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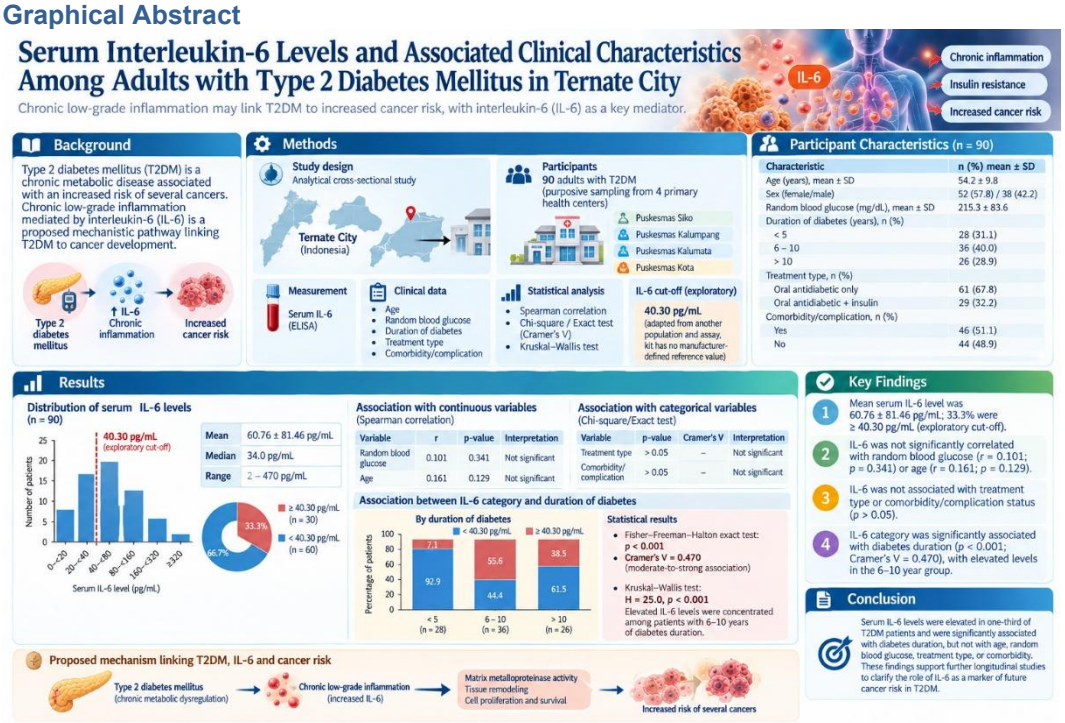
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Serum Interleukin-6 in Adults With Type 2 Diabetes Mellitus in Ternate City: A Cross-Sectional Study

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Graphical Abstract



Abstract: Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease associated with an increased risk of several cancers, and chronic low-grade inflammation mediated by interleukin-6 (IL-6) is a proposed mechanistic pathway linking the two conditions. This analytical cross-sectional study aimed to describe serum IL-6 concentrations among adults with T2DM in Ternate City and to examine their association with clinical characteristics, involving 90 T2DM patients recruited by purposive sampling from four primary health centers (Puskesmas Siko, Kalumpang, Kalumata, and Kota) in Ternate City. Serum IL-6 was measured by enzyme-linked immunosorbent assay (ELISA) and analyzed using Spearman correlation and chi-square/exact tests with Cramer's V effect size, with an exploratory cut-off of 40.30 pg/mL adapted from another population and assay, since the kit has no manufacturer-defined reference value. The mean IL-6 level was 60.76±81.46 pg/mL (median 34.0; range 2-470 pg/mL), and 33.3% were at or above the exploratory

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threshold. IL-6 was not significantly correlated with random blood glucose (r=0.101; p=0.341) or age (r=0.161; p=0.129), nor associated with treatment type or comorbidity/complication status (p>0.05). IL-6 category was significantly associated with diabetes duration (Fisher–Freeman–Halton exact p<0.001; Cramer's V=0.470, moderate-to-strong), with elevated levels concentrated among patients with 6-10 years of disease duration, corroborated by a Kruskal–Wallis test (H=25.0, p<0.001). Other associations and the cut-off are exploratory; the cross-sectional design cannot establish whether IL-6 is a marker of future cancer risk, which requires longitudinal study.

Keywords: Type 2 diabetes mellitus; Interleukin-6; Chronic inflammation; Diabetes duration; Cross-sectional study.

INTRODUCTION

Beyond its well-established microvascular and macrovascular complications, T2DM has increasingly been recognized as an independent risk factor for several malignancies, including cancers of the liver, biliary tract, pancreas, stomach, colorectum, kidney, bladder, breast, and endometrium, through shared pathophysiological mechanisms such as hyperinsulinemia, insulin-like growth factor signaling, hyperglycemia-induced oxidative stress, and chronic low-grade inflammation.[6] Cancer itself remains a major global health burden, with risk determined by a complex interplay of genetic, environmental, and lifestyle factors,[7] underscoring the importance of identifying modifiable or measurable biological indicators that could support early risk assessment in vulnerable populations such as patients with T2DM.

One candidate biological link between diabetes and cancer is interleukin-6 (IL-6), a pleiotropic pro-inflammatory cytokine secreted by adipocytes, macrophages, and other immune cells in response to metabolic stress. IL-6 has been shown to modulate insulin secretion from pancreatic beta-cells and to contribute to insulin resistance in T2DM.[8] Beyond its metabolic role, IL-6 is a well-recognized mediator of tumor-promoting inflammation, capable of activating the Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) pathway to drive cell proliferation, angiogenesis, and immune evasion within the tumor microenvironment.[9]

Elevated circulating IL-6 has repeatedly been reported in patients with T2DM compared with healthy individuals, with several studies proposing diagnostic cut-off values for identifying T2DM based on IL-6 concentration.[10] However, meta-analytic evidence indicates that the contribution of the IL-6 inflammatory pathway to T2DM risk at the population level is comparatively modest relative to adiposity-related mechanisms,[11] suggesting that once T2DM is established, disease-related factors such as duration of illness, glycemic control, and the presence of complications may more strongly influence IL-6 concentration.

Importantly, recent large cohort studies in patients with newly diagnosed T2DM have reported that circulating IL-6 may be associated with subsequent cancer risk. In a Danish cohort of 6,466 patients with newly diagnosed T2DM followed for a median of 8.8 years, baseline IL-6 was significantly associated with the development of obesity-related cancers, whereas tumor necrosis factor-alpha and high-sensitivity C-reactive protein were not predictive.[12] This particular finding has to date been reported only as a conference abstract, and independent peer-reviewed replication is still needed. Similarly, another Danish cohort study of over 11,000 patients with early T2DM demonstrated that the inflammatory biomarker YKL-40 was associated with increased risk of several cancers, particularly liver and bladder cancer,[13] and a Swedish cohort of more than 100,000 individuals with newly diagnosed T2DM found that routinely measured inflammatory and biochemical markers were associated with subsequent pancreatic cancer risk.[14] These findings, together with mechanistic evidence that obesity-driven chronic inflammation promotes a pro-tumorigenic microenvironment,[15] support the biological plausibility of IL-6 as part of the chronic inflammatory pathway linking

T2DM and carcinogenesis, rather than as a validated cancer-risk biomarker in its own right.

Despite this evidence, no reference cut-off value for serum IL-6 has been established for the ELISA reagent kit used in routine laboratory settings such as those available in Ternate City, and no local data describing IL-6 levels among T2DM patients in this region are available. Given the absence of a manufacturer-defined reference range, a cut-off value derived from a comparable population using the same general ELISA method, though a different assay kit, was adapted for exploratory use in this study; its portability to the present cohort and assay is uncertain and is discussed further below.[16] This study was therefore conducted to describe serum IL-6 concentrations among adults with T2DM in Ternate City and to explore their association with clinical characteristics-namely random blood glucose, age, diabetes duration, treatment type, and comorbidity/complication status. This cross-sectional design does not measure cancer occurrence; the T2DM-cancer literature is presented above only as biological rationale for future, dedicated longitudinal research, and is kept separate from the findings reported below.

MATERIALS AND METHOD

This study used an analytical cross-sectional design, given the inferential comparisons performed between serum IL-6 and clinical characteristics, conducted in four primary health center (Puskesmas) catchment areas in Ternate City, North Maluku Province, Indonesia, namely Puskesmas Siko, Puskesmas Kalumpang, Puskesmas Kalumata, and Puskesmas Kota. The initial study population consisted of 100 patients with T2DM domiciled in Ternate City who met Inclusion criteria: diagnosed with T2DM by a medical professional according to World Health Organization/IDF criteria (confirmed from each participant's medical record), aged ≥18 years, willing to provide a blood sample for IL-6 examination, and domiciled in Ternate City, whereas patients receiving high-dose immunomodulatory or anti-inflammatory medication were excluded. Participants were recruited using purposive sampling until the target of 100 respondents was reached. Of the 90 analyzed participants, 25 were recruited from the Puskesmas Kalumata catchment area, 12 from Puskesmas Kota, and 27 and 26 from Puskesmas Siko and Puskesmas Kalumpang, respectively. Recruitment took place from 27 June to 13 July 2026, after ethical approval had been obtained (11 June 2026; see Ethics Statement). The reference population comprised 2,065 patients with T2DM registered in 2025 at the four participating Puskesmas: Puskesmas Kalumpang (n=483), Puskesmas Kota (n=360), Puskesmas Siko (n=822), and Puskesmas Kalumata (n=400). The minimum sample size was calculated using the Slovin formula, $n = N/(1+Ne^2)$, where N is the reference population and e is the margin of error, set at 10%. This yielded a minimum sample size of 95.38, rounded up to 96 participants. A total of 100 eligible participants were recruited.

During laboratory examination, 10 blood samples did not meet the pre-analytical quality requirements for ELISA testing because of hemolysis and/or insufficient serum volume, and were therefore excluded. Consequently, 90 samples were included in the final analysis. Samples were tested once each, on each 96-well plate, six wells were allocated to the five-point standard curve and the blank, leaving 90 wells for patient samples, which matched the 90 analyzed samples exactly. Of the 10 excluded samples, 6 were excluded because of hemolysis and 4 because of insufficient serum volume. The 10 samples were therefore excluded solely because of hemolysis or insufficient serum volume during specimen processing, not because of any participant characteristic such as age.

Serum samples were processed and analyzed in batches organized by blood collection date, rather than by Puskesmas site. Venous blood was drawn in

the morning at 09:00 local time (WIT) into a plain (red-top) tube without anticoagulant, then centrifuged at 3,000 rpm for 15 minutes; the resulting serum was aliquoted into two Eppendorf tubes, one used for the RBG measurement and the other for the IL-6 assay, so that both measurements were performed on serum from the same blood draw. Serum was aliquoted and stored at −80°C prior to testing, following the kit manufacturer's recommended storage conditions, and repeated freeze-thaw cycles were avoided.

Serum IL-6 concentration was measured in serum by a sandwich enzyme-linked immunosorbent assay (ELISA) using a Human Interleukin-6 (IL-6) ELISA Kit (BT Lab, Biotechnology Laboratory; catalogue no. E0090Hu, 96-well/96-test format; lot no. 202605017; standard curve range 2-600 pg/mL; analytical sensitivity 1.03 pg/mL). For each plate, a five-point standard curve (20, 40, 80, 160, and 320 pg/mL) plus a zero standard/blank was run per the manufacturer's instructions, and results were read at 450 nm on a Thermo Scientific Multiskan SKY microplate spectrophotometer. Sample concentrations were calculated automatically by the instrument software (SkanIt) from a four-parameter logistic fit of the mean optical density of the five standards against their nominal concentrations; no additional calibrators were used and no sample dilution procedure was applied. Each sample was tested once, intra and inter assay precision (coefficient of variation <10% for both) were as reported by the kit manufacturer, and no additional independent internal quality-control materials beyond the standard curve and blank were run alongside patient samples-a limitation noted below. No sample required dilution or repeat testing. The manufacturer's stated analytical (standard curve) range for this kit is 2-600 pg/mL, but the calibration curve actually constructed for each plate spanned only the five non-zero standard points (20-320 pg/mL) plus the blank, as described above; the lowest observed value (2 pg/mL) therefore fell below, and the highest observed value (470 pg/mL) fell above, the highest calibrated standard point used to fit the curve on this plate. Concentrations for these samples were consequently obtained by extrapolation beyond the fitted calibration curve rather than by interpolation within it, which is a less certain basis for quantification and is treated as an additional limitation below.

Random blood glucose (RBG) was measured photometrically using a Microlab 300 clinical chemistry analyzer using serum as the specimen matrix, the RBG and IL-6 measurements were performed on serum aliquoted from the same blood draw. Data on age and treatment type were obtained by participant self-report. Diabetes duration and T2DM diagnosis were obtained from participants' medical records; however, diabetes duration was available from the records only in four categories (<1 year, 1-5 years, 6-10 years, and >10 years), and exact duration in years was not available. Comorbidity/complication status was obtained from participant self-report and cross-checked against each participant's medical record. This variable combined several conditions-eye disorders, hypertension, kidney disease, heart disease, dyslipidemia (elevated cholesterol), and gastric acid disorder (peptic/gastritis symptoms)-that were not all specifically defined as diabetic complications in the study protocol; the broader term "comorbidity/complication status" is therefore used throughout this manuscript rather than "complication status" alone. Treatment type was recorded from self-report as no current antidiabetic medication, oral antidiabetic medication, or insulin; because these data were self-reported, the no-medication category could reflect non-adherence to a prescribed regimen or a temporary period without therapy, and these two possibilities could not be distinguished in this dataset. RBG at the study visit was categorized descriptively as <200 mg/dL or ≥200 mg/dL, using the diagnostic threshold for diabetes,[17] This threshold is a diagnostic criterion for new-onset diabetes in an appropriate symptomatic context rather than a definition of adequate glycemic control in people already diagnosed with T2DM; a single random measurement cannot substitute for a sustained indicator of glycemic control, and HbA1c was not measured in this study.

Age was categorized according to the Indonesian Ministry of Health classification into young adult (26-35 years), late adulthood (36-45 years), early elderly (46-55 years), late elderly (56-65 years), and old age (>65 years). Because the ELISA reagent kit used in this study did not have a manufacturer-defined reference cut-off, serum IL-6 was categorized descriptively as below (<40.30 pg/mL) or at or above (≥40.30 pg/mL) using an exploratory threshold adapted from a study conducted in a comparable but not identical population (adults with prediabetes or newly diagnosed T2DM), which reported an area under the receiver operating characteristic curve (AUC) of 0.866, with 100% sensitivity and 60% specificity for distinguishing inflammatory status in that source study's own classification task; these performance figures describe that source study and task only and are not local performance estimates or measures of cancer prediction in the present cohort. That source study also used a different ELISA kit (Invitrogen, BMS213-2) from the kit used here (BT Lab); because concentrations from different immunoassays are not necessarily interchangeable without direct analytical comparison, the portability of this threshold to the present cohort and assay is uncertain, and the resulting categories are treated as exploratory only, with the actual IL-6 concentrations and their distribution retained as the primary description of these data.[16] Sex (male/female) was additionally recorded for each participant. The 40.30 pg/mL dichotomy described above was treated as a secondary, exploratory classification; the continuous IL-6 concentration was retained as the primary analytic outcome, as detailed below.

Data were processed using Microsoft Excel and analyzed using SPSS. Descriptive statistics (mean, standard deviation, median, minimum, and maximum) together with the median and interquartile range [IQR] for skewed variables were used to characterize numerical variables, and frequency distributions were used for categorical variables. Normality of numerical data was assessed using the Shapiro-Wilk test. Because IL-6, RBG, and age were not normally distributed, the association between IL-6 and RBG or age was examined using Spearman's rank correlation, with the strength of association interpreted using conventional effect-size criteria (r<0.30 = weak; 0.30-0.49 = moderate; ≥0.50 = strong). Ninety-five percent confidence intervals for each Spearman coefficient were derived using Fisher's z-transformation, and Wilson score 95% confidence intervals were calculated for the proportion of patients with elevated IL-6 within each duration group. Associations between IL-6 category and categorical variables (diabetes duration, treatment type, and comorbidity/complication status) were examined using the chi-square test, with Fisher's exact test applied when the expected cell count was below 5, for 2×2 tables, and with a Fisher–Freeman–Halton exact test (Monte Carlo exact procedure, 500,000 replications) applied for larger (r×c) tables in which more than 20% of cells had an expected count below 5, since the conventional Fisher's exact test is defined only for 2×2 tables, and the strength of each significant association was further quantified using Cramer's V effect size. A p-value <0.05 was considered statistically significant.

This study adhered to ethical research principles, including informed consent, anonymity, and confidentiality of participant data. The association between continuous IL-6 concentration and diabetes-duration groups was treated as the primary analysis. Because IL-6 was not normally distributed and diabetes duration was available only in four categorical groups (<1 year, 1–5 years, 6–10 years, and >10 years), IL-6 concentrations were compared across duration groups using the Kruskal–Wallis test, followed, where significant, by Dunn’s post-hoc pairwise comparisons with Holm’s correction for multiple testing. The association between the exploratory IL-6 category (<40.30 vs ≥40.30 pg/mL) and diabetes duration was assessed secondarily using the Fisher–Freeman–Halton exact test because of small expected cell counts, with Cramer’s V used to quantify the strength of association. Associations with RBG, age, treatment type, and comorbidity/complication status, together with the 40.30 pg/mL dichotomy itself,

were treated as exploratory, hypothesis-generating analyses. No correction for multiple comparisons was applied to these exploratory analyses, and their p-values should therefore be interpreted with caution. Because diabetes duration was available only in the four categories described above and exact duration in years was not available in this dataset, a Spearman correlation between continuous diabetes duration and IL-6 could not be performed.

A sensitivity analysis was performed by re-running the Kruskal–Wallis test after excluding the single highest IL-6 value (470 pg/mL) to assess its influence on the duration finding. A multivariable logistic regression adjusting for diabetes duration, age, sex, and comorbidity/complication status was initially attempted but was not retained in this report: because diabetes duration was available only in the four categories above and exact duration in years was not available, the model as originally specified had converted these bands into a numerical predictor using category midpoints, which is not an appropriate basis for a "per year" effect estimate. Re-specifying diabetes duration as a categorical predictor was not considered reliable given the very small number of participants in the >10-year band (n=2), which would not support stable coefficient estimation even with a penalized approach such as Firth logistic regression. This analysis is therefore not reported further; the Fisher–Freeman–Halton exact test and the Kruskal–Wallis test with Dunn's post-hoc comparisons on the continuous IL-6 measurement serve as the confirmatory analyses for the diabetes-duration association in this study.

RESULTS

Of the 90 respondents, the majority were in the early elderly group (46-55 years, 43.3%), had RBG below 200 mg/dL at the study visit (58.9%), had lived with T2DM for 1-5 years (71.1%), did not routinely take antidiabetic medication (54.4%), and had no recorded comorbidity/complication (72.2%), as shown in Table 1. Regarding sex, most participants were female (66/90, 73.3%), while 24/90 (26.7%) were male (Table 1).

Table 1. Distribution of Respondent Characteristics in Ternate City (n=90)

Characteristic	Category	n	%
Age	Young adult (26-35 y.o)	2	2.2
	Late adulthood (36-45 y.o)	6	6.7
	Early elderly (46-55 y.o)	39	43.3
	Late elderly (56-65 y.o)	28	31.1
	Old age (>65 y.o)	15	16.7
RBG	<200 mg/dL	53	58.9
	≥200 mg/dL	37	41.1
Diabetes duration	<1 year	11	12.2
	1-5 years	64	71.1
	6-10 years	13	14.4
	>10 years	2	2.2
Treatment type	No medication	49	54.4
	Oral antidiabetic	39	43.3
	Insulin	2	2.2
Comorbidity/complication status	None	65	72.2
	Present	25	27.8
Sex	Male	24	26.7
	Female	66	73.3

Source: Primary data, 2026.

The mean serum IL-6 level was 60.76±81.46 pg/mL (median 34.0; minimum 2; maximum 470 pg/mL). Shapiro-Wilk testing indicated that IL-6 (statistic 0.531; df 90; p<0.001), RBG (statistic 0.851; df 90; p<0.001), and age (statistic 0.929; df 90; p=0.0001) were all not normally distributed, as summarized in Table 2. Median [IQR] IL-6 was 34.0 [24.5–47.5] pg/mL.

Table 2. Descriptive Statistics of IL-6, RBG, and Age

Variable	n	Mean	SD	Median	Min	Max	IQR (Q1–Q3)
IL-6 (pg/mL)	90	60.76	81.46	34	2	470	24.5–47.5
RBG (mg/dL)	90	218.79	99.31	178.5	111	541	146.5–267.8
Age (years)	90	56.89	11.26	55	32	99	50–64

Source: Primary data, 2026.

Using the adapted cut-off of 40.30 pg/mL, 30 of 90 patients (33.3%) were at or above this threshold, while 60 patients (66.7%) were below it (Table 3). As noted in Methods, this dichotomization is a secondary, exploratory classification whose portability from the source study's population and assay is uncertain; the primary analyses reported below use the continuous IL-6 measurement, and the individual IL-6 concentrations are shown in Figure 1.

Table 3. Distribution of IL-6 Category (Cut-off 40.30 pg/mL)

IL-6 Category	n	%
Below threshold (<40.30 pg/mL)	60	66.7
At or above threshold (≥40.30 pg/mL)	30	33.3
Total	90	100

Source: Primary data, 2026.
Note: "Below"/"at or above" refer to an exploratory 40.30 pg/mL threshold adapted from a different population and a different ELISA kit; it is not a validated clinical reference range for this cohort or assay (see Methods).

Spearman correlation showed no significant association between IL-6 and RBG (r=0.101; p=0.341) (95% CI −0.11 to 0.30) or age (r=0.161; p=0.129) (95% CI −0.05 to 0.36); based on conventional effect-size criteria, both correlation coefficients fell within the weak category (r<0.30), indicating that although a positive trend was present, its practical strength was negligible (Table 4). These correlations were considered exploratory analyses; the confidence intervals indicate that the estimates are imprecise and cannot rule out a small-to-moderate association in either direction.

Table 4. Spearman Correlation of IL-6 with RBG and Age

Variable	n	r	p	Effect Size	95% CI Lower	95% CI Upper
IL-6 * RBG	90	0.101	0.3413	Weak	−0.11	0.30
IL-6 * Age	90	0.161	0.1289	Weak	−0.05	0.36

Source: Primary data, 2026.

Chi-square analysis showed no significant association between IL-6 category and treatment type (p=0.3152; Cramer's V=0.160, weak) or comorbidity/complication status (p=1.000; Cramer's V=0.000, none). For diabetes duration, the Fisher–Freeman–Halton exact test (principal test) showed a significant association (exact p<0.001; Cramer's V=0.470, moderate-to-strong; chi-square p=0.0002), with elevated IL-6 concentrated among patients with 6-10 years of disease duration (11 of 13 patients, 84.6%) compared with those with 1-5 years (17 of 64, 26.6%) or less than 1 year (1 of 11, 9.1%) (Tables 5 and 6). Because several expected cell counts in these tables were below 5, exact tests were used as the principal tests for these comparisons, reported below along with proportions with 95% confidence intervals, a Kruskal–Wallis test on the continuous IL-6 measurement, and a sensitivity analysis.

Table 5. Cross-Tabulation of IL-6 Category by Diabetes Duration

Diabetes Duration	Below (<40.3)	At/above (≥40.3)	Total	% At/Above Threshold (95% CI)
<1 year	10	1	11	9.1 (1.6–37.7)
1-5 years	47	17	64	26.6 (17.3–38.5)
6-10 years	2	11	13	84.6 (57.8–95.7)
>10 years	1	1	2	50.0 (9.5–90.5)
Total	60	30	90	33.3 (24.3–43.9)

Source: Primary data, 2026.
Note: "Below"/"at or above" refer to an exploratory 40.30 pg/mL threshold adapted from a different population and a different ELISA kit; it is not a validated clinical reference range for this cohort or assay (see Methods).

Table 6. Chi-Square Results and Cramer's V of IL-6 Category with Diabetes Duration, Treatment Type, and Comorbidity/Complication Status

Variable	χ^2	df	p	Cramer's V	Interpretation	Exact p (Fisher–Freeman–Halton / Fisher)
Diabetes duration	19.864	3	0.0002	0.47	Moderate-strong	<0.001 (primary)
Treatment type	2.309	2	0.3152	0.16	Weak	0.303 (exploratory)
Comorbidity/complication status	0	1	1.000	0	None	1.000 (exploratory)

Source: Primary data, 2026.

None of the 90 patients had a history of cancer; therefore, cancer history could not be statistically analyzed in relation to IL-6 level. Because four of the eight expected cell counts in the diabetes-duration table were below 5 (the smallest being 0.67; Table 6), the standard chi-square approximation is unreliable for this comparison. A Fisher–Freeman–Halton exact test (Monte Carlo exact procedure, 500,000 replications), taken as the principal inferential test for this comparison given the small expected cell counts, confirmed that the association between IL-6 category and diabetes duration was statistically significant (exact $p<0.001$); the magnitude of this association is better described by the Cramer's V effect size reported above (0.470, moderate-to-strong) than by comparing the two p-values, since a smaller p-value does not by itself indicate a stronger association. The proportion of patients with elevated IL-6 rose with duration category: 1/11 (9.1%; 95% CI 1.6–37.7%) for <1 year, 17/64 (26.6%; 95% CI 17.3–38.5%) for 1–5 years, 11/13 (84.6%; 95% CI 57.8–95.7%) for 6–10 years, and 1/2 (50.0%; 95% CI 9.5–90.5%) for >10 years (Table 5). The >10-year group contained only two participants, one above and one below the cut-off, and its wide confidence interval indicates that these two observations cannot establish a rising trend at the longest durations; this cell should be interpreted with caution rather than as evidence of a plateau or decline. The treatment-type comparison also included a very small stratum (2 insulin users), so the same small-expected-count limitation applies to its chi-square p-value; a Fisher–Freeman–Halton exact test gave a consistent result (exact $p=0.303$), supporting the conclusion of no significant association with treatment type. The comorbidity/complication status comparison (a 2×2 table with all expected counts ≥5) was adequately assessed by the continuity-corrected chi-square/Fisher's exact test already reported ($p=1.000$). Underlying IL-6-by-treatment and IL-6-by-comorbidity/complication counts are shown in Tables 7 and 8.

Table 7. Cross-Tabulation of IL-6 Category by Treatment Type

Treatment Type	Below (<40.3)	At/above (≥40.3)	Total
No medication	36	13	49
Oral antidiabetic	23	16	39
Insulin	1	1	2
Total	60	30	90

Source: Primary data, 2026.

Table 8. Cross-Tabulation of IL-6 Category by Comorbidity/Complication Status

Comorbidity/Complication Status	Below (<40.3)	At/above (≥40.3)	Total
Present	17	8	25
None	43	22	65
Total	60	30	90

Source: Primary data, 2026.

To confirm this pattern using the continuous IL-6 measurement rather than the exploratory 40.30 pg/mL dichotomy, a Kruskal–Wallis test compared IL-6 concentrations across the four duration groups and was highly significant (H=25.0, df=3, p<0.001; Table 9a), corroborating the categorical analysis. Median [IQR] IL-6 rose from 21.0 [20.0–22.0] pg/mL in the <1-year group to 34.0 [27.0–41.8] pg/mL in the 1–5-year group, 137.0 [59.0–247.0] pg/mL in the 6–10-year group, and 151.0 [78.0–224.0] pg/mL in the >10-year group (Table 9a; Figure 1). Dunn's post-hoc pairwise comparisons with Holm's correction (Table 9b) showed significantly higher IL-6 in the 6–10-year group than in both the <1-year group (adjusted p<0.001) and the 1–5-year group (adjusted p=0.005), and significantly higher IL-6 in the 1–5-year group than in the <1-year group (adjusted p=0.005); no pairwise comparison involving the >10-year group reached significance, consistent with its very small sample size (n=2) rather than an absence of effect. Figure 1 displays the individual IL-6 values by duration group and illustrates both the small cell sizes and the increasing spread of values with longer disease duration.

Table 9a. Median [IQR] Serum IL-6 by Diabetes Duration Group and Kruskal–Wallis Test

Diabetes Duration	n	Median IL-6 (pg/mL)	IQR
<1 year	11	21.0	20.0–22.0
1–5 years	64	34.0	27.0–41.8
6–10 years	13	137.0	59.0–247.0
>10 years	2	151.0	78.0–224.0

Source: Primary data, 2026
Note: (H=25.0, df=3, p<0.001)

Table 9b. Dunn's Post-Hoc Pairwise Comparisons of IL-6 by Diabetes Duration Group

Pairwise comparison	Holm-adjusted p
<1 year vs 1–5 years	0.005
<1 year vs 6–10 years	<0.001
<1 year vs >10 years	0.529
1–5 years vs 6–10 years	0.005
1–5 years vs >10 years	0.969
6–10 years vs >10 years	0.529

Source: Primary data, 2026

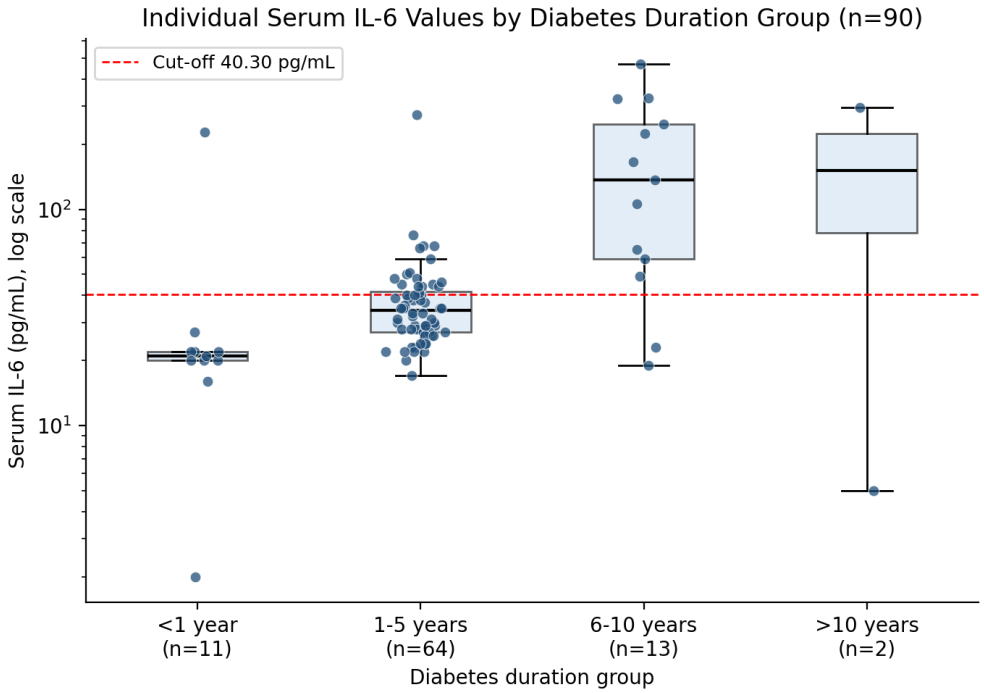


Figure 1. Individual serum IL-6 values by diabetes duration group (n=90), plotted on a log scale; boxes show median and interquartile range, and the dashed line marks the 40.30 pg/mL cut-off.

A sensitivity analysis excluding the single highest IL-6 value (470 pg/mL, from a participant with 6–10 years of diabetes duration) showed that the Kruskal–Wallis result remained materially unchanged ($H=23.2$, $p<0.001$, $n=89$), indicating that the duration association is not driven solely by this extreme observation. This value falls within the BT Lab Human IL-6 ELISA Kit's (Cat. No. E0090Hu) manufacturer-stated analytical range of 2–600 pg/mL, and the sample that produced it was handled according to the manufacturer's protocol (aliquoted and stored at −80°C, with freeze-thaw cycles avoided); however, as noted in Methods, it exceeds the highest calibration standard actually run on this plate (320 pg/mL) and was therefore obtained by extrapolation beyond the fitted standard curve rather than by interpolation within it. Consequently, this value cannot be described as definitively valid on analytical grounds alone; because repeat measurement or dilution-based confirmation was not performed, this is acknowledged as a limitation, and the sensitivity analysis above indicates that the overall duration finding does not depend on this single observation.

DISCUSSION

The predominance of patients in the early elderly group (46-55 years) with a relatively short diabetes duration (1-5 years) in this study reflects the broader epidemiological pattern of T2DM, which typically manifests in middle-aged and older adults as insulin sensitivity declines with age.[1] This demographic profile is clinically relevant, as advancing age and T2DM are both established, overlapping risk factors for several malignancies,[6,26] making this population relevant for exploring IL-6 as part of the chronic inflammatory pathway proposed to link T2DM and carcinogenesis, rather than as a validated cancer-risk biomarker.

Serum IL-6 was categorized using a cut-off value of 40.30 pg/mL adapted from Ahrițculesei et al.,[16] selected in the absence of a manufacturer-defined reference range for the kit used here; as detailed in Methods, the source study's population (prediabetes/newly diagnosed T2DM) and ELISA kit (Invitrogen, BMS213-2) differ from those of the present study (established T2DM; BT Lab kit), so this threshold is treated as exploratory rather than validated for this cohort.

Using this exploratory cut-off, one-third of participants were at or above the threshold; given the uncertain portability of this threshold noted above, this proportion is best read as a descriptive observation rather than a validated measure of clinical inflammatory burden. Adipose tissue is a major source of circulating IL-6, particularly under conditions of excess adiposity that commonly accompany T2DM,[18] and IL-6 additionally modulates insulin secretion from pancreatic beta-cells, linking it mechanistically to glycemic dysregulation.[8] Beyond its metabolic role, IL-6 is a well-established driver of tumor-promoting inflammation through activation of the JAK/STAT3 signaling pathway, which facilitates cell proliferation, angiogenesis, and immune evasion.[9] These mechanisms support the biological plausibility of IL-6 as part of the chronic inflammatory pathway linking T2DM and carcinogenesis, rather than establishing it as a validated cancer-risk biomarker.

IL-6 was not significantly associated with RBG, age, treatment type, or comorbidity/complication status in this study, and the corresponding effect sizes confirmed that these associations were weak to negligible in practical terms. As these comparisons were exploratory and were not adjusted for multiple testing, and as the corresponding 95% confidence intervals were wide, the following discussion should be read as possible interpretations rather than established explanations for these null findings. The lack of association with blood glucose is consistent with meta-analytic evidence indicating that the IL-6 inflammatory pathway explains only a modest proportion of diabetes risk at the population level, with adiposity-related mechanisms playing a comparatively larger role than acute glycemic fluctuations;[11] this may explain why a single random glucose measurement did not correlate strongly with IL-6 in patients who already carry an established T2DM diagnosis. Elevated IL-6 in relation to insulin resistance has similarly been shown to correlate more consistently with adiposity and insulin sensitivity than with glycemia alone, as demonstrated in other insulin-resistant populations such as women with polycystic ovary syndrome.[19] The absence of an age association contrasts with the concept of "inflammaging", in which IL-6 typically rises progressively with age in the general older population, as also reported in a large community-based cohort of older adults;[21,27] in this cohort, the effect of age may have been masked by the underlying chronic inflammatory state already present across age groups as a consequence of T2DM itself, in addition to the limited sample size. The lack of association with treatment type is difficult to interpret because, as noted in Methods, the 'no medication' category was self-reported and heterogeneous-potentially including patients non-adherent to a prescribed regimen and patients in a temporary period without therapy-which would blur any IL-6-lowering effect of antidiabetic medication such as that reported for metformin in patients with T2DM.[28] The absence of an association with comorbidity/complication status may be attributable to the non-specific comorbidity/complication variable used in this study (present/absent, without specifying the type of condition), whereas prior studies have found clearer IL-6 associations with specific microvascular complications, with serum IL-6 reported to be markedly higher among patients with diabetic retinopathy than controls (246.1±56.9 vs 67.22±33.35 pg/mL; p=0.01)[23] and among patients with diabetic nephropathy.[22]

In contrast, IL-6 category was significantly associated with diabetes duration, with a moderate-to-strong effect size (Cramer's V=0.470) and a markedly higher proportion of elevated IL-6 among patients with 6-10 years of disease duration. A comparable association between diabetes duration and IL-6 level has previously been reported in a study of 90 diabetic patients stratified by disease duration[24], although the direction of the relationship differed from the present findings; such discrepancies likely reflect differences in duration categories, study populations, and ELISA kits used across studies. Mechanistically, prolonged exposure to chronic hyperglycemia promotes the accumulation of advanced

glycation end-products (AGEs), which activate the receptor for AGEs (RAGE) and downstream NF-κB signaling, thereby increasing production of pro-inflammatory cytokines including IL-6;[25] this pathway has also been implicated as a mechanistic bridge linking diabetes with increased cancer risk through AGE-RAGE-mediated extracellular matrix remodeling and proliferative signaling.[20] The higher IL-6 observed among patients with longer diabetes duration in this study is therefore biologically plausible and identifies disease duration as a correlate worth further study, although whether this observation has any clinical monitoring utility was not tested here.

These findings were further reinforced when we moved beyond the exploratory categorical cut-off. The Fisher–Freeman–Halton exact test, appropriate given the small expected cell counts in this comparison, confirmed the categorical association with diabetes duration (exact $p<0.001$), and the Kruskal–Wallis test on the continuous IL-6 measurement showed the same pattern ($H=25.0$, $p<0.001$), with Dunn's post-hoc comparisons localizing the difference to the 6–10-year group relative to both shorter-duration groups. Furthermore, this association was not materially altered when the single highest IL-6 value was excluded in a sensitivity analysis. A multivariable logistic regression adjusting for age, sex, and comorbidity/complication status was initially attempted to test whether the duration association was independent of these covariates; however, because diabetes duration, although obtained from medical records, was available only in four categories rather than exact years, and the >10-year stratum contained only two participants, a numerically coded "per year" model was not an appropriate basis for inference, and this analysis is not reported further (see Methods and Limitations). Taken together, this convergence of exact and non-parametric approaches strengthens confidence that the duration–IL-6 association is not an artifact of the small cell counts or of a single extreme observation, even though the very small >10-year subgroup (n=2) still precludes any conclusion about whether IL-6 continues to rise, plateaus, or declines beyond ten years of disease duration, and independent confirmation by multivariable modeling awaits future studies that record exact diabetes duration in years.

Taken together, these findings describe a cross-sectional pattern of serum IL-6 in relation to diabetes duration in this population. They do not, by themselves, establish IL-6 as an indicator of cancer risk: no participant in this study had a cancer outcome, and the cross-sectional design cannot test the IL-6-cancer relationship directly. The biological rationale for pursuing this question in future work is strengthened by a Danish cohort study of patients with newly diagnosed T2DM, reported to date only as a conference abstract, in which baseline IL-6 was associated with subsequent obesity-related cancer risk over a median follow-up of 8.8 years; independent, peer-reviewed replication of this finding is still needed.[12] Comparable findings have been reported for other inflammatory biomarkers in early T2DM, including YKL-40 for liver and bladder cancer[13] and routinely measured biomarkers for pancreatic cancer,[14] collectively reinforcing chronic low-grade inflammation as a shared pathway linking T2DM with cancer development.[15] These studies involve different biomarkers and cohorts, however, and do not validate the specific assay or cut-off used here. Given that one-third of participants in this study were at or above the exploratory IL-6 threshold, concentrated among those with longer diabetes duration, this pattern is worth following up in dedicated longitudinal research; however, with only two participants followed beyond ten years and no cancer outcomes measured here, no clinical monitoring or screening recommendation can be drawn from this study. Furthermore, the interaction between accumulated AGEs and the RAGE receptor amplifies inflammatory pathways that sustain a pro-tumorigenic microenvironment,[29] which remains a plausible mechanistic pathway meriting direct investigation in future studies that measure cancer outcomes directly.[30]

Limitations

This study has several limitations that should be considered when interpreting these findings. First, diabetes duration was obtained from medical records but was available only in four categories (<1 year, 1-5 years, 6-10 years, and >10 years) rather than as exact years, which precluded a Spearman correlation between continuous duration and IL-6 as an additional confirmatory analysis; future studies should record exact duration. Second, 10 of the 100 recruited participants were excluded from analysis because their serum samples were hemolyzed (n=6) or of insufficient volume (n=4); these exclusions were due to specimen quality rather than participant characteristics, but the analyzed sample (n=90) is nevertheless smaller than the 100 participants originally recruited. After pre-analytical exclusions, the final analytical sample comprised 90 participants, which was below the initially calculated minimum sample size of 96 and may have reduced statistical precision, particularly in subgroup analyses. Third, comorbidity/complication status was recorded as a present/absent category covering eye disorders, hypertension, kidney disease, heart disease, dyslipidemia, and gastric acid disorder together, rather than as separate condition types, limiting comparison with studies reporting complication-specific IL-6 associations. Fourth, information on current infection, adiposity/body mass index, smoking status, other inflammatory disorders, recent procedures, and use of anti-inflammatory or glucose-lowering medication other than insulin was not systematically collected in this study-other than the pre-specified exclusion of patients receiving high-dose immunomodulatory or anti-inflammatory medication-so these variables could not be measured, excluded, or statistically adjusted for; because IL-6 is responsive to many of these conditions, their absence limits the ability to attribute the observed IL-6 pattern specifically to diabetes duration. Fifth, the 'no-medication' treatment category is heterogeneous: it may include patients non-adherent to a prescribed regimen or patients in a temporary period without therapy, and these two possibilities could not be distinguished in this dataset, further limiting interpretation of the treatment-type comparison. Sixth, the 40.30 pg/mL threshold was adapted from a different population (adults with prediabetes or newly diagnosed T2DM) and a different ELISA kit, so its reported performance characteristics (AUC, sensitivity, specificity) describe that source study and task only and do not necessarily apply here; glycemic status was also assessed by a single random blood glucose measurement only, since HbA1c was not available in this study. Relatedly, the calibration curve on each plate was fitted using five non-zero standard points spanning 20-320 pg/mL, narrower than the kit's manufacturer-stated analytical range of 2-600 pg/mL; the lowest (2 pg/mL) and highest (470 pg/mL) observed patient values therefore fell outside the calibrated range and were obtained by extrapolation rather than interpolation, which is a less certain basis for quantification, and repeat testing or dilution-based confirmation of these extreme values was not performed. Seventh, this was a single-time-point, purposively sampled study at a single city (Ternate City); each serum sample was assayed once rather than in duplicate, and no independent internal quality-control material was run alongside the standard curve, so assay reproducibility cannot be independently verified from this report. Finally, the >10-year duration subgroup (n=2) and the insulin-treated subgroup (n=2) were too small to draw firm conclusions; this same limitation, together with the availability of diabetes duration only in four categories rather than exact years, meant that a multivariable logistic regression estimating a "per year" effect of diabetes duration could not be reliably fitted and is not reported in this manuscript, and the cross-sectional design cannot establish temporality or causality between IL-6 and subsequent cancer risk.

CONCLUSION

Serum IL-6 levels among patients with type 2 diabetes mellitus in Ternate City were highly variable, and approximately one-third of patients were at or above

an exploratory threshold adapted from a different population and assay (see Methods); IL-6 level was not significantly associated with random blood glucose, age, treatment type, or comorbidity/complication status, with all corresponding effect sizes falling in the weak-to-negligible range, whereas IL-6 level was significantly associated with diabetes duration, with a moderate-to-strong effect size (Cramer's V=0.470) and elevated levels concentrated among patients who had lived with the disease for six to ten years. These findings describe the cross-sectional distribution of serum IL-6 in adults with T2DM in Ternate City and identify an exploratory association with diabetes duration. Because no participant had a cancer outcome and the design is cross-sectional, these results cannot establish IL-6 as an indicator of cancer risk, and no clinical practice recommendation can yet be drawn from them.

Dedicated longitudinal cohort studies that measure incident cancer, HbA1c, and other relevant clinical covariates are needed before the diabetes-duration-IL-6 pattern observed here can be translated into any clinical application. This duration association was corroborated by a Fisher–Freeman–Halton exact test and a Kruskal–Wallis test with Dunn's post-hoc comparisons on continuous IL-6 values, strengthening confidence that it is not a statistical artifact of small cell counts; a multivariable logistic regression was not retained because diabetes duration was available only in four categories rather than exact years and the >10-year stratum was too small to support a reliable model (see Limitations). Nonetheless, associations with RBG, age, treatment type, and comorbidity/complication status, as well as the 40.30 pg/mL cut-off itself, remain exploratory and were not corrected for multiple comparisons, and the very small >10-year and insulin-treated subgroups warrant cautious interpretation.

AUTHORS CONTRIBUTIONS

RP: conceptualization, methodology, investigation, formal analysis, writing (original draft), writing review & editing, supervision. AYA: investigation, data curation, writing (review) & editing. F: investigation, data curation, validation. A: methodology, formal analysis, writing (review) & editing. ZAH: validation, writing – review & editing, supervision. All authors have read and agreed to this submitted version of the manuscript.

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DATA AVAILABILITY STATEMENT

The deidentified data supporting this study are available from the corresponding author on reasonable request, subject to ethical and confidentiality requirements.

DISCLOSURE STATEMENT

The authors declare no relevant financial or nonfinancial competing interests.

ETHICS APPROVAL

This study was approved by the Health Research Ethics Committee of Poltekkes Kemenkes Ternate (approval number UM.02.03/F.XLVII.21/033/2026, dated 11 June 2026). All participants provided informed consent prior to data and specimen collection, and participant data were anonymized to protect confidentiality.

AI-ASSISTED STATEMENT

A generative AI assistant was used for language editing. The authors reviewed and take responsibility for the final scientific content and references.

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