

# Interleukin-6 as an Inflammatory Biomarker of Thyroid Dysfunction in Patients Undergoing Maintenance Hemodialysis: A Cross-Sectional Study

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# Abstract

## Background

Thyroid dysfunction is common in chronic kidney disease (CKD) and is increasingly linked to systemic inflammation. Interleukin-6 (IL-6), a pro-inflammatory cytokine, can alter the hypothalamic-pituitary-thyroid axis and peripheral thyroid hormone metabolism.

## Aims

To evaluate serum IL-6 as an inflammatory biomarker of thyroid dysfunction in CKD patients on maintenance hemodialysis, and to determine its independent predictive and discriminatory performance.

## Methods

This cross-sectional study included 65 consecutive patients receiving maintenance hemodialysis at Airlangga University Hospital, Surabaya. Associations between IL-6 and five thyroid parameters were examined using Spearman correlation with Bonferroni correction. Multivariable linear regression assessed the independent association of IL-6 with thyroid hormones after adjustment for age, sex, body mass index, hemodialysis duration, albumin, diabetes mellitus, and hypertension. ROC curve analysis with bootstrap-derived 95% confidence intervals evaluated discrimination for thyroid dysfunction.

## Results

Median IL-6 was 10.10 pg/mL (IQR 6.13–17.16). Thyroid dysfunction occurred in 48 patients (73.8%), most commonly low T3 syndrome (49.2%). IL-6 correlated positively with TSH ( $r = 0.344$ ; raw  $p = 0.005$ ; Bonferroni-adjusted  $p = 0.025$ ). In multivariable analysis, higher IL-6 was independently associated with lower total T3 ( $\beta = -0.0025$ ; 95% CI  $-0.005$  to  $-0.0001$ ;  $p = 0.040$ ;  $R^2 = 0.270$ , adjusted  $R^2 = 0.164$ ). IL-6 showed moderate discrimination (AUC = 0.665; 95% CI 0.528–0.799). A cutoff of  $\geq 10.10$  pg/mL with sensitivity 60.4%, specificity 76.5%, PPV 87.9%, NPV 40.6%.

## Conclusions

IL-6 is independently associated with reduced total T3 and shows moderate discriminatory ability for thyroid dysfunction. An IL-6 cutoff of 10.10 pg/mL have a potential role as a practical biomarker for thyroid dysfunction threshold, but this finding needs further research.

**Clinical Trial Registry:** ClinicalTrials.gov, TRN: NCT07328113, Registration date: 2 January 2026.

## INTRODUCTION

Chronic kidney disease (CKD) is a major global public health burden, affecting an estimated 700 million individuals worldwide. In addition its impact on kidney function, CKD is associated with a spectrum of endocrine disturbances, of which thyroid dysfunction is the most commonly encountered. The

prevalence of thyroid abnormalities in patients undergoing maintenance hemodialysis ranges from 20% to 65%, depending on the diagnostic criteria and thyroid parameters evaluated [1–3].

The most common endocrine disturbances encountered in CKD is the non-thyroidal illness syndrome (NTIS), also known as euthyroid sick syndrome, characterized by reduced triiodothyronine (T3) while thyroxine and TSH level are normal and without intrinsic thyroid disease. The pathophysiology in CKD involves impaired peripheral thyroid hormone metabolism, altered protein binding, uremia-related inhibition of iodothyronine transport, and accumulation of circulating inhibitors of thyroid hormone binding [4, 5].

Chronic low-grade systemic inflammation is a cardinal feature of the uremic milieu in hemodialysis patients. The hemodialysis procedure itself is a potent stimulus for cytokine release, particularly interleukin-6 (IL-6). Elevated IL-6 has been independently associated with cardiovascular events, malnutrition, and mortality in this population [6]. The interplay between an impaired immune response and ongoing immune stimulation may contribute to the low-grade systemic inflammation and altered cytokine balance observed in the uremic state. Despite thorough research, the mechanisms underlying the changes in thyroid hormone levels associated with NTI remain unclear.

IL-6 affects hypothalamo-pituitary-thyroid (HPT) axis through various mechanisms. In the peripheral circulation, IL-6 inhibits type 1 deiodinase (DIO1), the primary enzyme catalyzing peripheral T4-to-T3 conversion, while simultaneously activating type 3 deiodinase (DIO3), which accelerates T3 inactivation. IL-6 also reduces hepatic synthesis of thyroid hormone-binding globulin and downregulates thyroid hormone membrane transporters (MCT8, OATP1C1), impairing cellular uptake of thyroid hormones [7]. In the central, IL-6 may disrupt the normal negative feedback regulation of the HPT axis, potentially causing to TSH dysregulation.

Despite this mechanistic framework, clinical data specifically characterizing the independent association between circulating IL-6 and individual thyroid hormone parameters in the CKD hemodialysis population remain limited. Most prior studies have examined inflammatory markers as part of broader malnutrition-inflammation-atherosclerosis complexes without isolating the IL-6–thyroid axis relationship with adequate statistical [8, 9]. Furthermore, no prior study has provided a clinically applicable IL-6 threshold for identifying thyroid dysfunction in this population.

This study aimed to evaluate the association between serum IL-6 and thyroid hormone parameters using multiple comparison correction, determine whether IL-6 independently predicts T3 and TSH after adjusting for major clinical confounders, and to establish the discriminatory performance of IL-6 for thyroid dysfunction via ROC curve analysis, providing a practical biomarker threshold for clinical application.

## METHODS

### Study Design and Setting

This cross-sectional observational study was conducted at the Dialysis Unit of Airlangga University Hospital, Surabaya, Indonesia, from January 1 to March 31, 2024. The Ethics Committee of Airlangga University Hospital approved the study. The study was designed and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies.

## Participants

Consecutive sampling was applied to all eligible patients registered in the dialysis unit during the study period. Inclusion criteria were age  $\geq 21$  years, and CKD stage 5 with maintenance hemodialysis for  $\geq 3$  months. Exclusion criteria were prior diagnosis of thyroid disease, current use of thyroid-modulating medications, active infection or sepsis at data collection, and incomplete records for key study variables. A total of 65 patients fulfilled the eligibility criteria. No formal a priori sample size calculation was performed; all consecutive eligible patients registered in the dialysis unit during the 3-month study period were enrolled, yielding a convenience sample considered adequate for the primary correlation and regression analyses based on effect sizes reported in prior CKD-inflammation-thyroid literature.

## Bias

To minimize selection bias, consecutive sampling was used to enroll all eligible patients registered during the study period rather than convenience or purposive sampling. To minimize measurement bias, all laboratory analyses were performed in a single accredited laboratory using standardized assay protocols, and IL-6 and thyroid function tests were measured simultaneously from samples collected prior to the hemodialysis session to avoid dialysis-related fluctuation. Potential confounding by clinical and demographic factors was addressed a priori by including age, sex, BMI, hemodialysis duration, albumin, diabetes mellitus, and hypertension in the multivariable regression model.

## Data Collection

All clinical and laboratory data were extracted from electronic medical records. Extracted variables included sociodemographic characteristics, anthropometric measurements, comorbidities (diabetes mellitus, hypertension), hemodialysis parameters, nutritional status (Subjective Global Assessment, SGA), and complete laboratory panel.

## Laboratory Measurements

Serum IL-6 was measured using *Automatic Immunoassay Fluorescence* method with *Automatic Fluorescence Immunoassay Analyzer Vazyme QD-S2000*, with samples collected prior to the hemodialysis session. Thyroid function was assessed by simultaneous measurement of TSH (third-

generation electrochemiluminescence immunoassay; reference range 0.35–4.75  $\mu$ IU/mL), total T3 (reference 0.8–1.9 ng/mL), total T4 (reference 5.0–13.0  $\mu$ g/dL), free T3 (FT3; reference 2.28–4.56 pg/mL), and free T4 (FT4; reference 0.78–1.71 ng/dL). Data quality review identified systematic decimal entry errors in a subset of total T4, FT4, and FT3 records, which were verified against original laboratory reports and corrected prior to analysis. Thyroid dysfunction was defined as: Low T3 Syndrome (total T3 < 0.8 ng/mL, TSH not elevated [ $\leq$  4.75  $\mu$ IU/mL, including subnormal values]); Hypothyroidism (TSH > 4.75  $\mu$ IU/mL with low T3 or T4); or Subclinical Hypothyroidism (TSH > 4.75  $\mu$ IU/mL, normal T3 and T4). Patients meeting no criterion were classified as Normal.

## Statistical Analysis

Continuous variables are reported as median and interquartile range (IQR); categorical variables as frequencies and percentages. Normality was assessed by the Shapiro-Wilk test. Spearman rank correlation was used to assess associations between IL-6 and five thyroid parameters (TSH, total T3, total T4, FT3, FT4). Bonferroni correction was applied for five simultaneous tests (adjusted  $\alpha$  = 0.010). Missing data were handled using complete-case analysis for each specific test; the number of patients included in each analysis is reported alongside the corresponding result.

Multivariable linear regression was conducted to evaluate the independent effect of IL-6 on T3 and TSH. TSH was log-transformed prior to regression owing to positive skew. Covariates included age, sex, BMI, hemodialysis duration, serum albumin, diabetes mellitus, and hypertension. ROC curve analysis assessed IL-6 discriminatory performance for thyroid dysfunction; 95% confidence intervals for AUC were derived from 2,000 bootstrap iterations. The optimal cutoff was identified using the Youden index. Differences in IL-6 across thyroid categories were tested by Kruskal-Wallis, with pairwise post-hoc Mann-Whitney U tests and Bonferroni correction ( $\alpha$  = 0.017). All analyses used IBM SPSS Statistics version 20 (SPSS Inc., Chicago, IL, USA); bootstrap analyses were performed using Python (version 3.10). All p-values were two-tailed.

## Ethics

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was granted by the Research Ethics Committee of Universitas Airlangga Hospital (No. 175/KEP/2023), compliant with ICH-GCP and CIOMS–WHO Guidelines 2016. Written informed consent was obtained from all participants.

## RESULTS

### Participant Characteristics

Sixty-five CKD patients on maintenance hemodialysis were enrolled. The median age was 53 years (45–60), and 56.9% were male. Hypertension was present in 81.5% and diabetes mellitus in 47.7%. Median

BMI was 23.9 kg/m<sup>2</sup> and median hemodialysis duration was 3.0 years (1.0–4.25). The majority had good nutritional status (SGA 92.3%). Thyroid dysfunction was identified in 48 of 65 patients (73.8%): low T3 syndrome in 32 (49.2%), hypothyroidism in 15 (23.1%), and subclinical hypothyroidism in 1 (1.5%). Participant characteristics are shown in Table 1. One patient had incomplete records for hemodialysis duration and albumin and was excluded from the multivariable regression models (n = 64 for regression analyses); all other analyses, including descriptive statistics, correlation, and ROC analysis, included the full cohort (n = 65).

Table 1  
Participant Characteristic

| Characteristic                                                                                                                                                                                                                                                                                                       | N (%) or Median (range) | Reference Range |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-----------------|
| Age, years                                                                                                                                                                                                                                                                                                           | 53 (45–60)              | —               |
| Sex, male, n (%)                                                                                                                                                                                                                                                                                                     | 37 (56.9%)              | —               |
| BMI, kg/m <sup>2</sup>                                                                                                                                                                                                                                                                                               | 23.9 (22.4–27.6)        | —               |
| Hemodialysis duration, years                                                                                                                                                                                                                                                                                         | 3.0 (1.0–4.25)          | —               |
| Diabetes mellitus, n (%)                                                                                                                                                                                                                                                                                             | 31 (47.7%)              | —               |
| Hypertension, n (%)                                                                                                                                                                                                                                                                                                  | 53 (81.5%)              | —               |
| Good nutritional status (SGA), n (%)                                                                                                                                                                                                                                                                                 | 60 (92.3%)              | —               |
| Albumin, g/dL                                                                                                                                                                                                                                                                                                        | 3.59 (3.24–3.79)        | 3.5–5.0         |
| BUN, mg/dL                                                                                                                                                                                                                                                                                                           | 70.5 (54.2–87.3)        | —               |
| Creatinine, mg/dL                                                                                                                                                                                                                                                                                                    | 12.67 (9.76–15.01)      | —               |
| IL-6, pg/mL                                                                                                                                                                                                                                                                                                          | 10.10 (6.13–17.16)      | < 7.0           |
| TSH, $\mu$ IU/mL                                                                                                                                                                                                                                                                                                     | 2.20 (1.61–3.47)        | 0.35–4.75       |
| Total T3, ng/mL                                                                                                                                                                                                                                                                                                      | 0.75 (0.69–0.82)        | 0.8–1.9         |
| Total T4, $\mu$ g/dL                                                                                                                                                                                                                                                                                                 | 6.41 (5.40–7.36)        | 5.0–13.0        |
| Free T3, pg/mL                                                                                                                                                                                                                                                                                                       | 2.27 (2.11–2.51)        | 2.28–4.56       |
| Free T4, ng/dL                                                                                                                                                                                                                                                                                                       | 1.01 (0.87–1.14)        | 0.78–1.71       |
| Low T3 Syndrome, n (%)                                                                                                                                                                                                                                                                                               | 32 (49.2%)              | —               |
| Hypothyroidism, n (%)                                                                                                                                                                                                                                                                                                | 15 (23.1%)              | —               |
| Subclinical Hypothyroidism, n (%)                                                                                                                                                                                                                                                                                    | 1 (1.5%)                | —               |
| Normal thyroid function, n (%)                                                                                                                                                                                                                                                                                       | 17 (26.2%)              | —               |
| Baseline characteristics (n = 65). Data are median unless otherwise stated. BMI = body mass index; BUN = blood urea nitrogen; IL-6 = interleukin-6; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; FT3 = free triiodothyronine; FT4 = free thyroxine; SGA = Subjective Global Assessment. |                         |                 |

## Spearman Correlation between IL-6 and Thyroid Hormone Parameters

Spearman correlation with Bonferroni correction in Table 2 revealed a significant positive association between IL-6 and TSH ( $r = +0.344$ ,  $p = 0.005$ ,  $p$  Bonferroni = 0.025). A borderline negative correlation was observed between IL-6 and total T3 ( $r = -0.277$ ,  $p = 0.025$ ,  $p$  Bonferroni = 0.126), which did not survive

correction for multiple comparisons. No significant correlations were found between IL-6 and FT4 ( $r = -0.062$ ,  $p = 0.623$ ), FT3 ( $r = -0.110$ ,  $p = 0.385$ ), or total T4 ( $r = -0.150$ ,  $p = 0.233$ ).

Table 2  
Correlation between IL-6 and Thyroid Function Parameters

| Thyroid Parameter                                                                                                                                                                                                                                                                                                      | N  | Spearman r   | p-value (raw) | p-value (Bonferroni) | Interpretation    |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|--------------|---------------|----------------------|-------------------|
| TSH                                                                                                                                                                                                                                                                                                                    | 65 | $r = +0.344$ | $p = 0.005$   | $p = 0.025$          | Significant *     |
| Total T3                                                                                                                                                                                                                                                                                                               | 65 | $r = -0.277$ | $p = 0.025$   | $p = 0.126$          | Not significant † |
| Free T3 (FT3)                                                                                                                                                                                                                                                                                                          | 65 | $r = -0.110$ | $p = 0.385$   | $p = 1.000$          | Not significant   |
| Free T4 (FT4)                                                                                                                                                                                                                                                                                                          | 65 | $r = -0.062$ | $p = 0.623$   | $p = 1.000$          | Not significant   |
| Total T4                                                                                                                                                                                                                                                                                                               | 65 | $r = -0.150$ | $p = 0.233$   | $p = 1.000$          | Not significant   |
| <i>Spearman rank correlation between IL-6 and thyroid function parameters with Bonferroni correction (5 simultaneous tests; adjusted <math>\alpha = 0.010</math>). * Significant after Bonferroni correction. † Significant at nominal level (<math>p &lt; 0.05</math>) but not after multiple testing correction.</i> |    |              |               |                      |                   |

## Multivariable Linear Regression

Results of multivariable linear regression for total T3 ( $n = 64$ ) are presented in Table 3. The T3 model was statistically significant (F-test  $p = 0.020$ ;  $R^2 = 0.270$ ; adjusted  $R^2 = 0.164$ ), with IL-6 as an independent and significant predictor of T3 ( $\beta = -0.0025$ , 95% CI:  $-0.005$  to  $-0.000$ ,  $p = 0.040$ ). Each 1 pg/mL increase in IL-6 was independently associated with a 0.0025 ng/mL decrease in total T3 after controlling for all covariates. Diabetes mellitus showed a borderline negative association with T3 ( $\beta = -0.055$ ,  $p = 0.081$ ). No other covariate reached statistical significance in the T3 model.

Table 3  
Multivariable Linear Regression Analysis

| Variable                                                                                                                                                                                                                                      | $\beta$ | SE    | p-value | 95% Confidence Interval |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------|---------|-------------------------|
| IL-6                                                                                                                                                                                                                                          | -0.0025 | 0.001 | 0.040 * | [- 0.005, - 0.000]      |
| Age                                                                                                                                                                                                                                           | -0.001  | 0.001 | 0.307   | [- 0.004, 0.001]        |
| Sex (male)                                                                                                                                                                                                                                    | + 0.017 | 0.030 | 0.576   | [- 0.044, 0.078]        |
| BMI                                                                                                                                                                                                                                           | + 0.004 | 0.004 | 0.276   | [- 0.004, 0.012]        |
| Hemodialysis duration                                                                                                                                                                                                                         | -0.004  | 0.009 | 0.660   | [- 0.021, 0.013]        |
| Albumin                                                                                                                                                                                                                                       | + 0.065 | 0.048 | 0.182   | [- 0.031, 0.161]        |
| Diabetes mellitus                                                                                                                                                                                                                             | -0.055  | 0.031 | 0.081   | [- 0.118, 0.007]        |
| Hypertension                                                                                                                                                                                                                                  | -0.067  | 0.039 | 0.095   | [- 0.146, 0.012]        |
| <i>Multivariable linear regression – predictors of total T3 (n = 64). <math>R^2 = 0.270</math>, Adjusted <math>R^2 = 0.164</math>, F-test <math>p = 0.020</math>. * <math>p &lt; 0.05</math>. SE = standard error; BMI = body mass index.</i> |         |       |         |                         |

In the TSH model, the overall model was not statistically significant (F-test  $p = 0.654$ ;  $R^2 = 0.097$ , adjusted  $R^2 = -0.034$ ), and IL-6 did not independently predict log-TSH ( $\beta = 0.016$ ,  $p = 0.087$ ) after controlling for confounders.

## ROC Curve Analysis

ROC curve analysis evaluated IL-6 discriminatory performance for thyroid dysfunction in Table 4. IL-6 demonstrated statistically significant moderate discriminatory ability (AUC = 0.665; 95% CI: 0.528–0.799). The optimal cutoff by the Youden index was IL-6  $\geq 10.10$  pg/mL, yielding a sensitivity of 60.4%, specificity of 76.5%, PPV of 87.9%, and NPV of 40.6%. Given the high prevalence of thyroid dysfunction (73.8%), the PPV reflects the probability of confirming dysfunction when IL-6 exceeds this threshold.

Table 4  
Discriminatory performance of IL-6 for Thyroid Dysfunction

| ROC Parameter                                                                                                                                      | Value                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|
| N                                                                                                                                                  | 65                      |
| Thyroid dysfunction prevalence                                                                                                                     | 48/65 (73.8%)           |
| AUC                                                                                                                                                | 0.665                   |
| 95% CI (bootstrap, 2000 iterations)                                                                                                                | 0.528–0.799             |
| Optimal cutoff (Youden index)                                                                                                                      | IL-6 $\geq$ 10.10 pg/mL |
| Sensitivity                                                                                                                                        | 60.4%                   |
| Specificity                                                                                                                                        | 76.5%                   |
| Positive Predictive Value (PPV)                                                                                                                    | 87.9%                   |
| Negative Predictive Value (NPV)                                                                                                                    | 40.6%                   |
| <i>Thyroid dysfunction = Low T3 Syndrome, Hypothyroidism, or Subclinical Hypothyroidism. AUC = area under the curve; CI = confidence interval.</i> |                         |

## IL-6 Levels across Thyroid Categories

Median IL-6 showed a gradient pattern across thyroid categories: Normal 7.43 (IQR: 5.05–9.71), Hypothyroidism 10.70 (IQR: 7.31–12.73), and Low T3 Syndrome 15.80 pg/mL (IQR: 6.73–20.48). Kruskal-Wallis test did not reach statistical significance ( $H = 4.777$ ,  $p = 0.092$ ). Post-hoc comparison between the Normal and Low T3 Syndrome groups was not statistically significant (Mann-Whitney U:  $p = 0.038$ ;  $p$  Bonferroni = 0.113).

## DISCUSSION

This cross-sectional study demonstrated that IL-6 is an independent predictor of total T3 in CKD patients on maintenance hemodialysis ( $\beta = -0.0025$ ,  $p = 0.040$ ; adjusted  $R^2 = 0.164$ ), and exhibits moderate discriminatory ability for thyroid dysfunction (AUC = 0.665; 95% CI: 0.528–0.799). The positive Bonferroni-corrected correlation between IL-6 and TSH ( $r = +0.344$ ,  $p_{\text{Bonferroni}} = 0.025$ ) further supports a role for systemic inflammation in HPT axis dysregulation in this population.

The findings that elevated IL-6 independently predicts lower T3, after adjusting for major clinical confounders, is consistent with established mechanisms. Wajner et al. demonstrated that IL-6 directly promotes NTIS in human cells by inhibiting DIO1 (reducing T4-to-T3 conversion) and activating DIO3 (accelerating T3 degradation), while also downregulating thyroid hormone transporters MCT8 and OATP1C1, impairing cellular T3 uptake [7]. Our findings support this mechanism in patients undergoing hemodialysis and build on previous studies that reported only univariable associations.

The negative IL-6 and T3 correlation ( $r = -0.277$ ) did not survive Bonferroni correction ( $p_{\text{Bonferroni}} = 0.126$ ). However, in the multivariable regression model, IL-6 remained a statistically significant, independent predictor of T3 ( $p = 0.040$ ) after adjusting for age, sex, BMI, hemodialysis duration, albumin, diabetes mellitus, and hypertension. This finding is consistent with recent studies in CKD and dialysis populations showing that inflammatory markers, including IL-6, are independently associated with low T3 levels and low T3 syndrome, even after controlling for demographic and clinical confounders

In patients with advanced CKD, serum T3 has been shown to be inversely related to inflammatory status (CRP and IL-6) and positively related to markers of nutritional and protein metabolism, supporting the concept that low T3 in CKD reflects, at least in part, the malnutrition–inflammation complex. Similarly, in cohorts with impaired kidney function, multivariate regression analyses have identified eGFR and inflammatory burden as independent determinants of circulating thyroid hormone levels, particularly fT3. Low T3 syndrome is also common in dialysis patients and has been linked to higher inflammatory activity and worse clinical outcomes, further underscoring the interplay between inflammation, kidney dysfunction, and thyroid hormone metabolism.

Although the unadjusted correlation between IL-6 and T3 in our study was modest and did not survive correction for multiple testing, the persistence of IL-6 as an independent predictor in the adjusted model provides additional evidence that inflammation may contribute to the pathogenesis of low T3 syndrome in hemodialysis patients. Mechanistically, experimental and clinical data suggest that pro-inflammatory cytokines such as IL-6 can promote nonthyroidal illness syndrome by altering deiodinase activity (downregulating DIO1 and upregulating DIO3), thereby reducing peripheral conversion of T4 to T3 and increasing reverse T3. Taken together, our results align with contemporary evidence that IL-6–mediated inflammation is one of several drivers of altered thyroid hormone metabolism in advanced CKD, alongside malnutrition, comorbidity burden, and uremic toxicity.

The biological plausibility of these associations is well-supported. IL-6 inhibits DIO1, reducing peripheral T4-to-T3 conversion; activates DIO3, accelerating T3 inactivation; and downregulates thyroid hormone transporters MCT8 and OATP1C1, impairing cellular T3 uptake [7]. In the hemodialysis setting, these IL-6-driven mechanisms are compounded by uremia-induced inhibition of iodothyronine deiodination, metabolic acidosis, protein-energy malnutrition, and accumulated organic acids – creating a milieu uniquely susceptible to thyroid hormone dysregulation.

The ROC analysis identified IL-6  $\geq 10.10$  pg/mL as an optimal screening threshold for thyroid dysfunction (AUC = 0.665; 95% CI: 0.528–0.799). The high PPV (87.9%) at this cutoff is clinically relevant given the high background prevalence of thyroid dysfunction (73.8%) in this population. While the AUC of 0.665 indicates moderate rather than high discriminatory ability, the CI does not cross 0.5, and the specificity of 76.5% enables practical rule-in utility. IL-6 measurement is already available in many centers managing CKD-HD patients; this threshold could trigger thyroid function evaluation in patients not routinely screened [10].

This study has several strengths. Consecutive sampling reduced selection bias. Data quality review identified and corrected systematic decimal entry errors in total T4, FT4, and FT3 records, ensuring analytical integrity across all five thyroid parameters. Multiple statistical methods were applied – Spearman correlation with Bonferroni correction, multivariable regression, and ROC analysis – providing converging lines of evidence. The multivariable analysis is a methodological advance over univariable correlation alone, establishing the independence of the IL-6–T3 relationship.

Several limitations should be acknowledged. The cross-sectional design precludes causal inference. The sample was drawn from a single tertiary center over three months, potentially limiting generalizability and not accounting for seasonal variation in IL-6. Findings may not be directly generalizable to CKD-HD populations with different ethnic backgrounds, dialysis modalities, or healthcare settings, and should be validated in multicenter cohorts before broader clinical application. The sample size ( $n = 65$ ), while sufficient for primary analyses, yields a wide ROC CI (0.528–0.799), reflecting limited precision in biomarker threshold estimation. The IL-6 assay platform was not specified in original records; future studies should report assay characteristics to enable comparison. Potential confounders not captured include dialysis adequacy (Kt/V), residual renal function, erythropoietin use, and specific medication classes. Total T4, FT3, and FT4 values for a subset of patients required correction from original records; while verified, this introduces a minor data quality caveat [11].

In clinical practice, routine monitoring of IL-6 in CKD patients on maintenance hemodialysis may serve as a low-cost flag for thyroid dysfunction risk. Patients with  $\text{IL-6} \geq 10.10 \text{ pg/mL}$  may benefit from formal thyroid function assessment regardless of symptoms. The IL-6–thyroid axis also represents a potential therapeutic target: anti-IL-6 strategies, already in clinical use for inflammatory indications, may theoretically attenuate thyroid hormone dysregulation in CKD, a hypothesis meriting prospective evaluation. Future studies should employ multicenter designs, longitudinal follow-up, and formal external validation of the reported IL-6 cutoff.

## CONCLUSION

In patients with CKD undergoing maintenance hemodialysis, IL-6 is an independent predictor of reduced total T3 and demonstrates moderate discriminatory ability for thyroid dysfunction ( $\text{AUC} = 0.665$ , 95% CI: 0.528–0.799). An IL-6 threshold of 10.10 pg/mL provides a practical screening cutoff with a positive predictive value of 87.9%. These findings support further prospective, multicenter validation of IL-6 as an inflammatory biomarker for thyroid dysfunction in this high-risk population.

## Declarations

### Ethics Approval

Conducted per the Declaration of Helsinki. Ethics approval: Research Ethics Committee, Universitas Airlangga Hospital (No. 175/KEP/2023); ICH-GCP and CIOMS–WHO 2016 compliant. Written informed consent obtained from all participants.

## **Consent for Publication**

Not applicable. No individually identifiable participant data are included.

## **Data Availability**

Dataset available upon reasonable request to the corresponding author.

## **Competing Interests**

All authors declare no competing interests.

## **Funding**

No external funding was received for this study.

## **Authors' Contributions**

SWM: Conceptualization, methodology, validation, supervision, and writing—review and editing.

FDR: Conceptualization, methodology, formal analysis, data curation, project administration, and writing—original draft.

PO: Investigation, data curation, and writing—original draft.

MT: Methodology, supervision, interpretation of the findings, and writing—review and editing.

AT: Investigation, resources, clinical interpretation of the findings, and writing—review and editing.

DK: Investigation, data curation, clinical interpretation of the findings, and writing—review and editing.

SWM and FDR had full access to the study data. FDR performed the statistical analyses, and SWM independently verified the results. All authors critically reviewed the manuscript, approved the final version for submission, and agreed to be accountable for all aspects of the work.

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## Figures

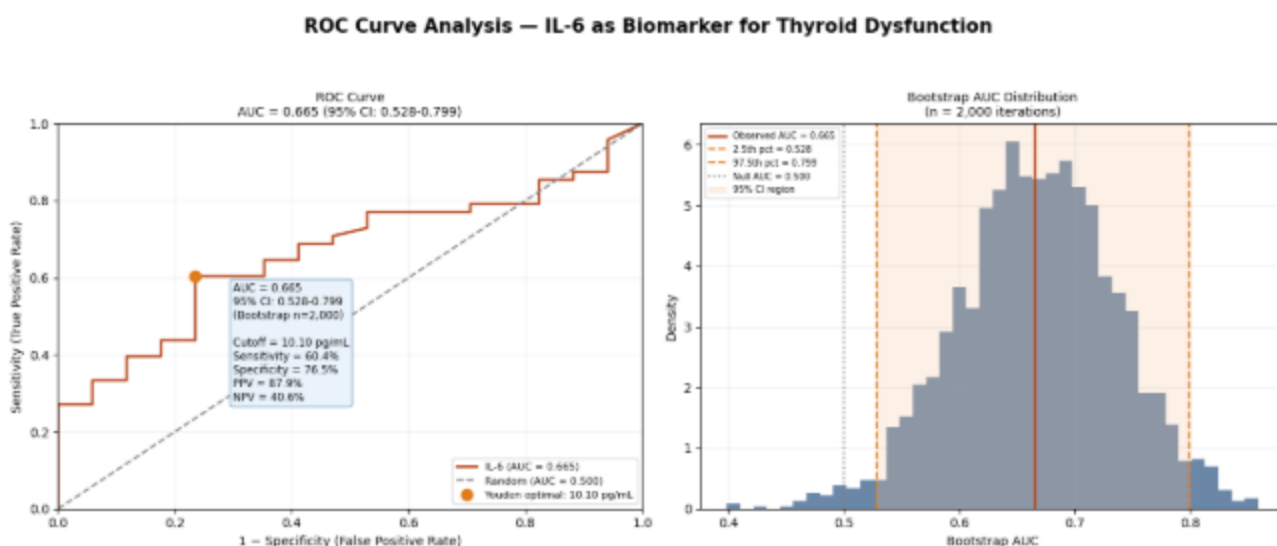


Figure 1

