RESEARCH ARTICLE

TGFB1 rs1800470 Polymorphism is Associated with Circulating TGF-β1 Levels and Left Ventricular Geometry in Hypertensive Patients

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Abstract

BACKGROUND: Transforming growth factor β1 (TGF-β1) is a major mediator of myocardial fibrosis and cardiac remodeling in hypertension. *TGFB1* (rs1800470) and *MTHFR* (rs1801133) are known for their roles in TGF-β1 regulation and cardiovascular remodeling, with *MTHFR* rs1801133 potentially influencing TGF-β1–mediated fibrosis through homocysteine metabolism. However, genetic determinants and relationship of these polymorphism with left ventricular (LV) structure remain unclear in the Indonesian population. Clarifying these associations may improve risk stratification and precision care. Therefore, this study was conducted to assess the associations of these polymorphisms and TGF-β1 levels with LV remodeling in essential hypertension.

METHODS: Sixty-four adults subjects with essential hypertension were included in this cross-sectional study, and their blood samples were taken. Genotyping of the *MTHFR* and *TGFB1* genes was performed using polymerase chain reaction (PCR), followed by sequencing. Serum TGF-β1 was measured by enzyme-linked immunosorbent assay (ELISA), while LV mass index (LVMI) and relative wall thickness (RWT) were assessed by echocardiography.

RESULTS: *TGFB1* rs1800470 was significantly associated with higher TGF-β1 levels (p=0.013). In the recessive model, TT homozygotes had higher TGF-β1 than CC+CT carriers (β=1.444; standardized β=0.353; p=0.004). TGF-β1 correlated with LDL cholesterol and diastolic blood pressure (r=0.302; p=0.015 and r=0.277; p=0.027). The TT genotype was associated with higher RWT under recessive and overdominant models (p=0.021 and p=0.028).

CONCLUSION: *TGFB1* rs1800470 is associated with circulating TGF-β1 concentrations in essential hypertension, suggesting a potential role in hypertensive cardiac remodeling.

KEYWORDS: hypertension, *TGFB1* polymorphism, TGF-β1, cardiac remodeling, left ventricular geometry, myocardial fibrosis.

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Introduction

Hypertension remains a major modifiable risk factor for global cardiovascular morbidity and mortality, affecting more than one billion people worldwide despite significant advances in pharmacological therapy.(1) In addition to its hemodynamic burden, hypertension causes structural cardiac remodeling, particularly left ventricular hypertrophy (LVH), which independently predicts heart failure, arrhythmias, and cardiovascular death.(2,3) Interestingly, the magnitude and geometric pattern of left ventricular (LV) remodeling vary significantly among individuals with similar levels and duration of blood pressure exposure, suggesting that biological determinants beyond mechanical load influence myocardial structural adaptation.(4) Identifying molecular and genetic contributors to this variability is crucial for refining risk stratification and understanding the pathogenesis of hypertensive cardiac remodeling.

Pathological left ventricular remodeling in hypertension is characterized by extracellular matrix expansion, interstitial fibrosis, and progressive myocardial stiffening. Transforming growth factor-β1 (TGF-β1) is a key regulator of profibrotic signaling and a central mediator in pressure-induced myocardial remodeling.(5) In response to pressure overload, TGF-β signaling is upregulated early and promotes fibroblast activation, myofibroblast differentiation, and collagen deposition via canonical SMAD-dependent and non-canonical signaling cascades.(6,7) Experimental models consistently show that increased TGF-β signaling precedes marked hypertrophy, while inhibition of this pathway reduces myocardial fibrosis and preserves ventricular compliance.(8) In clinical settings, elevated circulating TGF-β1 levels have been associated with a detrimental remodeling phenotype and increased myocardial stiffness, highlighting its translational relevance in human hypertensive heart disease.(9) However, significant interindividual variability in circulating TGF-β1 levels remains unexplained.

Genetic variation in the main profibrotic and metabolic pathways may partly explain this heterogeneity. The *TGFB1* T29C (rs1800470) polymorphism, located in exon 1, has been associated with altered transcriptional activity and differential TGF-β1 production.(10,11) TGF-β1 plays a key role in oxidative stress–mediated fibrosis, which may be driven by hyperhomocysteinemia associated with the *MTHFR* C677T (rs1801133) polymorphism. Accordingly, genetic variation in *MTHFR* rs1801133 may contribute to interindividual differences in profibrotic signaling and cardiovascular remodeling through its influence on homocysteine metabolism. Experimental evidence suggests that homocysteine can enhance myocardial fibrosis through redox-sensitive mechanisms that converge on TGF-β activation, providing a biological basis for the interaction between these pathways.(12–14) However, contemporary human data integrating functional genetic variation, circulating profibrotic mediators, and quantitative left ventricular remodeling phenotypes within an integrated framework remain limited. From the perspective of precision cardiovascular medicine, defining the genetic determinants of remodeling can improve genomic risk stratification beyond conventional clinical predictors and help identify individuals who are susceptible to maladaptive myocardial structural adaptations.(15)

Despite growing interest in genetic determinants of cardiovascular remodeling, most available data have been derived from European or East Asian populations.(16,17) Data from Southeast Asian populations, particularly Indonesia, remains scarce. Therefore, we investigated whether the functional variants of *TGFB1* rs1800470 and *MTHFR* rs1801133 are associated with TGF-β1 levels in the circulation and left ventricular remodeling in hypertensive patients in Indonesia. We hypothesized that these polymorphisms contribute to interindividual differences in profibrotic signaling and myocardial structural adaptation, thereby identifying potential molecular determinants of hypertensive cardiac remodeling.

Methods

Study Design and Subject Recruitment

A cross-sectional observational study was conducted at Universitas Airlangga Hospital, Surabaya, Indonesia. A total of 64 adult patients (≥21 years) with clinically stable essential hypertension were included. Hypertension was defined based on current guideline criteria or current use of antihypertensive medication.(18) Exclusion criteria were subjects with secondary hypertension, heart failure with reduced ejection fraction, significant valvular heart disease, myocardial infarction within the last 6 months, known cardiomyopathy, chronic inflammatory or autoimmune disease, active cancer, chronic kidney disease stage ≥4, and the use of antifibrotic or immunomodulatory therapy.

Clinical Data and Blood Sample Collection

Basic demographic characteristics (age, sex, race, and education level), cardiovascular risk factors (hypertension

status, diabetes mellitus, smoking status, heart rate, and lipid profile), medication use, and anthropometric measurements were recorded using a standardized case report form. Blood pressure was measured using a validated Omron HEM 7156A digital sphygmomanometer device after ≥5 minutes of seated rest. The average of three consecutive readings was used for analysis. Peripheral venous blood samples were collected from all subjects under standardized conditions using vacutainer tubes, preferably in the morning after an overnight fast. Samples were promptly centrifuged, aliquoted, and stored at −80°C until used for the biomarker analysis.

TGF-β1 Enzyme-linked Immunosorbent Assay (ELISA) Analysis

All laboratory examinations were conducted at Institute of Tropical Disease, Universitas Airlangga, Surabaya, Indonesia following the standard procedure. Serum TGF-β1 concentrations were quantified using Elabscience® TGF-β1 ELISA Kit (Cat.No. E-EL-0162; Elabscience, Houston, TX, USA). Briefly, standards and samples were added to antibody-coated wells, followed by incubation with biotinylated detection antibody and HRP-conjugate, with intermediate washing steps. The reaction was developed using a chromogenic substrate and stopped prior to measurement. Absorbance was read at 450 nm, and concentrations were calculated from a standard curve. The assay sensitivity was 0.09 ng/mL, with a detection range of 0.16–10 ng/mL. Samples were analyzed in duplicate, and mean values were used for analysis.

Echocardiographic Assessment

Transthoracic echocardiography was performed using a standard protocol in accordance with current American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) recommendations. (19) Images were acquired by an experienced sonographer and analyzed offline by investigators blinded to clinical and genetic data, biomarkers, and genotypes. Left ventricular mass (LVM) is calculated using the modified Devereux cube formula and indexed based on body surface area to obtain the left ventricular mass index (LVMI). Relative wall thickness (RWT) is calculated as:

$$RWT = \frac{2 \times \text{posterior wall thickness}}{\text{LV end-diastolic diameter}}$$

Left ventricular geometry was categorized as normal geometry, concentric remodeling, concentric LVH, eccentric LVH.

DNA Extraction and Genotyping

DNA extraction was performed using a QIAamp DNA blood mini kit (Cat. No. 51104; Qiagen, Inc., Hilden, Germany) according to the manufacturer's instructions. DNA purity and concentration were assessed by a microvolume spectrophotometer (NanoDrop Lite, Thermo Fisher Scientific, Waltham, MA, USA).

Genotyping of *MTHFR* rs1801133 (C677T) and *TGFB1* rs1800470 (T29C) polymorphisms was performed using polymerase chain reaction (PCR) followed by Sanger sequencing for allele confirmation. For *MTHFR* rs1801133, amplification was performed using a forward primer: 5′-CATCCCTCGCCTTGAACAG-3′ and a reverse primer: 5′-GGACGATGGGGCAAGTGAT-3′. Thermal cycling conditions consisted of initial denaturation at 94°C for 5 minutes, followed by 35 cycles of denaturation at 94°C for 30 seconds, annealing at 57°C for 20 seconds, extension at 72°C for 35 seconds, and final extension at 72°C for 7 minutes. The thermal cycling conditions were modified from previous literature.(20)

For *TGFB1* rs1800470, amplification was performed using a forward primer: 5′-TTCCCTCGAGGCCCTCCTA-3′ and a reverse primer: 5′-GCCGCAGCTTGGACAGGAT-3′. Thermal cycling started with an initial denaturation at 94°C for 5 minutes, followed by 32 cycles of 94°C for 30 seconds, annealing at 61°C for 30 seconds, extension at 72°C for 35 seconds, and final extension at 72°C for 7 minutes. (21) The PCR products were analyzed using agarose gel electrophoresis which showed 296 bp amplicon for *TGFB1* gene and 233 bp amplicon for *MTHFR* gene (Supplementary 1). Subsequently, Sanger DNA sequencing was carried out using the ABI Prism 3500× L Genetic Analyzer 24 capillaries after the sample preparation for bands showing positive results in electrophoresis. While PCR followed by Sanger sequencing provides high analytical accuracy, formal quality control metrics such as call rates and genotyping error rates were not systematically assessed.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 29 (IBM Corporation, Armonk, NY, USA) and visualization was conducted with GraphPad Prism version 9 (GraphPad Software, San Diego, CA, USA). Numerical variables are expressed as mean±SD or median (IQR), whereas categorical variables are reported as frequencies and proportions. Group comparisons and association analyses were performed as appropriate. Regression analyses were conducted to evaluate relationships between genetic variants, clinical variables,

and study outcomes. A p-value<0.05 was considered statistically significant.

Results

Baseline Characteristics of the Study Population

A total of 64 patients with essential hypertension were included in the analysis, as shown in Table 1. The mean age was 61.0±10.1 years with female predominance (78.1%). The mean body mass index (BMI) was 26.3±4.8 kg/m². Mean systolic and diastolic blood pressures (DBP) were 134.2±18.9 mmHg and 78.9±13.1 mmHg, respectively. The mean heart rate was 78.16±12.0 beats per minute. Metabolic parameters showed mean total cholesterol 175.3±38.1 mg/dL, HDL 47.5±9.2 mg/dL, and LDL 109.5±32.2 mg/dL; elevated LDL was present in 56.3% of participants. Elevated total cholesterol and low HDL were observed in 20.3% and 18.8%, respectively. Diabetes mellitus was present in 31.3%, and 14.1% reported a history of smoking.

Distribution of *TGFB1* rs1800470 and *MTHFR* rs1801133 Genotypes

All three *TGFB1* rs1800470 genotypes were observed (Figure 1A). Genotype distribution was CC 25.0% (n=16), CT 53.1% (n=34), and TT 21.9% (n=14), with CT being the most common (Table 2). Under the dominant model (CT+TT *vs.* CC), 75.0% carried the T allele, while under the recessive model (TT *vs.* CC+CT), 21.9% were TT homozygotes. Genotype frequencies were in Hardy–Weinberg equilibrium (p=0.611).

Table 1. Baseline characteristics of the study population.

Variable	Values (n=64)
Age (years), mean±SD	61.0±10.1
Female sex, n (%)	50 (78.1)
Body mass index (kg/m²) mean±SD	26.3±4.8
Systolic blood pressure (mmHg), mean±SD	134.2±18.9
Diastolic blood pressure (mmHg), mean±SD	78.9±13.1
Heart rate (beats/min), mean±SD	78.16±12.0
Total cholesterol (mg/dL), mean±SD	175.3±38.1
Elevated total cholesterol, n (%)	13 (20.3)
HDL cholesterol (mg/dL), mean±SD	47.5±9.2
Low HDL cholesterol, n (%)	12 (18.8)
LDL cholesterol (mg/dL), mean±SD	109.5±32.2
Elevated LDL cholesterol, n (%)	36 (56.3)
Diabetes mellitus, n (%)	20 (31.3)
Current or former smoking, n (%)	9 (14.1)

Furthermore, The *MTHFR* rs1801133 heterozygous variant was identified (Figure 1B). Genotype distribution was CC 77.3% (n=49) and CT 22.7% (n=15), with no TT homozygotes detected (Table 2). Allele frequencies were 0.88 for C and 0.12 for T, and expected genotype frequencies were consistent with the Hardy–Weinberg principle (p=0.288). However, these analyses were performed in a case-only population without a non-hypertensive control group.

Circulating TGF-β1 was Associated with LDL Cholesterol, DBP, and *TGFB1* rs1800470

Circulating TGF-β1 concentrations were significantly higher in participants with elevated LDL cholesterol compared

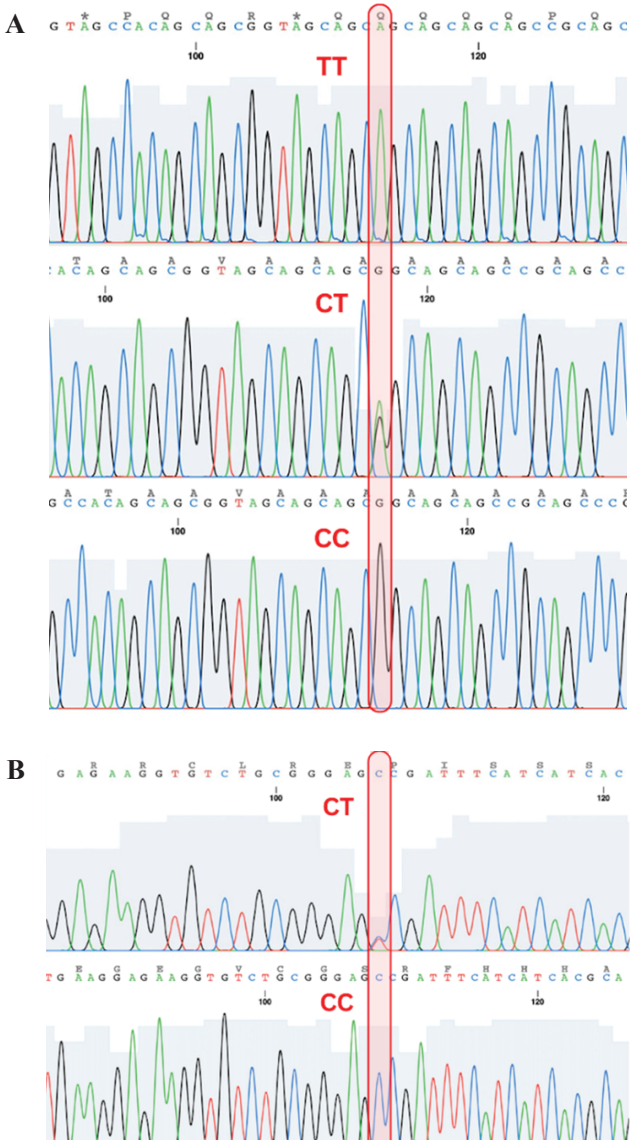

Figure 1. Representative Sanger sequencing chromatograms. A: *TGFB1* rs1800470; B: *MTHFR* rs1801133 polymorphism.

Table 2. Genotype frequencies of *TGFB1* rs1800470 and *MTHFR* rs1801133.

Variant	Genotype	n (%)
TGFB1 rs1800470	CC	16 (25.0)
	CT	34 (53.1)
	TT	14 (21.9)
MTHFR rs1801133	CC	49 (77.3)
	CT	15 (22.7)
	TT	0 (0.0)

with those with normal LDL levels (p=0.031) (Figure 2A). Consistently, LDL cholesterol demonstrated a positive correlation with TGF-β1 levels (r=0.302, p=0.015) (Figure 2B). DBP was also positively correlated with circulating TGF-β1 concentrations (r=0.277, p=0.027) (Figure 2C). No significant differences in TGF-β1 levels were observed according to sex, ethnicity, educational level, smoking status, history of diabetes mellitus, HDL cholesterol status, or total cholesterol levels (all p>0.05).

Circulating TGF-β1 levels differed across TGFB1 rs1800470 genotypes (CC, CT, TT; overall p=0.013) (Figure 3A). Post hoc comparisons demonstrated that individuals with the TT genotype exhibited significantly higher TGF-β1 levels compared with both CC (p=0.045) and CT genotypes (p=0.003). The median TGF-β1 levels were 4.01 (2.60–4.51) in the CC genotype, 3.13 (1.98–4.10) in CT, and 4.57 (3.73–5.40) in TT. No significant difference was observed between CC and CT genotypes. Under the recessive model (TT *vs.* CC+CT), TT carriers showed higher TGF-β1 (p=0.004, Figure 3B), whereas dominant and overdominant models were not significant. Additionally, the TT genotype was associated with higher RWT under recessive (p=0.021) and overdominant (p=0.028) models (Figure 3C-D), with no differences under the dominant model.

Circulating TGF-β1 was Associated with Age, DBP, LDL Cholesterol, and *TGFB1* rs1800470, While LV Geometry Parameters was Linked to Age

In linear regression analyses, circulating TGF-β1 showed potential associations with age (β=−0.044; standardized β=−0.264; p=0.035), DBP (β=0.036; standardized β=0.277; p=0.027), and LDL cholesterol (β=0.016; standardized β=0.302; p=0.015), with LDL contributing the most (R^2=0.091). Elevated LDL status was also potentially associated with higher TGF-β1 (β=−0.919; standardized β=−0.270; p=0.031). Under genetic modeling, the recessive TGFB1 rs1800470 model (TT *vs.* CC+CT) showed a potential association (β=1.444; standardized β=0.353; p=0.004; R^2=0.125), indicating TT homozygotes had approximately 1.4 ng/mL higher TGF-β1 than CC+CT carriers. No other demographic or clinical variables were significant (all p>0.05).

For structural parameters, LVMI was potentially associated with age (β=−0.951; standardized β=−0.260; p=0.038; R^2=0.067), while lipid levels, blood pressure, and genetic models showed no significant associations. Similarly, RWT was potentially associated with age (β=−0.004; standardized β=−0.267; p=0.033; R^2=0.071), with no other variables reaching significance (Table 3).

No Significant Association Between *MTHFR* C677T Polymorphism and LV Geometry

LV geometric patterns did not differ significantly between *MTHFR* rs1801133 genotypes (p=0.129). Among CC

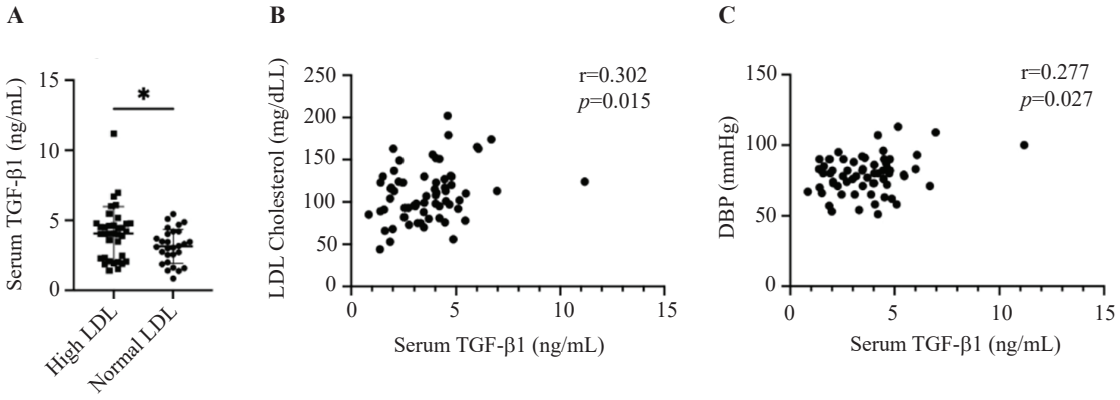

Figure 2. Association between circulating TGF-β1 and clinical variables. A: TGF-β1 levels in high *vs.* normal LDL cholesterol groups (Tested with independent T-test). B: Correlation between LDL cholesterol and TGF-β1 (Tested with Pearson correlation). C: Correlation between diastolic blood pressure and TGF-β1 (Tested with Pearson correlation).

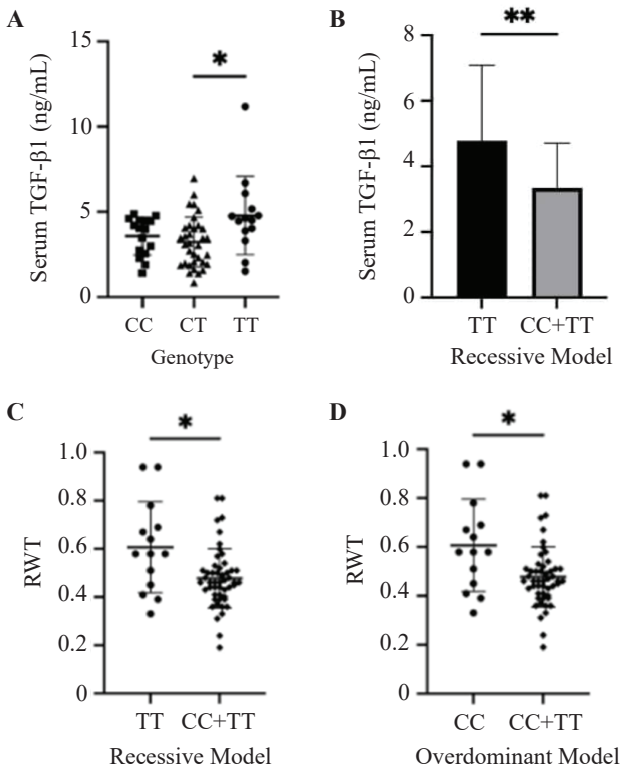

Figure 3. Circulating TGF-β1 concentrations and RWT according to *TGFB1* rs1800470 genotype. A: TGF-β1 levels (ng/mL) across genotypes (CC, CT, TT), analyzed using one-way ANOVA. B: TGF-β1 levels (ng/mL) under the recessive model (TT *vs.* CC+CT). C: RWT under the recessive model (TT *vs.* CC+CT). D: RWT under the overdominant model (CT *vs.* CC+TT). Statistical comparisons in panels (B–D) were performed using independent t-tests.

carriers, 24.5% had normal geometry, 18.4% concentric remodeling, and 57.1% concentric hypertrophy; no eccentric hypertrophy was observed. Among CT carriers, 20.0% had normal geometry, 20.0% concentric remodeling, 46.7% concentric hypertrophy, and 13.3% eccentric hypertrophy. Overall, LV geometric patterns did not differ significantly between genotypes.

Discussion

Southeast Asian populations display substantial genetic heterogeneity due to complex historical admixture, which may influence allele frequencies and genotype–phenotype associations. In this cross-sectional study of Indonesian patients with essential hypertension, *TGFB1* rs1800470 was associated with circulating TGF-β1, with the strongest effect in the recessive model: TT homozygotes had higher TGF-β1 levels, accounting for 12.5% of the variation. *TGFB1* was also associated with RWT, but not with LVMI. The *MTHFR* rs1801133 showed no association with left ventricular geometry.

TGF-β1 is the primary regulator of myocardial fibrosis and extracellular matrix remodeling. Pressure overload activates TGF-β signaling early in the remodeling cascade, promoting fibroblast activation, myofibroblast differentiation, and collagen deposition through the canonical SMAD-dependent pathway and noncanonical pathways.(7) Experimental inhibition of TGF-β1 signaling reduces myocardial fibrosis and improves ventricular compliance, underscoring its causal role in pathological remodeling.(22) Despite its established profibrotic role, determinants of variability in circulating TGF-β1 remain unclear; our findings suggest that *TGFB1* genetic variation may contribute to this variability.

One plausible candidate is the *TGFB1* rs1800470 polymorphism. Rs1800470 is a missense variant in the *TGFB1* signal peptide region (c.29C>T; p.Pro10Leu) that may affect protein processing and secretion.(23) TGF-β1 is an immunomodulatory cytokine that regulates immune balance by inhibiting T-cell proliferation and cytotoxic differentiation.(24) Moreover, TGF-β1 contributes to fibrotic processes and is actively involved in tissue repair and structural remodeling.(25) Our findings suggest that common genetic variants contribute to interindividual

Table 3. Linear regression analysis.

Outcome	Predictor	β	Standardized β	*p*-value	R^2
Circulating TGF-β1	Age	−0.044	−0.264	0.035	–
	Diastolic BP	0.036	0.277	0.027	–
	LDL cholesterol	0.016	0.302	0.015	0.091
	Elevated LDL status	−0.919	−0.270	0.031	–
	TGFB1 rs1800470 (TT vs CC+CT)	1.444	0.353	0.004	0.125
LVMI	Age	−0.951	−0.260	0.038	0.067
RWT	Age	−0.004	−0.267	0.033	0.071

differences in circulating profibrotic mediators. Consistent with this, previous studies reported that the *TGFB1* rs1800470 CC genotype is inversely associated with TGF-β1 levels, indicating higher profibrotic activity in T allele carriers.(26) However, conflicting results have also been reported, where the T allele was associated with lower TGF-β1 levels.(16) These inconsistencies may reflect population-specific genetic backgrounds, with the heterogeneous Indonesian population potentially exhibiting distinct effects of *TGFB1* variants. Compared to other continents, the frequency of the minor T allele of SNP rs1800470 in Indonesia is smaller than in Europe, yet larger than in Africa, America, South Asia, and East Asia.(27,28) However, these findings should be interpreted as exploratory and hypothesis-generating rather than confirmatory given the relatively small sample size, particularly the limited number of TT homozygotes. In addition, the influence of rs1800470 on circulating TGF-β1 and disease risk may be modulated by interactions with surrounding variants within the same haplotype block. As the present study did not account for haplotypic configurations, it remains possible that the observed associations stem from other variants inherited alongside rs1800470 due to high linkage disequilibrium (LD), rather than the effect of rs1800470 alone.(29) Comprehensive haplotype analysis in larger, multi-ethnic samples is essential to clarify these contributions.

A positive correlation was observed between circulating TGF-β1, LDL cholesterol, and DBP. Independent stressors such as elevated DBP and LDL levels may promote oxidative stress, which could facilitate activate and intensifies profibrotic signaling cascades in the myocardium. Oxidized LDL has been shown to stimulate TGF-β signaling through oxidative stress–dependent pathways, promoting fibroblast activation and extracellular matrix deposition.(30) These findings suggest a potential interaction between metabolic factors and hemodynamic load in modulating circulating TGF-β1 levels, with the *TGFB1* genotype modulating the magnitude of the response. In line with earlier research, TGF-β1 overexpression is linked to both vascular remodeling and hypertensive end-organ damage, and that blockade of TGF-β1 signaling attenuates myocardial fibrosis in experimental pressure-overload models.(31,32)

Although rs1800470 was associated with circulating TGF-β1 levels, its structural impact appeared limited. The *TGFB1* genotype was associated with RWT but not with LVMI, suggesting a preferential effect on ventricular geometry rather than overall hypertrophy. This discrepancy may reflect distinct pathophysiological processes, with RWT primarily capturing concentric remodeling driven by extracellular matrix deposition and interstitial fibrosis, whereas LVMI reflects cumulative myocardial growth that is more strongly influenced by disease duration, hemodynamic load, and systemic factors.(33–35) From a clinical perspective, these findings may support risk stratification, as early identification of individuals with enhanced profibrotic signaling may help detect subclinical concentric remodeling and inform more targeted management strategies in hypertensive heart disease.

In addition, the limited sensitivity of conventional echocardiographic parameters, such as RWT, to detect fibrosis-related remodeling, compared with advanced imaging modalities such as cardiac magnetic resonance imaging, may partly explain this finding.(36) While an unexpected inverse relationship between age and LV mass was observed, the low coefficient of determination suggests that structural variability is driven more by long-term therapy exposure and disease duration than by chronological aging itself.(37,38)

The absence of a relationship between *MTHFR* rs1801133 and structural phenotypes should be interpreted with caution. The rs1801133 variant reduces enzyme activity and is associated with hyperhomocysteinemia and increased cardiovascular risk.(39) Experimental data show that homocysteine promotes myocardial fibrosis through TGF-β signaling activation mediated by oxidative stress.(30,40) Absence of TT homozygotes precluded evaluation of the recessive model and substantially reduced statistical power, thereby limiting the interpretability of genotype–phenotype associations. Additionally, the lack of homocysteine measurements restricted further evaluation of the proposed homocysteine-mediated pathway.

This study has several strengths. First, to our knowledge, this is the first study evaluating the association between *TGFB1* rs1800470 polymorphism, circulating TGF-β1 concentrations, and left ventricular remodeling in an Indonesian hypertensive population. Second, the study integrates genetic analysis, circulating biomarkers, and echocardiographic structural parameters within a single cohort. Third, genotyping was confirmed using PCR followed by Sanger sequencing, which represents a high-accuracy method for variant detection. However, several limitations should be considered. The small sample size may have limited statistical power, particularly for *TGFB1* recessive models and *MTHFR*. Adjustment for confounders was limited, as several relevant variables (*e.g.*, homocysteine levels, hypertension duration, and medication use) were unavailable. Haplotype structures were not analyzed, and residual confounding due to population

stratification cannot be excluded. In addition, formal quality control metrics, including call rates and genotyping error rates, were not systematically assessed or reported, which may limit confidence in genotyping reliability. The observed associations should be interpreted with caution due to potential unmeasured confounding. The ≥21-year age threshold may also limit comparability with studies using ≥18 years. Given the multiple statistical comparisons performed across two polymorphisms, several genetic models, and multiple phenotypic outcomes (TGF-β1, LVMI, and RWT), the risk of type I error remains; thus, findings should be considered exploratory and require validation in larger cohorts, ideally incorporating more sensitive imaging modalities such as cardiac MRI for improved assessment of early myocardial fibrosis. Future longitudinal studies in broader populations are needed to determine the clinical implications of this genetic variant in hypertensive heart disease.

Conclusion

In conclusion, *TGFB1* rs1800470 polymorphism showed a potential association with higher TGF-β1 levels in patients with essential hypertension, with the strongest effect observed under a recessive genetic model. These findings indicate that genetic variation within *TGFB1* contributes to interindividual differences in systemic profibrotic signaling. However, *TGFB1* genotype was significantly associated with RWT but not with LVMI, and the *MTHFR* C677T variant showed no detectable structural or biomarker associations.

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Authors Contribution

HS contributed to study conceptualization, data collection, and investigation. LM and DC developed the study methodology and performed the statistical analyses. HS, LM, LK, RC, ES, PP, and DC contributed to drafting the manuscript. CD provided critical review and editorial revisions. All authors read and approved the final manuscript.

Ethical Statement

The study protocol was in accordance with the principles of the Declaration of Helsinki and was approved by Universitas Airlangga ethics committee (No. 277/EC/KEPK/FKUA/2025). Written informed consent was obtained from all subjects who agreed to participate in this study, and all subjects had received a thorough explanation of the study previously.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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