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Quantitative Serum Determination of Angiotensin II and Transforming Growth Factor- β as Biochemical Indicators of Acute Coronary Syndrome Severity: Diagnostic Cutoffs and Correlation with Cardiac Injury Markers

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ABSTRACT: Angiotensin II (Ang II), the bioactive octapeptide of the renin-angiotensin system (RAS), and transforming growth factor- β (TGF- β), a 25-kDa homodimeric cytokine, are biochemically coupled molecules central to vascular tone regulation and fibroblast signalling. Both have been implicated in the pathobiology of acute coronary syndrome (ACS), yet their quantitative behaviour across the STEMI/NSTEMI spectrum is incompletely defined. The present case-control study determined serum Ang II and TGF- β by sandwich ELISA in 120 strictly screened subjects (60 controls, 30 STEMI, 30 NSTEMI), and examined the relationship of these analytes with conventional biochemical markers of cardiac injury, lipid metabolism, and glycaemia. Both analytes displayed a graded elevation across the three groups (control < NSTEMI < STEMI; all $p < 0.001$ by Kruskal-Wallis test). TGF- β achieved the highest single-analyte diagnostic accuracy for ACS versus control (AUC 0.994; 95% CI: 0.981–1.000) at a cutoff of 193.86 pg/mL. Ang II reached AUC 0.946 at 24.82 pg/mL. The Spearman correlation between Ang II and TGF- β was 0.805 ($p < 0.001$), the tightest pairing in the dataset, consistent with the established upstream role of Ang II in inducing TGF- β expression. Strong correlations with CK-MB ($\rho = 0.789$ and 0.828) and HbA1c ($\rho = 0.694$ and 0.732) further support the analytical validity of these markers as biochemical indicators of acute myocardial injury severity.

INTRODUCTION

The renin-angiotensin system (RAS) and the transforming growth factor- β (TGF- β)/Smad signalling axis constitute two of the most extensively characterised regulatory networks in cardiovascular biology. Angiotensin II, an octapeptide (Asp-Arg-Val-Tyr-

Ile-His-Pro-Phe), arises from sequential enzymatic processing of hepatic angiotensinogen: renin cleaves the precursor to angiotensin I (a decapeptide), and angiotensin-converting enzyme (ACE) removes a C-terminal dipeptide to yield the active form.¹ Ang II exerts pleiotropic effects through G-protein-coupled AT1 receptors—vasoconstriction, aldosterone release, sodium retention, and a less widely appreciated pro-fibrotic action mediated through downstream Smad and reactive oxygen species (ROS) signalling.²

TGF- β is a multifunctional cytokine secreted in a latent form that requires activation by integrins, proteases, or mechanical force. Once activated, TGF- β binds heterotetrameric type I/II serine–threonine kinase receptors at the cell surface, leading to phosphorylation of Smad2 and Smad3, complex formation with Smad4, and nuclear translocation to drive transcription of extracellular matrix components and pro-fibrotic genes.³ In addition to this canonical Smad-dependent pathway, TGF- β engages non-canonical signalling through MAPK, PI3K-Akt, and Rho-family GTPases, contributing to a remarkably broad biological footprint.

The two molecules are biochemically coupled: Ang II directly induces TGF- β expression in cardiac fibroblasts, vascular smooth muscle cells, and proximal tubular cells through AT1 receptor–mediated activation of Smad and AP-1 transcription factors.^{4,5} The cascade—Ang II $\rightarrow$ AT1R $\rightarrow$ TGF- β induction $\rightarrow$ Smad2/3 phosphorylation $\rightarrow$ collagen and fibronectin transcription—constitutes a recognised pathway through which the RAS contributes to cardiac remodelling. Whether and how this pathway is reflected in circulating concentrations of both analytes during the acute phase of myocardial ischaemia has been variably reported, with confounding by diabetes mellitus, renal dysfunction, and concurrent RAS-modulating therapy complicating interpretation of many prior studies.

Quantitative measurement of serum Ang II is technically challenging. The peptide is rapidly degraded *ex vivo* by aminopeptidases and carboxypeptidases, with a circulating half-life of approximately 15–20 seconds.⁶ Reliable determination requires inhibition of these enzymes at the point of sample collection, typically by the addition of a peptidase inhibitor cocktail to the collection tube. TGF- β , by contrast, circulates predominantly bound to latency-associated peptide and latent TGF- β -binding protein; commercial ELISA kits routinely incorporate an acid activation step to release the active form before quantification.⁷

The present study quantifies serum Ang II and TGF- β by sandwich ELISA in patients with STEMI and NSTEMI alongside age-matched healthy controls, derives optimal diagnostic cutoffs by receiver operating characteristic analysis, and examines correlations with conventional biochemical markers—CK-MB, troponin, HbA1c, and the lipid profile. Two additional analytes (galectin-3 and ST2/IL-1RL1) are reported in summary form for context; their detailed immunological interpretation appears elsewhere.

EXPERIMENTAL

Study design and setting

This case-control study was conducted (December 23, 2024, to June 13, 2025). at the Department of Chemistry and Biochemistry, College of Medicine, Al-Nahrain University, Baghdad, with recruitment at the cardiac centre of Al-Imamain Al-Kadhmain Teaching Medical City. The Institutional Review Board of the College of Medicine approved the protocol; all participants provided written informed consent in keeping with the Declaration of Helsinki. *The study was approved by institutional review board (IRB) of college of medicine/ Al-Nahrain university with reference I.D (20241014) in (11\2\2025).*

Subjects

A total of 120 individuals aged 35–85 years were enrolled in three groups: 30 patients with STEMI, 30 with NSTEMI, and 60 age-matched apparently healthy controls. Diagnosis was based on electrocardiographic changes, regional wall motion abnormality on echocardiography, and elevated high-sensitivity troponin or CK-MB.⁸ Exclusion criteria comprised liver dysfunction, renal dysfunction, malignancy, myocarditis, prior cardiac surgery, pregnancy, and known diabetes mellitus. The exclusion of diabetes was particularly stringent: chronic hyperglycaemia activates AT1 receptor signalling and induces TGF- β expression independently of cardiac pathology, which would have substantially confounded the analyte measurements under study.

Reagents and chemicals

Commercial sandwich enzyme-linked immunosorbent assay (ELISA) kits were obtained for quantification of angiotensin II, transforming growth factor- β (TGF- β), galectin-3, and ST2/IL-1RL1. Enzymatic colorimetric reagent kits for total cholesterol,

triglycerides, LDL-cholesterol, urea, creatinine, and liver enzymes were obtained from standard commercial suppliers. HbA1c was determined by latex-enhanced immunoturbidimetry; CRP was determined by the same principle. All reagents were of analytical grade and were used as supplied. Deionised water (resistivity $\geq 18 \text{ M}\Omega\cdot\text{cm}$) was used throughout.

Sample collection and pre-analytical handling

Fasting venous blood (approximately 7 mL) was drawn from each participant in the morning. Two millilitres were collected into K₂EDTA tubes for haematological parameters and HbA1c. Two millilitres into tri-sodium citrate (3.2%) for D-dimer. The remainder was collected into plain (no additive) tubes, allowed to clot at room temperature for 20 minutes, then centrifuged at 3000 rpm ($\approx 1600 \times g$) for 10 minutes. Serum was aspirated immediately and divided into aliquots. The first set of aliquots was used directly for measurement of lipid profile, CRP, creatinine, urea, and liver enzymes by enzymatic colorimetric methods on an automated analyser. Aliquots intended for ELISA were stored at -20°C in polypropylene microtubes and assayed within 8 weeks. Freeze-thaw cycles were avoided.

Quantification of angiotensin II and TGF- β

Serum Ang II and TGF- β were measured by sandwich ELISA per the manufacturer's instructions. In brief, standards and serum samples (50 μL each) were added to wells pre-coated with capture antibody. After incubation at 37°C for 30 minutes, the plates were washed (five cycles, 350 μL /well wash buffer), and horseradish peroxidase (HRP)-conjugated detection antibody was added. After a second incubation and wash cycle, 3,3',5,5'-tetramethylbenzidine (TMB) chromogen substrate was added; the reaction was stopped with 2 M sulphuric acid, and absorbance was read at 450 nm with reference correction at 630 nm on a microplate reader. For TGF- β measurement, latent complexes were activated by acid pre-treatment (1 M HCl) followed by neutralisation prior to capture, in accordance with the kit protocol. Each sample was assayed in duplicate; the mean absorbance was used to compute concentration against a four-parameter logistic standard curve.

Conventional biochemical assays

Total cholesterol was determined by the CHOD-PAP enzymatic method (cholesterol oxidase / peroxidase / phenol-aminoantipyrine chromogen); triglycerides by the GPO-PAP method (glycerol kinase / glycerol-3-phosphate oxidase); LDL-cholesterol by direct enzymatic determination. Urea was measured by the Berthelot reaction following urease hydrolysis, and creatinine by the alkaline picrate (Jaffe) method. CK-MB and high-sensitivity troponin were determined by immunochemiluminescent assay on a clinical analyser.

Statistical analysis

Data were analysed in Python 3.10 (SciPy 1.10, StatsModels 0.14, scikit-learn 1.3). Normality was tested by the Shapiro–Wilk test; most continuous variables departed from normality, and data are therefore reported as median (interquartile range). Group comparisons across the three study groups used the Kruskal–Wallis H test followed by Dunn's post-hoc pairwise tests with Bonferroni correction. Spearman's rank correlation coefficient (ρ) was computed for bivariate associations. Receiver operating characteristic (ROC) curves were constructed and the area under the curve (AUC) was estimated with 2000-iteration bootstrap 95% confidence intervals. Optimal cutoffs were identified using the Youden index ($J = \text{sensitivity} + \text{specificity} - 1$). Binary logistic regression was used to compute odds ratios (OR) with 95% CI. Two-tailed $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Demographic and biochemical profile

The three study groups were well-matched for age (controls: median 59.5 years; STEMI: 60.0; NSTEMI: 59.0; $p = 0.974$) and sex distribution ($p = 0.396$). The biochemical profile reflected the expected pattern of acute coronary injury: troponin and CK-MB were markedly elevated in both ACS groups, with CK-MB additionally separating STEMI from NSTEMI (Table 1). The lipid profile showed an atherogenic pattern in patients, with cholesterol and LDL approximately 50–60% higher than in controls, consistent with the dyslipidaemic substrate of coronary artery disease. HbA1c was modestly elevated in both ACS groups despite the exclusion of diabetics, a finding likely reflecting stress hyperglycaemia or subclinical dysglycaemia.

Table 1. Demographic and biochemical profile of the three study groups

Variable	Control (n=60)	STEMI (n=30)	NSTEMI (n=30)	p-value*
Age (years)	59.50 (55.00–61.00)	60.00 (54.25–61.75)	59.00 (56.00–61.00)	0.974
Sex (M/F)	37/22	21/9	23/7	0.396
Troponin (ng/mL)	0.01 (0.01–0.01)	4.17 (0.73–11.34)	0.75 (0.15–10.65)	< 0.001
CK-MB (ng/mL)	1.47 (1.15–1.83)	4.40 (3.96–5.30)	2.75 (2.57–3.11)	< 0.001
HbA1c (%)	4.90 (4.57–5.20)	5.97 (5.82–6.17)	5.96 (5.86–6.15)	< 0.001
CRP (mg/L)	1.83 (0.90–2.90)	4.60 (2.84–12.97)	3.94 (2.57–5.54)	< 0.001
Total cholesterol (mg/dL)	185.70 (150.00–210.00)	290.00 (255.25–335.50)	294.00 (260.00–354.75)	< 0.001
LDL (mg/dL)	110.00 (90.00–130.25)	200.00 (168.50–247.50)	200.00 (177.25–246.25)	< 0.001
Triglycerides (mg/dL)	130.50 (105.75–150.00)	200.00 (120.75–243.25)	200.00 (140.75–252.00)	< 0.001
Creatinine (mg/dL)	0.99 (0.83–1.15)	1.29 (0.88–1.46)	1.31 (0.87–1.41)	< 0.001
Urea (mg/dL)	27.70 (21.73–32.12)	46.05 (21.75–52.38)	47.10 (21.88–50.92)	0.002

Data are median (IQR) or counts. *Kruskal-Wallis H test for continuous; chi-square for sex.

Quantitative behaviour of Ang II and TGF- β

Serum Ang II rose from a median of 14.30 pg/mL in controls to 29.64 pg/mL in NSTEMI and 56.30 pg/mL in STEMI—representing 2.1-fold and 3.9-fold elevations respectively (Table 2). The Kruskal-Wallis statistic was 84.39 ($p < 0.001$), with all three pairwise comparisons remaining significant after Bonferroni correction (each $p < 0.001$). The Ang II fold-change in STEMI exceeded that of any other analyte measured in this study, consistent with vigorous RAS activation in response to acute haemodynamic compromise (Fig. 1).

TGF- β concentrations followed an analogous trajectory: 123.11, 238.68, and 341.14 pg/mL across control, NSTEMI, and STEMI groups ($H = 97.11$, $p < 0.001$). The epsilon-squared effect size for TGF- β ($\eta^2 = 0.813$) was the largest observed for any variable in this study, indicating that group membership accounted for over 80% of the variance in TGF- β concentration. The corresponding values for galectin-3 ($\eta^2 = 0.768$) and ST2/IL-1RL1 ($\eta^2 = 0.757$) were also substantial, confirming that the four investigational biomarkers together describe a coherent biochemical signature.

Table 2. Investigational biomarkers across study groups

Biomarker (pg/mL)	Control (n=60)	STEMI (n=30)	NSTEMI (n=30)	η^2
Angiotensin II	14.30 (11.21–19.88)	56.30 (48.27–86.07)	29.64 (26.83–40.18)	0.704
TGF- β	123.11 (76.67–149.74)	341.14 (321.05–441.31)	238.68 (220.52–264.21)	0.813
Galectin-3	117.74 (96.86–166.88)	385.02 (367.07–412.53)	261.25 (228.64–316.48)	0.768
ST2/IL-1RL1	364.70 (322.67–608.51)	1357.90 (1204.47–1837.80)	856.69 (740.68–1001.12)	0.757

Data are median (IQR). All inter-group comparisons $p < 0.001$ by Kruskal-Wallis. η^2 = epsilon-squared effect size.

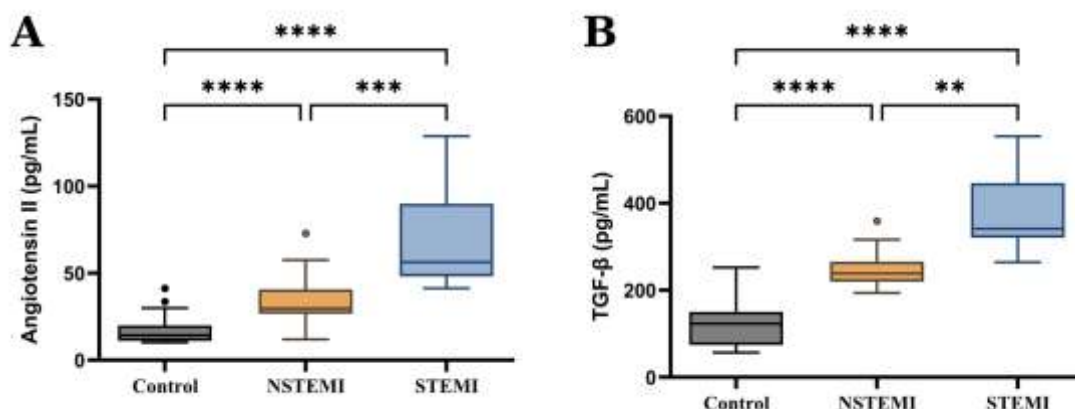


Fig. 1. Serum concentrations of the principal investigational analytes across study groups. (A) Angiotensin II and (B) TGF-β both rise sequentially from control through NSTEMI to STEMI, the angiotensin II fold-change being the largest of any measured analyte. Boxes denote the interquartile range; horizontal lines, medians; whiskers extend to 1.5×IQR. Significance brackets: ** $p < 0.01$, *** $p < 0.001$ (Dunn's post-hoc, Bonferroni-corrected).

Diagnostic cutoff determination by ROC analysis

Receiver operating characteristic analysis was used to derive analytically useful cutoff concentrations (Table 3). TGF-β achieved the highest overall diagnostic performance—AUC 0.994 (95% CI: 0.981–1.000) for ACS versus control discrimination at a cutoff of 193.86 pg/mL, with 100% sensitivity and 98.3% specificity. This represents near-perfect analytical separation and approaches the theoretical limit of the test. Ang II reached AUC 0.946 for the same comparison at a cutoff of 24.82 pg/mL (sensitivity 95.0%, specificity 86.7%).

For the more challenging STEMI versus NSTEMI discrimination, TGF-β yielded AUC 0.958 (cutoff 319.49 pg/mL; sensitivity 83.3%, specificity 96.7%) and Ang II reached AUC 0.942 (cutoff 42.47 pg/mL; sensitivity 96.7%, specificity 83.3%). These figures are notable: separating two forms of acute myocardial injury using a single serum analyte at AUC > 0.94 represents quantitative discrimination that has practical implications for laboratory-based triage.

Table 3. ROC curve analysis for serum Ang II and TGF-β

Comparison / Analyte	AUC (95% CI)	Cutoff (pg/mL)	Sens.	Spec.
ACS vs Control				
Angiotensin II	0.946 (0.899–0.979)	24.82	95.0%	86.7%
TGF-β	0.994 (0.981–1.000)	193.86	100.0%	98.3%
STEMI vs Control				
Angiotensin II	0.999 (0.997–1.000)	41.30	100.0%	98.3%
TGF-β	1.000 (1.000–1.000)	264.34	100.0%	100.0%
NSTEMI vs Control				
Angiotensin II	0.892 (0.811–0.956)	24.82	90.0%	86.7%
TGF-β	0.989 (0.961–1.000)	193.86	100.0%	98.3%

STEMI vs NSTEMI				
Angiotensin II	0.942 (0.868–0.990)	42.47	96.7%	83.3%
TGF- β	0.958 (0.899–0.996)	319.49	83.3%	96.7%

AUC by 2000-iteration bootstrap; optimal cutoff by Youden index.

Correlations with conventional biochemical markers

Both Ang II and TGF- β correlated most strongly with CK-MB ($\rho = 0.789$ and 0.828 respectively, $p < 0.001$ for each), then with troponin ($\rho = 0.638$ and 0.747 ; Table 4, Fig. 2). The stronger association with CK-MB than with troponin may reflect temporal kinetics: CK-MB rises and falls more rapidly than troponin, and may have aligned more closely with the timing of blood sampling. Both analytes also correlated strongly with HbA1c ($\rho = 0.694$ and 0.732), a finding that suggests an interaction between glycaemic milieu and biochemical activation, even in the absence of clinically diagnosed diabetes. Lipid parameters—cholesterol, LDL, and to a lesser extent triglycerides—showed positive correlations with both analytes, consistent with the known overlap between dyslipidaemic and RAS-activated cardiovascular pathology.

Table 4. Spearman correlation coefficients (ρ) of Ang II and TGF- β with conventional biochemical parameters ($n = 120$)

Parameter	Angiotensin II	TGF- β
CK-MB	0.789***	0.828***
Troponin	0.638***	0.747***
HbA1c	0.694***	0.732***
LDL	0.560***	0.636***
Total cholesterol	0.526***	0.638***
Triglycerides	0.259**	0.287**
CRP	0.491***	0.482***
Creatinine	0.318***	0.329***
Urea	0.252**	0.270**
Age	0.058 (NS)	−0.021 (NS)
Inter-marker (Ang II vs TGF- β)	—	0.805***

** $p < 0.01$, *** $p < 0.001$. NS = not significant.

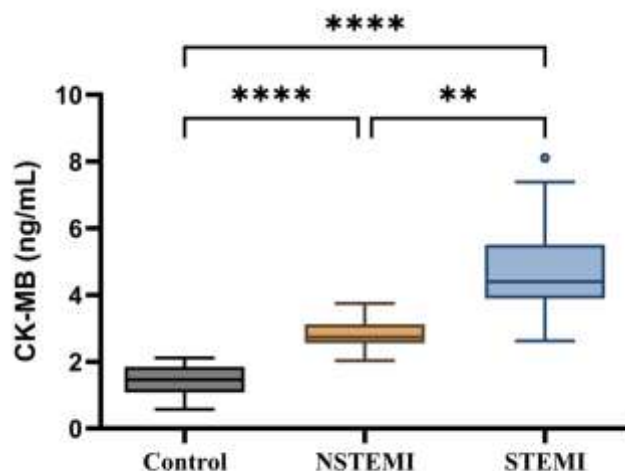


Fig. 2. Serum CK-MB across study groups. CK-MB—the conventional marker with which both Ang II and TGF- β correlated most strongly ($\rho = 0.789$ and 0.828)—shows three-tier separation (Control < NSTEMI < STEMI), distinguishing the two infarct phenotypes where most routine markers do not.

Inter-analyte relationship and pathway implications

Ang II and TGF- β showed the tightest correlation among the four investigational biomarkers ($\rho = 0.805$, $p < 0.001$), consistent with the established biochemical pathway in which Ang II directly induces TGF- β transcription via AT1 receptor activation. The closely coupled rise of both analytes in proportion to ACS severity is, at minimum, consistent with synchronous activation of the RAS–TGF- β axis in vivo. Whether this reflects a true cascade (Ang II driving TGF- β release) or parallel activation by a common upstream stimulus (ischaemia-induced cytokine activation) cannot be determined from cross-sectional concentration data alone.

Logistic regression analysis

Binary logistic regression confirmed both analytes as significant univariate predictors of ACS (Table 5). The odds ratio per unit increase was 1.237 (95% CI: 1.144–1.338, $p < 0.001$) for Ang II and 1.096 (95% CI: 1.043–1.152, $p < 0.001$) for TGF- β . The apparently smaller OR for TGF- β reflects its higher concentration scale, not weaker prediction. After adjustment for age and sex, both analytes retained significance ($p < 0.001$), and the TGF- β model yielded the highest pseudo- R^2 (0.886) of any tested biomarker. An ordinal logistic model coding severity as Control (0) < NSTEMI (1) < STEMI (2) confirmed a dose-response relationship: Ang II OR = 1.221 ($p < 0.001$) and TGF- β OR = 1.070 ($p < 0.001$).

Table 5. Univariate logistic regression for prediction of ACS

Predictor	OR	95% CI	p-value
Angiotensin II	1.237	1.144–1.338	< 0.001
TGF- β	1.096	1.043–1.152	< 0.001
Galectin-3	1.039	1.023–1.055	< 0.001
ST2/IL-1RL1	1.013	1.007–1.018	< 0.001
CRP	2.157	1.533–3.036	< 0.001
LDL	1.053	1.034–1.072	< 0.001
Creatinine	30.49	6.033–154.06	< 0.001

OR = odds ratio per unit increase; CI = confidence interval.

DISCUSSION

The graded elevation of Ang II and TGF- β across the control $\rightarrow$ NSTEMI $\rightarrow$ STEMI continuum is biochemically coherent. Acute coronary occlusion produces a fall in cardiac output, baroreflex-mediated sympathetic activation, and renin release; the resulting cascade rapidly increases circulating Ang II. The magnitude of the response is expected to scale with the severity of haemodynamic compromise, which in turn correlates with infarct size. The 3.9-fold elevation in Ang II observed here in STEMI patients is consistent with this haemodynamic argument and exceeds the fold-changes reported in chronic stable coronary disease.⁹

TGF- β occupies a downstream position in the pathway and integrates input from multiple stimuli: Ang II, mechanical strain, ischaemic injury, and infiltrating inflammatory cells all promote its release. The exceptionally large effect size for TGF- β ($\eta^2 = 0.813$) suggests that this analyte integrates these signals with particular efficiency. Its diagnostic accuracy (AUC 0.994 for ACS versus control) approaches the analytical ceiling and may reflect this integrative property—small contributions from many activated pathways summing to produce a robust quantitative signal.¹⁰

The strong inter-analyte correlation ($\rho = 0.805$) is one of the more striking findings. It is consistent with the canonical Ang II $\rightarrow$ TGF- β induction pathway documented *in vitro* and in animal models. The fact that the two analytes track so closely in human serum, in the acute setting, lends biochemical credibility to the proposition that this pathway is meaningfully engaged in human ACS pathophysiology. Whether interrupting the cascade pharmacologically—through ACE inhibition, AT1 receptor blockade, or direct TGF- β antagonism—translates to clinical benefit beyond what is currently achieved with conventional therapy remains a separate question requiring intervention trials.

Limitations of the present work must be acknowledged. Serum Ang II is notoriously labile, and despite careful pre-analytical handling, some loss of analyte cannot be excluded; the absolute concentrations reported here should be interpreted with this caveat. The cross-sectional design captures a single time point, missing the dynamic behaviour of both analytes over the course of ACS. The single-centre recruitment limits external generalisability, and the strict exclusion of diabetes—while methodologically valuable—restricts applicability to the broader ACS population. Finally, the cutoffs derived here are population-specific and require validation in independent cohorts before any clinical implementation.

CONCLUSION

Serum Ang II and TGF- β behave as quantitative biochemical indicators of acute coronary syndrome severity, with TGF- β achieving exceptional diagnostic accuracy (AUC 0.994 for ACS versus control). Both analytes track sequentially across the control $\rightarrow$ NSTEMI $\rightarrow$ STEMI severity gradient, and their tight inter-correlation ($\rho = 0.805$) supports the biochemical hypothesis of a coordinated Ang II $\rightarrow$ TGF- β cascade engaged during acute myocardial injury. The cutoff concentrations derived here—193.86 pg/mL for TGF- β and 24.82 pg/mL for Ang II in the ACS-versus-control comparison—offer analytically useful reference values that warrant further validation in independent populations.

DECLARATIONS

Ethical statement

Not applicable.

Data availability

the raw data supporting the conclusions of this article are available from the authors upon reasonable request.

Author contributions

VI: conceptualization, formal analysis, investigation, methodology, validation, visualization, writing, and original draft; GPM: formal analysis, investigation, methodology, validation, visualization, writing, and original draft; NZ: Writing, review, editing, and supervising.

Conflict of interest

None declared.

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