For both these changes, p-values were < 0.001.

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IL-6 was elevated in a step-wise fashion. It was lowest in controls, higher in hyperthyroid, even higher in heart disease and highest in combined disease. proBNP was the most discriminating analyte. It was very low in controls, slightly elevated in hyperthyroidism, and elevated about 15 times in the two cardiac groups. The values of IL-6 and proBNP are presented as median (interquartile range) as these were not normally distributed (Table 3b).

Table 3. Thyroid hormones and cardiac/inflammatory biomarkers across the four groups (mean ± SD), with the omnibus test statistic and p-value.

Marker	Healthy Control	Hyperthyroidism +Carbimazole	Heart Disease	Heart Disease +Hyperthyroidism	Test	p
FT3 pg/mL	3.12 ± 0.38	5.67 ± 0.72	3.03 ± 0.44	5.77 ± 0.92	F = 206.98	<0.001
FT4 ng/dL	1.23 ± 0.14	2.23 ± 0.23	1.16 ± 0.17	2.36 ± 0.38	F = 244.38	<0.001
TSH mIU/L	2.08 ± 0.66	0.11 ± 0.06	2.17 ± 1.07	0.09 ± 0.04	F = 115.82	<0.001
IL6 pg/mL	1.92 ± 0.77	4.07 ± 1.07	6.32 ± 1.55	7.62 ± 1.78	F = 147.92	<0.001
proBNP pg/mL	59.91 ± 28.28	116.00 ± 39.27	919.45 ± 310.63	847.22 ± 237.75	H = 112.87	<0.001

Table 3b. Median (interquartile range) of the non-normally distributed biomarkers IL-6 and proBNP.

Marker	Healthy Control	Hyperthyroid	Heart Disease	HD + Hyperthyroid
IL6 pg/mL	2.0 (1.4–2.4)	4.0 (3.3–4.7)	6.4 (5.2–7.4)	7.5 (6.4–9.1)
proBNP pg/mL	54.7 (40.2–75.9)	110.2 (97.2–144.2)	844.4 (722.2–1128.4)	831.0 (690.2–964.0)

Post-hoc pairwise comparisons

A post hoc test by Dunn identified where the group differences were (Table 4). All comparisons made with the control group were significant for IL-6, and hyperthyroidism was not different from either of the cardiac groups. There was only one instance of a non-significant IL-6 contrast (heart disease versus combined disease), but the trend was in favour of the combined group. ProBNP levels were different for both cardiac groups compared with the controls and with hyperthyroidism, but not between the two cardiac groups. This pattern indicates that proBNP marks the presence of structural heart disease, whereas IL-6 adds information about the inflammatory load contributed by thyroid overactivity.

Table 4. Dunn post-hoc pairwise comparisons (Bonferroni-adjusted) for IL-6 and proBNP.

Comparison	z	Adjusted p	Significant
Interleukin-6 (pg/mL)			
Control vs Hyperthyroid	-4.43	<0.001	Yes
Control vs Heart Disease	-7.87	<0.001	Yes
Control vs HD+Hyperthyroid	-9.46	<0.001	Yes
Hyperthyroid vs Heart Disease	-3.08	0.012	Yes
Hyperthyroid vs HD+Hyperthyroid	-4.50	<0.001	Yes
Heart Disease vs HD+Hyperthyroid	-1.42	0.931	No
proBNP (pg/mL)			
Control vs Hyperthyroid	-3.26	0.007	Yes
Control vs Heart Disease	-8.87	<0.001	Yes
Control vs HD+Hyperthyroid	-8.53	<0.001	Yes
Hyperthyroid vs Heart Disease	-5.01	<0.001	Yes
Hyperthyroid vs HD+Hyperthyroid	-4.71	<0.001	Yes
Heart Disease vs HD+Hyperthyroid	0.31	1.000	No

The thyroid hormones were found to have a pattern of change that was the exact opposite of what was found in the groups. FT4 and FT3 distinguished the hyperthyroid groups from the non-hyperthyroid groups and TSH distinguished the non-hyperthyroid groups from the hyperthyroid groups. There were no difference in either hormone between the 2 hyperthyroid groups or between the control and isolated cardiac groups, all of which indicate that the thyroid axis was normal in the pure cardiac group.

Correlation analysis

A network of associations was found (Table 5, Figure 1) when Spearman correlation was calculated for the entire sample. proBNP correlated positively with IL-6, with creatinine, and with urea – cardiac stress with inflammation, and renal impairment. There was a correlation between IL-6 with FT3 and FT4, indicating the inflammatory role of thyroid overactivity. As expected in normal feedback, FT4 was inversely correlated with TSH, and negatively related to total cholesterol. These relationships lend themselves to the interpretation that the measured markers are located along a common axis of cardiothyroid-metabolic relationships.

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Table 5. Selected Spearman correlations across the whole sample (n = 140).

Variable pair	Spearman ρ	p-value	Significant
proBNP – IL6	0.769	<0.001	Yes
proBNP – FT4	0.219	0.009	Yes
proBNP – Creatinine	0.603	<0.001	Yes
IL6 – FT4	0.351	<0.001	Yes
IL6 – FT3	0.343	<0.001	Yes
FT4 – TSH	-0.762	<0.001	Yes
FT4 – Total	-0.042	0.623	No
FT3 – Triglycerides	-0.070	0.408	No
TSH – LDL	-0.020	0.816	No
IL6 – Glucose	0.620	<0.001	Yes
proBNP – Urea	0.653	<0.001	Yes

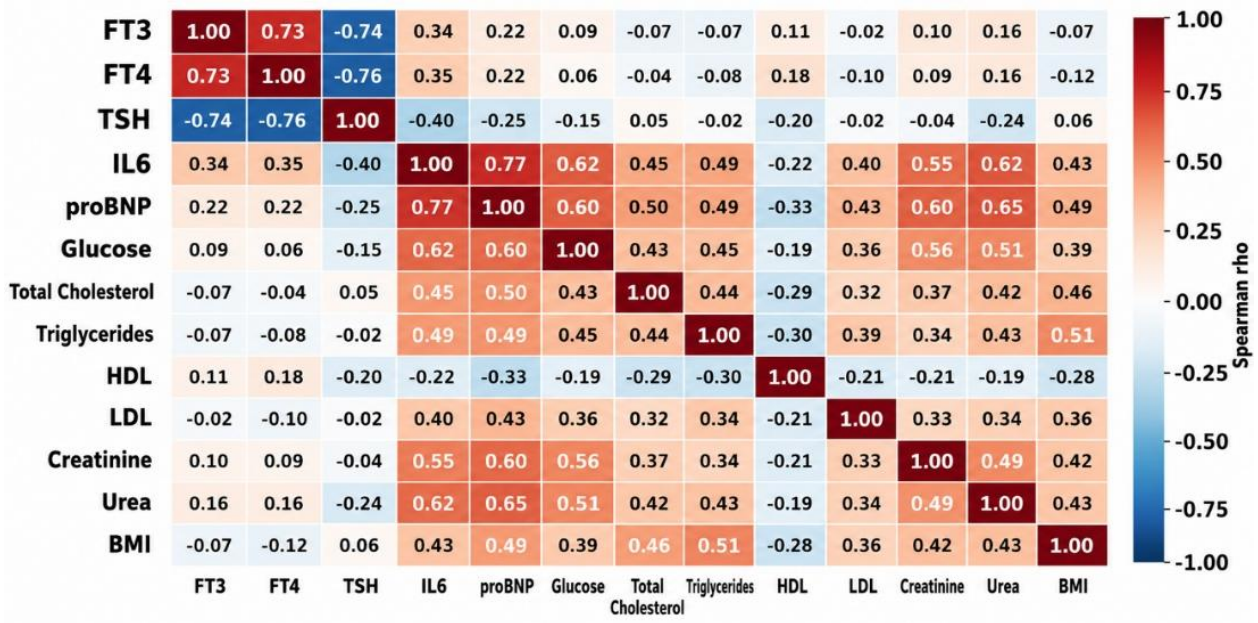

Figure 1. Spearman correlation matrix of the measured parameters across the whole sample. Warm colours denote positive correlation and cool colours negative correlation.

ROC curve analysis

Each biomarker's diagnostic value was quantified with ROC analysis (Table 6). proBNP was able to almost completely discriminate between heart disease and non-cardiac states with an AUC of 1.000 and a cut-off of approximately 359 pg/mL. IL-6 also showed good performance in heart disease with AUC = 0.969. The near-perfect AUCs of FT4 (1.000), FT3 (0.999) and TSH (0.979) as classifiers of hyperthyroidism indicate the thyroid hormones' importance as markers. The outcomes of these are displayed in Figure 2 and Figure 3.

Table 6. Receiver-operating-characteristic (ROC) results for the key biomarkers. AUC = area under the curve; CI = confidence interval.

Classifier	AUC	95% CI	Cut-off	Sens. %	Spec. %	p
proBNP – heart disease	1.000	1.000–1.000	≥ 359.06	100.0	100.0	<0.001
IL-6 – heart disease	0.969	0.937–1.000	≥ 5.08	90.0	93.8	<0.001
FT4 – hyperthyroidism	1.000	1.000–1.000	≥ 1.51	100.0	100.0	<0.001
FT3 – hyperthyroidism	0.999	0.994–1.000	≥ 4.13	98.3	100.0	<0.001
TSH – hyperthyroidism	0.979	0.952–1.000	≤ 0.23	100.0	97.5	<0.001
IL-6 – HD+Hyper vs HD	0.706	0.574–0.837	≥ 8.13	43.3	93.3	0.002
proBNP – HD+Hyper vs HD	0.553	0.407–0.700	≤ 1002	86.7	36.7	0.475

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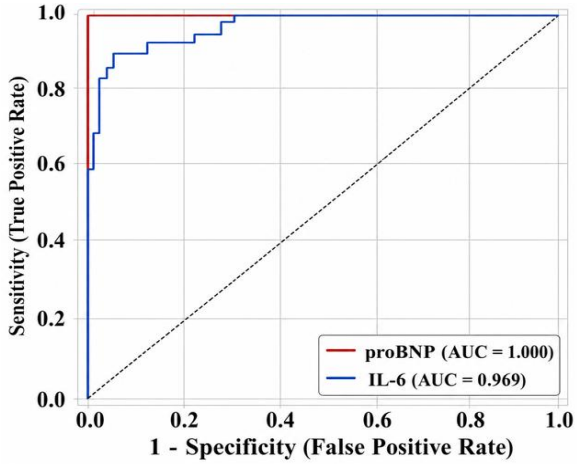

Figure 2. ROC curves of proBNP and IL-6 for detecting heart disease. proBNP achieves complete separation, and IL-6 follows closely.

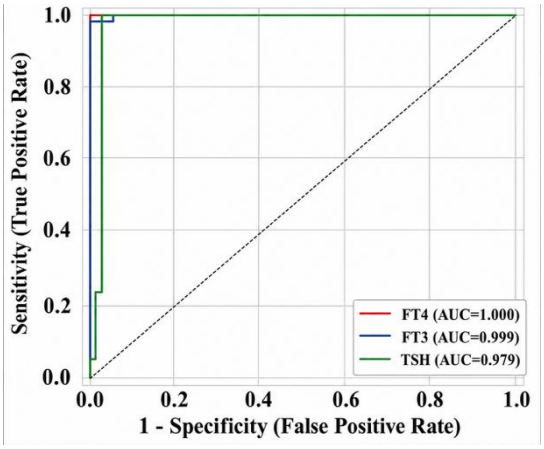

Figure 3. ROC curves of FT4, FT3 and TSH for detecting hyperthyroidism. All three thyroid markers are near-perfect classifiers.

A subsequent analysis was conducted in just the two cardiac groups to determine whether the markers might be useful for the identification of superimposed hyperthyroidism (Figure 4). Here IL-6 showed useful discrimination (AUC 0.706, p = 0.002) but proBNP showed no discrimination (AUC 0.553, p = 0.475). This is the key novel discovery: Within the confines of existing heart disease, proBNP may not identify thyroid involvement, but IL-6 may. The value of IL-6 above approximately 8 pg/mL was very specific (93%) for combined thyro-cardiac disease.

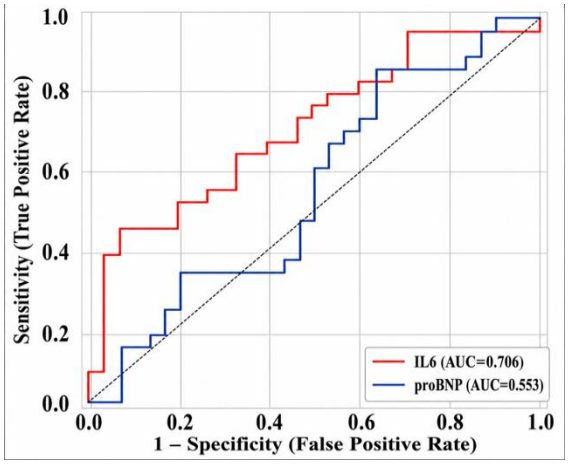

Figure 4. ROC curves separating combined heart disease with hyperthyroidism from isolated heart disease. IL-6 remains informative, whereas proBNP loses discriminatory value.

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IV. DISCUSSION

The data demonstrate a marked compartmentalisation of the actions of the two cardiac markers. proBNP is able to detect structural heart disease, while IL-6 reflects the inflammatory load imposed by thyroid overactivity. This is a clinically useful division and to our knowledge, the four-group division has not been described previously exactly as it is done here.

As expected in the cardiac groups, proBNP increased dramatically. The release of these peptides is due to myocardial wall stress and plays a key role in the diagnosis of heart failure[9]. They have a well proven diagnostic and prognostic value in clinical and therapeutic practice[10]. The proBNP's ROC is near-perfect in our sample, which is consistent with the good separation found in previous studies [9]. It should be noted that thyroid dysfunction can lead to increased natriuretic-peptides, too [11]. Our data found that proBNP was slightly increased in isolated hyperthyroidism compared with controls, and correlated with the meta-analysis results showing that NT-proBNP is increased in patients with overt hyperthyroidism, even in the absence of HF[11]. This interpretation is based on early observations of increased levels of natriuretic peptides in hyperthyroidism, irrespective of the presence of cardiac dysfunction[18].

The progressive rise of interleukine- 6 is also informative. Both levels of IL-6 and its action are powerful and independent prognostic markers in heart failure[7] and higher circulating levels correlate with a broad spectrum of adverse cardiovascular events[8]. We found that there was already a raised inflammatory signal in isolated hyperthyroidism and the highest in combined disease, suggesting that thyroid overactivity adds an inflammatory signal to the cardiac signal. This concept was translated to the ability of IL-6 to distinguish combined disease from isolated heart disease, which proBNP was not able to. It suggests that if the patient has unexpectedly high IL-6 for a heart-failure patient, he or she might have unrecognized hyperthyroidism.

As it was to be, the thyroid hormone results were clear. In both groups of hyperthyroid patients, levels of FT3 and FT4 were elevated, while levels of TSH were suppressed, and all three markers were close to the ideal classification thyroid hormone.Both hyperthyroid groups showed elevated FT3 and FT4 and suppressed levels of TSH, which were all near-perfect classifiers of hyperthyroidism. This is in line with the robust and well characterised associations between thyroid status and cardiac disease[1]. Hyperthyroidism has been known to be a cause of arrhythmia and heart failure[4] and heart failure is prevalent in hyperthyroid individuals[6]. Thyroid abnormalities have been associated with cardiovascular events both in the subclinical and overt state, but not equally in all populations[16]. Thyroid function has also been associated with mortality in chronic heart failure [17] and further supporting the importance of thyroid function monitoring in cardiac patients.

The metabolic and renal results are supportive. The lower level of cholesterol and LDL in the hyperthyroid group is indicative of the heightened lipid turnover of thyrotoxicosis which has been observed in recent reviews of lipoprotein change in endocrine disease[13]. The higher glucose in the cardiac groups is in line with the close links between thyroid disorders and glucose homeostasis[12]. This increase in creatinine and urea for the cardiac groups, and the correlation with proBNP, are examples of the cardio-renal interaction which is now known to occur in thyroid disease[14]. Lastly, the administration of carbimazole in our hyperthyroid group is representative of current practice; long-term antithyroid drugs are highly effective and well tolerated[15] and reversion to normal euthyroid state is expected to eliminate many of the abnormalities mentioned[5].

There are some caveats to be noted. The design is cross sectional and therefore can't make any statements of causation. The sample was limited to one centre and this may restrict generalisability. Natriuretic peptides and IL-6 were only measured once, and heart disease echocardiographic staging was not available for this analysis. The near-perfect ROC values are impressive, yet in part may be attributed to the clear clinical distinction of the groups and need to be replicated in a larger, less select population. Previously, the relationship was found with natriuretic peptides in various thyroid function categories[20] and in thyroid states[19] and indicates a real relationship, but the relationship is sensitive to assay and case mix.

V. CONCLUSION

This study compared inflammatory, cardiac, thyroid, metabolic and renal markers among four clinically defined groups. There are three major conclusions that stand out. ProBNP is a great tool for determining structural heart disease but it does not detect overactive thyroid disease. Second, the level of interleukin-6 increases progressively from healthy to hyperthyroid to cardiac to combined thyro-cardiac disease; it is the only marker which appears to distinguish the combined thyro-cardiac disease from cardiac disease. Thirdly, thyroid hormones continue to be excellent predictors of hyperthyroidism and they track along with the metabolic and renal changes observed in the cardiac groups. The results together support the use of simultaneous biomarker profiling in the patient population at the interface of thyroid and cardiac diseases. Determination of IL-6 together with proBNP and thyroid hormones may enable to identify the patient with a complicated heart disease because of thyroid overactivity, and so to direct the treatment more precisely. Further prospective, multicentre imaging endpoint studies are required to validate these findings and assess their usefulness in clinical practice.

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