SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Association between signal peptide-CUB-EGF domain-containing protein 1 (SCUBE1) and thrombotic or ischemic cardiovascular and cardiopulmonary diseases: A systematic review

Muhammad Abi Ghoffari Siregar, MD[1], Hirowati Ali, MD, PhD[1,2,3,5], Rizki Rahmadian, MD, PhD[4,5]

[1]Graduate School of Biomedical Sciences, Faculty of Medicine, Universitas Andalas, Indonesia, [2]Department of Biochemistry, Faculty of Medicine, Universitas Andalas, Indonesia, [3]Division of Research and Development, Andalas University Hospital, Indonesia, [4]Department of Surgery, Faculty of Medicine, Universitas Andalas, Indonesia, [5]Tissue Bank and Biomaterial, Dr.M.Djamil Hospital, Indonesia

ABSTRACT

Introduction: Signal peptide-CUB-EGF domain-containing protein 1 (SCUBE1) is a platelet- and endothelium-associated glycoprotein implicated in platelet activation, thrombus propagation, and endothelial injury. Because these processes underpin thrombo-inflammatory cardiovascular and cardiopulmonary diseases, circulating SCUBE1 has attracted interest as a candidate biomarker. This systematic review aimed to critically synthesize comparative clinical evidence on circulating SCUBE1 levels across thrombotic or ischemic cardiovascular and cardiopulmonary conditions relative to control or comparator groups.

Materials and Methods: A systematic search of PubMed, ScienceDirect, and SpringerLink was conducted for English-language studies published from 1 January 2015 to 27 September 2025. The protocol was prospectively registered in PROSPERO (CRD420251178563). Eligibility was guided by a PECO framework and included observational and diagnostic accuracy studies that measured circulating SCUBE1 in serum or plasma and reported patient-comparator data. Two reviewers independently screened studies, extracted data, and assessed methodological quality using design-specific Joanna Briggs Institute tools and ROBINS-I. Owing to clinical and methodological heterogeneity, findings were synthesized narratively without meta-analysis.

Results: Nine studies were included (four cross-sectional, three case-control, one cohort, and one diagnostic accuracy study). SCUBE1 levels were generally higher in patients with thrombotic or ischemic cardiovascular and cardiopulmonary diseases than in comparators, supporting associations with platelet-endothelial activation, thrombotic burden, endothelial dysfunction, and ischemia-reperfusion stress. However, absolute concentrations varied markedly across studies, precluding direct comparison and limiting interpretability of proposed cut-off values. Eight studies had moderate risk of bias and one had serious risk.

Conclusion: SCUBE1 is a biologically plausible but still investigational biomarker; robust multicenter prospective studies with standardized assays are required before clinical translation in routine clinical practice.

KEYWORDS:
Thrombo-inflammation, cardiovascular disease, platelet aggregation, SCUBE1, thrombosis

INTRODUCTION

Atherosclerotic cardiovascular disease remains a leading cause of morbidity and premature mortality worldwide. Many major events occur when chronic vascular injury culminates in platelet-rich thrombosis, such as in acute coronary syndromes and procedure-related complications. Accordingly, biomarkers capturing platelet-endothelial activation could complement established markers that primarily reflect necrosis (e.g., cardiac troponins) or fibrin turnover (e.g., D-dimer), particularly when thrombotic burden and endothelial injury are central to clinical presentation.[1-3]

Signal peptide-CUB-EGF-like domain-containing protein 1 (SCUBE1) is a platelet- and endothelium-associated glycoprotein released during early platelet activation and endothelial perturbation. Experimental and clinical observations suggest that circulating SCUBE1 may track platelet aggregation, platelet-endothelial interaction, and thrombus stabilization, making it a plausible biomarker candidate in thrombotic and thrombo-inflammatory disease states.[4-6]

Clinical studies have reported altered SCUBE1 levels across diverse cardiovascular and cardiopulmonary conditions, including acute coronary syndromes and percutaneous coronary intervention (PCI)-related complications, pulmonary embolism, hypertension-related vascular injury, and post-cardiac arrest physiology.[7-14] However, findings are dispersed across small and heterogeneous studies that differ in design, patient phenotypes, sampling time, biological

This article was accepted: 7 March 2026
Corresponding Author: Hirowati Ali
Email: hirowatiali@med.unand.ac.id

matrix (serum/plasma), assay platforms, and reported concentration ranges. These differences limit interpretability, complicate comparisons of absolute values and cut-offs, and leave the incremental value of SCUBE1 beyond established biomarkers uncertain.[6]

Therefore, this systematic review aims to map and narratively synthesize comparative clinical evidence on circulating SCUBE1 levels across thrombotic or ischemic cardiovascular and cardiopulmonary conditions versus comparator groups, and to identify methodological gaps that must be addressed before considering clinical translation.[15]

MATERIALS AND METHODS

Protocol Registration

This systematic review protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) to promote methodological transparency and reduce unnecessary duplication. The protocol was prospectively registered in PROSPERO (CRD420251178563; https://www.crd.york.ac.uk/PROSPERO/view/CRD420251178563). No amendments were made to the protocol after registration.

Search Strategy and Study Selection

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[16] We systematically searched PubMed, ScienceDirect, and SpringerLink for eligible studies published between 1 January 2015 and 27 September 2025. To improve both comprehensiveness and transparency, the search strategy combined SCUBE1-related terms with broader thrombotic, thrombo-inflammatory, and disease-specific concepts relevant to cardiovascular and cardiopulmonary conditions. These included platelet aggregation, thrombosis, thrombo-inflammation, atherosclerosis, acute coronary syndrome, myocardial infarction, no-reflow, stent thrombosis, pulmonary embolism, hypertension, hypertension-mediated organ damage, and cardiac arrest or post-cardiac arrest states. Controlled vocabulary was used where available, particularly in PubMed, whereas equivalent free-text terms were applied in ScienceDirect and SpringerLink. Boolean operators were used to structure the search strategy by combining core concepts with "AND" and related or synonymous terms with "OR." A representative search structure was as follows: ("SCUBE" [tiab] OR "SCUBE1" [tiab]) AND ("Platelet Aggregation" [Mesh] OR "Thrombosis" [Mesh] OR "Thromboinflammation" [Mesh]) AND ("Cardiovascular Disease" [Mesh] OR "Atherosclerosis" [Mesh] OR "Acute Coronary Syndrome" [Mesh] OR "Myocardial Infarction" [Mesh] OR "Pulmonary Embolism" [Mesh] OR "Hypertension" [Mesh] OR "Cardiac Arrest" [Mesh] OR "Post-Cardiac Arrest Syndrome" [Mesh] OR "no-reflow" [tiab] OR "stent thrombosis" [tiab] OR "hypertension-mediated organ damage" [tiab]) AND ("Biological Markers" [Mesh] OR "biomarker" [tiab]). The full database-specific search strategy is provided in the main manuscript or appendix, in accordance with journal formatting requirements.

We also used a PECO framework to guide eligibility and data extraction, defined as followss: (1) Population (P): Adults with thrombotic or ischemic cardiovascular and cardiopulmonary conditions. (2) Exposure (E): Elevated circulating SCUBE1 levels (measured in serum/plasma). (3) Comparison (C): Healthy controls or clinical comparators without the target condition. (4) Outcome (O): Difference in circulating SCUBE1 concentration between exposed and comparator groups.

Two reviewers (MAGS, RR) independently screened titles and abstracts, followed by full texts, against the eligibility criteria. Disagreements were resolved by discussion, and when necessary, by consultation with a third reviewer (HA). No automation tools were used in the selection process.

Eligibility Criteria

We included observational clinical studies (cross-sectional, case-control, cohort) and diagnostic accuracy studies that: (1) Enrolled participants with thrombotic or ischemic cardiovascular/cardiopulmonary conditions; (2) Measured circulating SCUBE1 in serum or plasma; (3) Reported SCUBE1 values in patients and a concurrent control/comparator group (healthy controls or clinical comparators).

We excluded abstracts without full text, duplicates, case reports, narrative reviews, and studies without a comparator group or without extractable SCUBE1 data.

Data Extraction

Data extraction was performed independently by two reviewers (MAGS and RR) using a standardized data-collection form adapted from previous studies.16 For each included study, the following information was extracted: (1) Study identification (author's name, year, design study). (2) Type of disease (primary condition and relevant subtypes) and assay. (3) Total sample (n). (4) SCUBE1 levels (ng/mL). (5) Pathophysiologic pathway. (6) Mechanistic role in SCUBE1 elevation.

Discrepancies in data extraction were resolved through discussion between the two reviewers (MAGS and RR). When consensus could not be reached, a third reviewer (HA) was consulted to make the final decision. All disagreements and their resolutions were documented in the extraction database.

We screened titles and keywords, then reviewed full texts against the inclusion criteria. We extracted data into structured tables capturing authors, year, disease context, biological mechanisms, SCUBE1 values, and references. A PRISMA flow diagram summarized study selection in Figure 1. Figure 2 displayed SCUBE1 increase leading to platelet aggregation and thromboinflammation.

Assessment of Study Quality

Methodological quality was assessed using design-appropriate Joanna Briggs Institute critical appraisal tools. Risk of bias was assessed using Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I), focusing on confounding, participant selection, exposure classification, deviations from intended interventions, missing data, outcome measurement, and selective reporting.

Study Outcomes
The primary outcome was the difference in circulating SCUBE1 concentration between patient and comparator groups. SCUBE1 levels were analyzed as continuous variables and expressed in ng/mL. Where alternative units were reported, values were converted to ng/mL when feasible; otherwise, measurements were presented as originally reported with clear unit specification. Secondary outcomes included diagnostic performance measures such as area under the receiver-operating characteristic curve (AUC), sensitivity, specificity, and reported cut-off values, as well as associations between SCUBE1 levels and clinically relevant outcomes including thrombotic burden, hypertension-mediated organ damage, and return of spontaneous circulation.

For each included study, the following data were extracted: author and year of publication, study design, sample size, clinical condition and comparator definition, SCUBE1 levels in patient and control groups, pathophysiological pathway, proposed mechanistic role of SCUBE1, summary statistics (mean ± standard deviation or median with interquartile range), and any reported diagnostic or prognostic thresholds. When data were incomplete or unclearly reported, analyses were based on the available published information without imputation, and study authors were not contacted.

For continuous SCUBE1 concentrations we extracted group means and standard deviations (or medians and interquartile ranges when provided). Because of substantial heterogeneity, these effect measures were summarized descriptively without quantitative pooling.

RESULTS

Study Selection
Literature searches in PubMed, ScienceDirect, and SpringerLink were conducted from July 10 to September 10, 2025, with a final update on September 27, 2025. Applying a 2015-2025 publication window yielded 332 records; after limiting to original research, 262 underwent title and abstract screening. Removal of 195 duplicates and 42 abstract-only records left 25 full-text articles, of which nine (three case-control, four cross-sectional, one cohort, one diagnostic accuracy) met all inclusion criteria and were included in the review (Figure 1).

Of the 25 full texts, 16 were excluded, mainly due to absence of a control or comparator group, no SCUBE1 measurement, or outcome reporting that did not allow meaningful comparison. Restricting the search to English-language, full-text publications and not searching trial registries may have introduced reporting bias, favouring positive or biomarker-focused studies. The extent of this bias cannot be quantified from the available data and should be considered when interpreting the findings.

Main Findings
Across the included studies, SCUBE1 generally tracked clinical states characterized by platelet activation, thrombus formation, endothelial perturbation, hypoxia, or ischemia-reperfusion stress. Higher SCUBE1 concentrations were reported in acute coronary syndromes, PCI-related thrombotic complications, pulmonary embolism, hypertension-related vascular injury, and post-cardiac arrest states relative to comparator groups.

However, the evidence should be interpreted cautiously. Although the direction of association was broadly consistent, absolute SCUBE1 concentrations varied markedly across studies and were not directly interchangeable. This variation likely reflects differences in assay kits, biological matrices, sampling timing, disease severity, and study design. As a result, the current literature supports a repeated biological signal rather than a unified diagnostic threshold (Table I, Figure 2).

Across all included studies, circulating SCUBE1 concentrations were measured using enzyme-linked immunosorbent assay (ELISA), with absorbance read at 450 nm, and results were reported as mean ± standard deviation (SD) or median (interquartile range, IQR) according to data distribution in the original studies. Despite differences in clinical settings and assay methodologies, SCUBE1 levels were consistently higher in patient groups than in controls across cardiovascular, thrombo-inflammatory, and hypertensive conditions, reflecting underlying platelet activation, endothelial dysfunction, thrombus burden, microvascular obstruction, and ischemia-reperfusion injury. However, the small number of studies within each clinical domain and substantial heterogeneity in study design, populations, and analytical platforms precluded quantitative meta-analysis or sensitivity analyses; therefore, findings were synthesised and presented descriptively.

Critical Appraisal
Methodological quality was assessed using design-specific Joanna Briggs Institute tools. Overall, the included studies were acceptable for inclusion in a narrative systematic review, but several recurring limitations were identified. Case-control studies showed reasonable exposure and outcome measurement but incompletely reported matching procedures, group comparability, and confounding control. Cross-sectional studies generally described study populations and measurements adequately, although explicit adjustment strategies for confounding were not always clear. The single cohort study provided useful prognostic information but was limited by incomplete reporting of baseline outcome status and follow-up handling. The diagnostic accuracy study used an appropriate reference standard, but uncertainty remained regarding patient selection and threshold pre-specification.

Risk of Bias
Risk of bias was assessed using ROBINS-I across the included non-randomized studies. Overall, eight studies were judged to be at moderate risk of bias and one study at serious risk of bias. The most common concerns were residual confounding, participant selection, and incomplete adjustment for disease severity. In contrast, exposure measurement and outcome assessment were generally acceptable across studies. These findings indicate that the current evidence base is informative but methodologically limited, and that conclusions regarding diagnostic or prognostic performance should remain cautious.

Table I: Circulating SCUBE1 levels and associated pathophysiological mechanisms across clinical conditions

Author's name, year, design study	Type of disease, assay	Total Sample (n)	SCUBE1 levels (ng/mL)	Pathophysiologic Pathway	Mechanistic Role in SCUBE1 Elevation
Ertan Sönmez et al. 2015, cross-sectional[7]	Acute coronary syndrome (STEMI & NSTE-ACS) vs non-cardiac chest pain. ELISA kit for human SCUBE1; Catalog No. CSBE15005 h, Cusabio Biotech Co., Wuhan, Hubei, P.R. China). ELISA reader: Multiskan FC Microplate Photometer (Thermo Scientific Microplate Photometer, Multiskan FC, USA) Wavelength: 450 nm	Control: Healthy (45) Patients: STEMI (45), NSTE-ACS (65), NCCP (80)	Control: 0.34±0.11 Patients: STEMI 0.56±0.16, NSTEMI 0.46±0.13, NCCP 0.37 ±0.10)	Platelet activation and thrombosis	Platelet α-granules release SCUBE1 during acute plaque rupture and thrombosis; SCUBE1 stabilizes thrombus by mediating platelet, endothelial adhesion.
Hasan Ata Bolayır et al. 2017, case-control[9]	No-reflow phenomenon after primary PCI (STEMI), Kit ELISA for human SCUBE1 ELISA reader: VersaMax Microplate Reader (Molecular Devices, Sunnyvale, CA, USA) Wavelength: 450 nm	Control: Healthy (50) Patients: STEMI with NR phenomenon (42), STEMI with Primary PCI (100)	Control: 34±8.4 Patients: STEMI with NR phenomenon 97.2±8.9, STEMI with primary PCI 51±6.2	Platelet aggregation and microvascular obstruction	Persistent platelet activation and microembolization after PCI cause endothelial injury and SCUBE1 release.
Hasan Ata Bolayır et al. 2018, case-control[17]	Late stent thrombosis (presenting as STEMI) Kit ELISA for human SCUBE1 ELISA reader: VersaMax Microplate Reader (Molecular Devices, Sunnyvale, CA, USA) Wavelength: 450 nm Type of disease, assay	Control: Healthy (50) Patients: STEMI with ST (40), STEMI without ST (100)	Control: 30±7.4 Patients: STEMI without ST group 48.2±8.9, at admission 67.6±6.9 and at hospital discharge 50±7.6 in the STEMI with late ST group)	Atherothrombosis at stent site	Platelet hyperreactivity on stent surfaces induces thrombus formation and SCUBE1 secretion.
A. Yıldırım et al. 2020, cohort[8]	STEMI (angiographic thrombus burden during PPCI) ELISA kit with 0.3ng/mL 90ng/mL detection range (catalog number E3142Hu, Shanghai, China) ELISA reader: VERSAmax tuneable microplate reader at 450nm (Molecular Devices, Sunnyvale, CA, USA) Wavelength: 450 nm	Control: Low thrombus burden (51) Patients: High thrombus burden (37)	Control: Low thrombus burden 53.7±15.6 Patients: High thrombus burden 87.7±16.1	Atherothrombotic load	SCUBE1 increases with platelet adhesion and thrombus size in infarct-related arteries.
Murat Güzél et al. 2019, cross-sectional[12]	Essential hypertension (dipper vs non-dipper) ELISA kit (Elabscience® kits made in China ELISA)	Control: Healthy (24) Patients: Dipper Hypertension (30), Non-dipper Hypertension (46)	Control: 1.19 (0.71-1.65) Patients: Dipper 1.68 (0.94-3.90), Non Dipper 2.30 (1.47-5.32)	Endothelial dysfunction and shear stress	Non-dipper hypertension causes continuous endothelial stress; endothelial cells overexpress SCUBE1.
Betül Ayça Yamak et al. 2025, cross-sectional[13]	Hypertension-mediated organ damage (HMOD) ELISA) kit with a detection range of 1 ng/mL to 400 ng/mL (E3142Hu, BT-LAB, Shanghai, China). ELISA reader: VERSAmax tunable microplate reader (Molecular Devices, Sunnyvale, CA, USA). Wavelength: 450 nm	Control: Healthy (36) Patients: HT group (79): with HMOD (39), without HMOD (40)	Control: 75.64 (52.71-110.36) Patients: HT group 160.70 (124.12-319.80), with HMOD (311.27(137.86-460), without HMOD 142.53(110.56-178.19).	Microvascular damage in hypertension	Endothelial SCUBE1 up-regulated by chronic vascular remodeling and oxidative stress.

Table I: Circulating SCUBE1 levels and associated pathophysiological mechanisms across clinical conditions

Author's name, year, design study	Type of disease, assay	Total Sample (n)	SCUBE1 levels (ng/mL)	Pathophysiologic Pathway	Mechanistic Role in SCUBE1 Elevation
Nigar Dirican et al. 2016, diagnostic test accuracy[10]	Pulmonary embolism (CTPA-confirmed). ELISA kit (Elabscience Biotechnology Co., Ltd., China, Catalog no:E–EL–H5405, Lot:AK0015NOV30024). ELISA reader: BIOTEK semiautomatic	Control: Healthy (25) Patients: PE (32), Non-PE (25)	Control: 0.47 (0.32 1.40) Patients: PE 0.90 (0.50 4.92), Non-PE 0.38 (0.28 1.48)	Hypoxia and thrombo inflammation	Hypoxia triggers platelet-endothelial activation; SCUBE1 acts as a complementary biomarker to D-dimer.
Lu Xiao et al. 2021, cross-sectional[11]	Pulmonary embolism Commercial ELISA kit assay (Cusabio, Cat No: CSB-E15005h, Wuhan, China)	Control: Healthy (89) Patients: CTPA confirmed PE (143), Suspicious PE (34)	Control: Healthy (4.40 ±3.23) Patients: CTPA confirmed PE (14.28±7.74), suspicious patients (11.11±4.48)	Hypoxia-driven endothelial stress	Thrombus formation and hypoxic endothelium stimulate SCUBE1 release; marker of vascular occlusion.
C. Yılmaz et al. 2022, case-control[14]	Cardiopulmonary arrest-post return of spontaneous circulation (ROSC) Human SCUBE-1 ELISA kit (MyBioSource, USA; Lot No. BMS9305694). The assay detection range was 0.63-40 ng/mL. ELISA reader/microplate reader: Thermo Scientific, USA Wavelength: 450 nm	Control: Non survivor group (25) Patient: ROSC group (25)	Control: Non survivor group 10.8 (1.7-21.9) Patient: ROSC group 15.4(9.3-26.3).	Systemic ischemia-reperfusion	Global ischemia and reperfusion injury cause platelet and endothelial activation with massive SCUBE1 release.

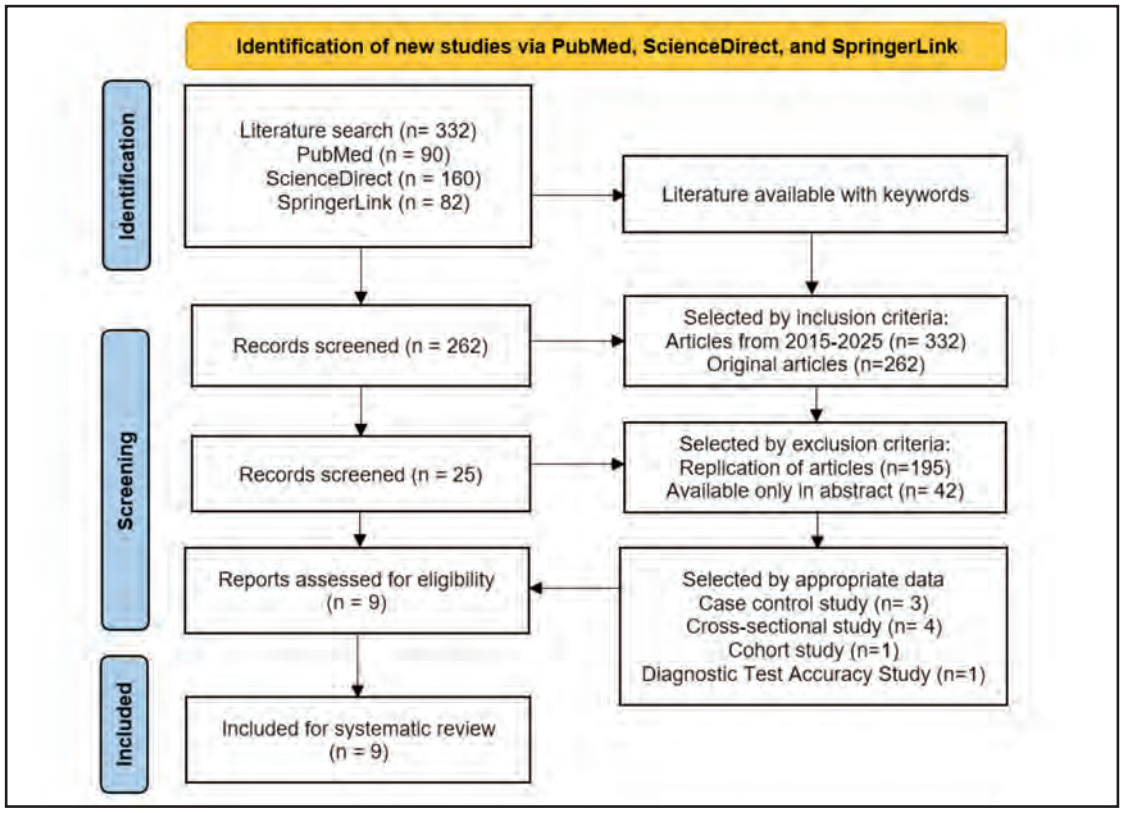

Fig. 1: Flow Chart of Study Selection (PRISMA)[16]

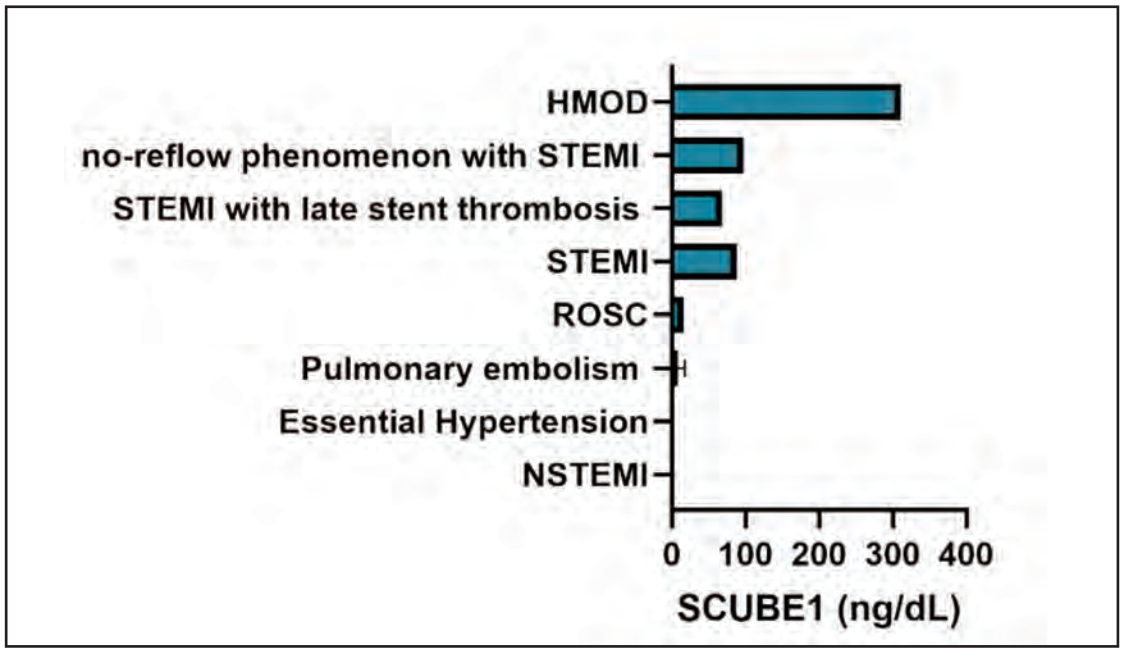

Fig. 2: SCUBE1 levels across different clinical conditions. All measurements were performed using enzyme-linked immunosorbent assay (ELISA). Although different studies used different ELISA kits and microplate readers, all results were reported in ng/mL. Data distribution between control and comparison groups met the assumption of normality

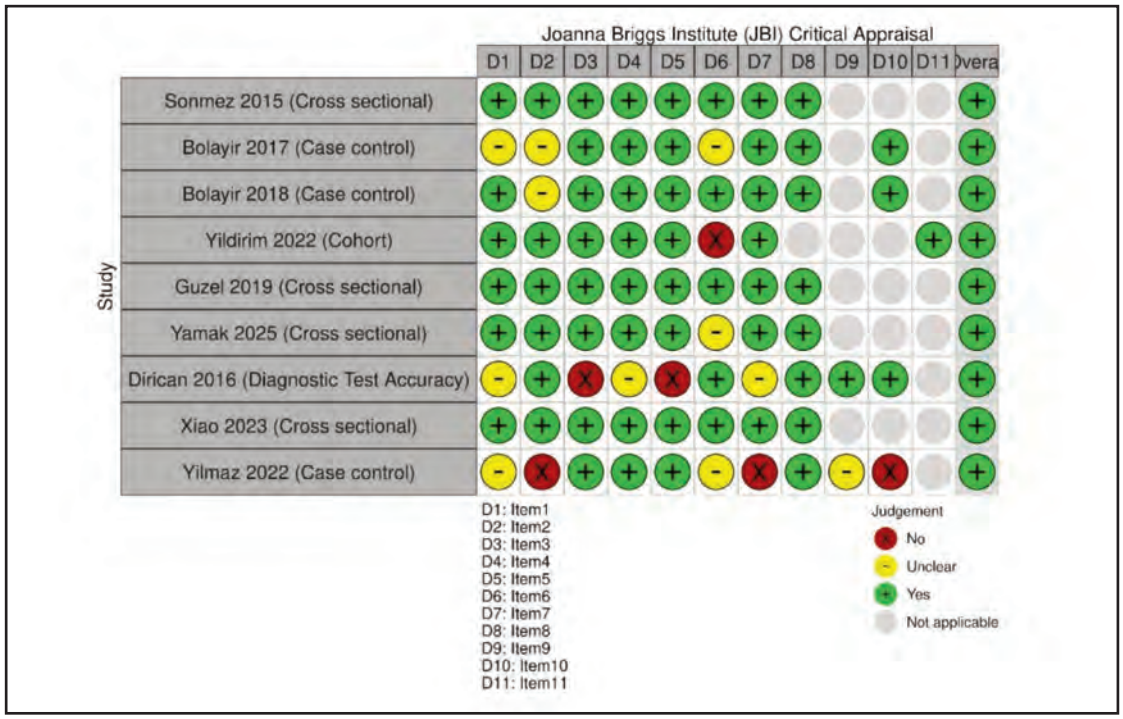

Fig. 3: Joanna Briggs Institute (JBI) Critical Appraisal. Each study was evaluated using a design-specific JBI checklist; therefore, the number of domains varies according to study design. Judgements are defined as follows: Yes indicates the criterion was met; Unclear indicates insufficient information; No indicates the criterion was not met; and Not applicable indicates the item was not relevant to the specific study design or fell beyond the available domains (e.g., fewer than D11 in some designs)

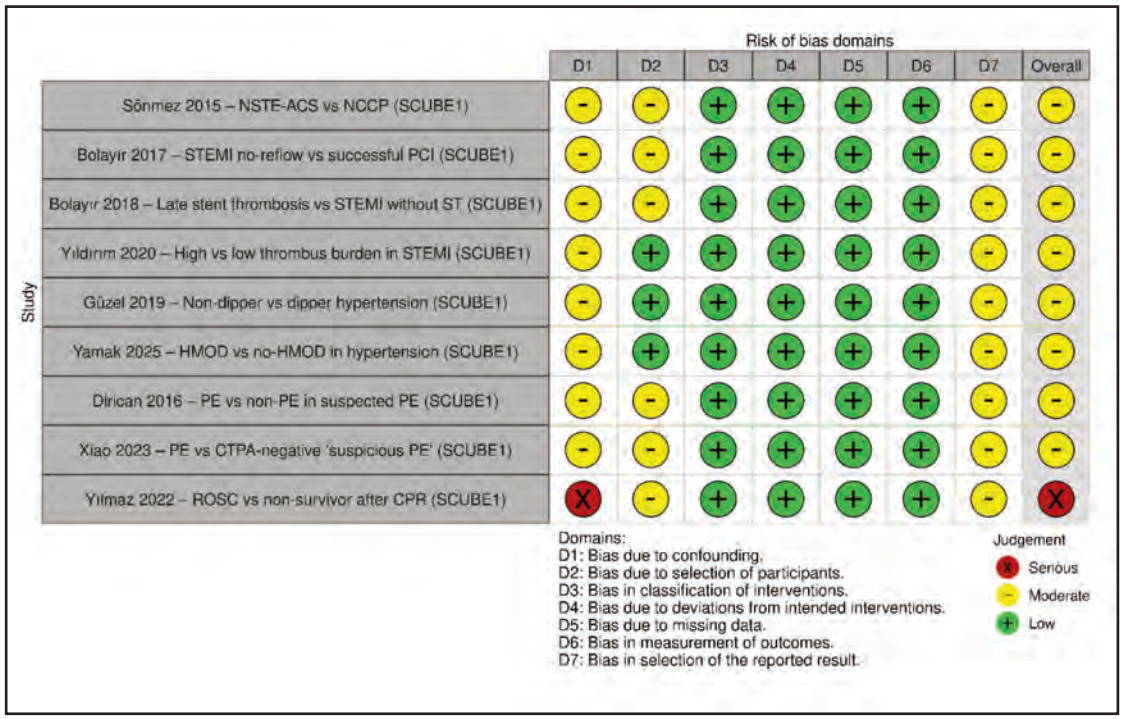

Fig. 4: Risk of bias was assessed using the ROBINS-I tool for non-randomized studies across seven domains (D1-D7). Overall judgements are classified as Serious, indicating high risk of bias; Moderate, indicating acceptable but notable methodological limitations; and Low, indicating minimal risk of bias

DISCUSSION

SCUBE1 and Acute Coronary Syndrome

SCUBE1 is a membrane-associated glycoprotein stored in platelet α-granules and presented on the surface of activated endothelium. Upon platelet activation, it is cleaved and released into the circulation as a soluble adhesion molecule. Through its EGF-like repeats and CUB domain, soluble SCUBE1 can bridge neighboring activated platelets and facilitate their interaction with subendothelial structures, providing a mechanistic link between biochemical release and the formation of platelet-rich arterial thrombi. In the setting of acute coronary syndrome (ACS), this biology translates into a measurable rise in circulating SCUBE1 during episodes of plaque disruption and thrombosis, where platelet activation is both an early and central event.[4,7]

For NR phenomenon after primary PCI, SCUBE1 tracked microvascular risk. In a prospective STEMI study (n=142), mean SCUBE1 was about 97 ng/mL in NR, 51 ng/mL with successful reflow and 34 ng/mL in controls. SCUBE1 independently predicted NR, consistent with a model of intense platelet activation, distal embolization, endothelial injury, and microvascular obstruction (MVO). Recent reviews NR and MVO support these mechanisms and highlight their prognostic significance. Clinically, elevated pre-PCI SCUBE1 in STEMI may flag NR-prone lesions and prompt microvascular protection strategies. However, the evidence is preliminary and needs standardized assays and external validation.[9,18]

SCUBE1 also appears to index thrombotic propensity in late stent thrombosis (LST). In STEMI with angiographic LST patients, at-presentation SCUBE1 (pre-PCI) exceeded levels in healthy controls and in STEMI without LST. On multivariable analysis, SCUBE1 remained an independent predictor. A cutoff near 59.2 ng/mL yielded an area under curve AUC of 0.97 with sensitivity and specificity 83%. These findings align with a high-reactivity, platelet-driven LST biology and suggest triage value at presentation, particularly when post-PCI TIMI flow is suboptimal. Key limitations include single-center design and lack of assay standardization.[17]

After primary PCI for ST-elevation myocardial infarction (STEMI), SCUBE1 correlates with angiographic thrombus burden. In a prospective primary PCI (PPCI) cohort (n=88), higher SCUBE1 was associated with high thrombus load. A threshold above 65.63 ng/mL predicted heavy thrombus with an area under the curve of 0.93 and remained an independent predictor alongside troponin. These findings align with interventional strategies for large thrombus, such as intensified antithrombotic and selective rather than routine aspiration. However, current ACC/AHA/SCAI (2025) and ESC (2023) guidelines do not endorse SCUBE1 testing in acute coronary syndromes. Evidence is promising but not practice changing. Overall, SCUBE1 integrates platelet activation and thrombus biology across the ACS spectrum, yet clinical adoption awaits multicenter validation, assay harmonization, and proof of incremental decision value.[12,19,20]

SCUBE1 and Pulmonary Embolism

SCUBE1 is expressed by vascular endothelium and platelets. Soluble SCUBE1 supports platelet-platelet adhesion and platelet-matrix interactions, which accelerates thrombus growth in vivo. Genetic depletion of soluble SCUBE1 or antibody blockade reduces arterial thrombosis in mice without excess bleeding. In the pulmonary circulation, SCUBE1 also influences BMPR2-related signaling, linking platelet activation and endothelial dysfunction in acute pulmonary embolism (PE).[4,21-23]

A case-control study by Dirican reported higher plasma SCUBE1 in confirmed PE than in non-PE and healthy groups. A cutoff of 0.49 ng/mL yielded an area under the curve (AUC) of 0.79 with sensitivity 100% and specificity 64%. A larger cross-sectional study by Xiao showed higher SCUBE1 in CT-confirmed PE than in suspected PE and healthy controls. A cutoff of 7.789 ng/mL produced an AUC of 0.919 with sensitivity 81.25% and specificity 92.13%. Levels declined at three-month follow-up. An emergency-department study in 2025 observed lower SCUBE1 in PE than in matched controls, underscoring assay heterogeneity and the importance of sampling time and patient factors such as body mass index (BMI).[10-11]

SCUBE1 reflects platelet-driven thrombosis and endothelial perturbation central to PE and shows diagnostic promise as an adjunct in probability-based pathways. At present, major guidelines prioritize pretest probability, age-adjusted D-dimer, and imaging, and they do not recommend SCUBE1 for routine use. Priorities include assay harmonization, kinetic profiling versus symptom onset, and multicenter validation of decision thresholds and incremental value over D-dimer across risk strata.[11,24]

SCUBE1 and Hypertension

In essential hypertension, circulating SCUBE1 tends to be higher than in normotensive controls and shows modest relations with 24-hour blood pressure burden, consistent with hemodynamic load driving platelet-endothelial activation and microvascular injury.[12] Chronic pressure and shear increase endothelial dysfunction, oxidative stress, and small-vessel remodeling. These changes promote microvascular rarefaction, hypoperfusion, and fibrosis that define HMOD.25 Consistent with this pathophysiology, hypertensive patients show higher SCUBE1 than controls, with the highest levels in HMOD. In a comparative study, SCUBE1 independently predicted HMOD with fair diagnostic performance. Organ-specific cutoffs clustered near 200-360 ng/mL, supporting its role as a severity indicator rather than a presence-absence marker.[13]

Night-time blood pressure behavior modifies vascular stress. Non-dippers, who lack the expected nocturnal fall, show greater endothelial activation and platelet reactivity.[26] In newly diagnosed essential hypertension, SCUBE1 exceeded levels in healthy controls and was highest in non-dippers. Soluble CD40 ligand (sCD40L) was also elevated. These findings link an ambulatory phenotype to a biologic marker of thrombo-inflammation and help explain greater target-organ injury with non-dipping.[12]

Practically, SCUBE1 can complement ambulatory blood pressure monitoring (ABPM) to flag higher-risk patients. Targets include non-dippers and those with suspected early

HMOD when imaging and routine labs are equivocal. Interpret SCUBE1 within a composite judgment that includes ABPM, renal indices, retinal assessment, and cardiac imaging. Current evidence is cross-sectional and largely single-center, and absolute cutoffs vary by organ system and assay. Serial measurements under standardized therapy and prospective outcome studies are needed before routine use.[12-13]

SCUBE1 and Cardiopulmonary Arrest (Post ROSC)

During cardiac arrest and the early minutes after return of spontaneous circulation (ROSC), ischemia reperfusion and a massive catecholamine surge trigger endothelial activation and glycocalyx shedding with brisk platelet activation and microthrombosis. These signals map to the severity of postcardiac arrest syndrome and track neurologic and survival outcomes, which makes the platelet-endothelial axis a target for early bedside risk stratification.[27-28] In acute atherothrombotic states, circulating SCUBE1 rises and mirrors platelet activation, which is central to early postcardiac arrest microvascular failure and relevant to ROSC biology.[29]

Clinically, a prospective adult CPR study reported higher at-presentation SCUBE1 in patients who achieved ROSC than in those without ROSC. A threshold near 9 ng/mL yielded AUC 0.74, sensitivity 100%, specificity 48%, and negative predictive value 100% for predicting ROSC. This supports rule-out utility when values are low but is insufficient for definitive decisions. SCUBE1 should be interpreted alongside physiologic monitoring and guideline-directed post-arrest care, not as a stand-alone trigger. Evidence remains limited to small, single-center cohorts with modest specificity, so SCUBE1 is best viewed as a biologically meaningful adjunct for early assessment of platelet-endothelial activation after ROSC.[14]

Taken together, the available evidence suggests that SCUBE1 may reflect a biologically meaningful intersection between platelet activation, endothelial injury, and thrombo-inflammatory burden across multiple cardiovascular and cardiopulmonary conditions. Nevertheless, the present evidence base remains small, largely observational, and methodologically heterogeneous. The consistency of directional elevation across studies is encouraging, but it should not be mistaken for proof of immediate clinical utility.

A major limitation of the field is the lack of assay standardization. Differences in ELISA platforms, biological matrices, sampling timing, comparator selection, and disease severity make direct comparison of absolute concentrations and proposed cut-off values inappropriate. Accordingly, SCUBE1 should currently be interpreted as an investigational biomarker with mechanistic plausibility rather than as a clinically validated diagnostic or prognostic test.

Another important limitation concerns search comprehensiveness. Although the review included three major databases and a prospectively registered protocol, biomarker studies involving SCUBE1 are dispersed across multiple disease-specific literatures rather than a single unified research domain. The revised manuscript therefore clarifies the broader disease-specific search concepts used to capture this evidence more transparently. Even so, the restriction to English-language full-text studies and the absence of grey-literature retrieval mean that some relevant studies may still have been missed.

LIMITATIONS

This systematic review has several limitations. First, the search was restricted to three databases and English-language full-text publications, which may have increased the risk of reporting and language bias. Second, the included studies were clinically and methodologically heterogeneous with respect to disease context, sampling conditions, assay platforms, and comparator definitions. Third, the predominance of small, non-randomized, single-center studies limits the certainty of the evidence. These factors reduce confidence in any single threshold value and preclude direct quantitative comparison of absolute SCUBE1 concentrations across studies.

CONCLUSION

This systematic review suggests that circulating SCUBE1 is frequently elevated in thrombotic and ischemic cardiovascular and cardiopulmonary conditions and most plausibly reflects platelet-endothelial activation within a broader thrombo-inflammatory process. However, the current evidence base remains limited by small sample sizes, observational study designs, assay heterogeneity, and inconsistent thresholds across studies. SCUBE1 should therefore be regarded as an investigational biomarker rather than a clinically established one until larger prospective multicenter studies provide standardized measurement approaches, external validation, and evidence of incremental value over existing clinical pathways.

ACKNOWLEDGEMENTS

The author expresses sincere gratitude to everyone who contributed to this research and extends special thanks to his home institution, the Master's Program in Biomedical Sciences, Faculty of Medicine, Universitas Andalas, Padang, Indonesia, for its continuous support.

CONFLICT OF INTEREST

The authors declare that they have no financial or personal relationships that could inappropriately influence, or be perceived to influence, the work reported in this manuscript.

FUNDING

This work received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The authors' home institution (Master's Program in Biomedical Sciences, Faculty of Medicine, Universitas Andalas) provided general academic support but had no role in the design, conduct, analysis, or reporting of this review.

DATA AVAILABILITY

The data extraction forms, detailed JBI and ROBINS-I

assessments, and numerical values underlying Figures 1-4 are available from the corresponding author on reasonable request. No analytic code was used beyond standard spreadsheet calculations.

REFERENCES

1. Vaduganathan M, Mensah GA, Turco JV, Fuster V, Roth GA. The Global Burden of Cardiovascular Diseases and Risk: A Compass for Future Health. J Am Coll Cardiol. 2022. 80(25): 2361-71.
2. Kraler S, Mueller C, Libby P, Bhatt DL. Acute coronary syndromes: mechanisms, challenges, and new opportunities. Eur Heart J. 2025;46(29): 2866-89.
3. Sandoval Y, Apple FS, Mahler SA, Body R, Collinson PO, Jaffe AS. High-sensitivity cardiac troponin and the 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guidelines for the evaluation and diagnosis of acute chest pain. Circulation 2022; 146(7): 569-81.
4. Lin YC, Sahoo BK, Gau SS, Yang RB. The biology of SCUBE. J Biomed Sci 2023; 30(1): 33.
5. Akdoğan E, Ayaz T, Kırbaş A, Rakıcı H. Is SCUBE1 helpful to predict the arterial thrombotic risk in patients with multiple myeloma: a preliminary study. Hippokratia 2019; 23(1): 21-4.
6. Brambilla M, Josefsson EC, Ramström S, Di Minno A, Di Minno MND, Gangatirkar P, et al. Biomarkers of in vivo platelet activation in coronary artery disease: a systematic review and meta-analysis: communication from the SSC of the ISTH. J Thromb Haemost 2025; 23(12): 3989-4009.
7. Sonmez E, Turkdogan KA, Karabacak M, Civelek C, Yilmaz C, Ozer OF, et al. The diagnostic role of signal peptide-C1r/C1s, Uegf, and Bmp1-epidermal growth factor domain-containing protein 1 in non-ST-elevation acute coronary syndrome. Am J Emerg Med 2015; 33(1): 21-4.
8. Yıldırım A, Küçükosmanoğlu M, Koyunsever NY, Çekici Y, Doğduş M, Saraçoğlu E, et al. Association between serum SCUBE1 levels and thrombus burden in patients with ST-segment elevation myocardial infarction. Acta Cardiol 2021;76(7):777-84.
9. Bolayır HA, Güneş H, Kıvrak T, Şahin Ö, Akaslan D, Kurt R, et al. The role of SCUBE1 in the pathogenesis of no-reflow phenomenon presenting with ST segment elevation myocardial infarction. Anatol J Cardiol 2017; 18(2): 122-7.
10. Dirican N, Duman A, Sağlam G, Arslan A, Öztürk Ö, Atalay S, et al. The diagnostic significance of signal peptide-complement C1r/C1s, Uegf, and Bmp1-epidermal growth factor domain-containing protein-1 levels in pulmonary embolism. Ann Thorac Med 2016; 11(4): 277-82.
11. Xiao L, Wang M, Yang S, Li S, Huang Q, Xu L, et al. The diagnostic potential of plasma SCUBE-1 concentration for pulmonary embolism: a pilot study. Clin Respir J 2023; 17(4): 263-9.
12. Guzel M, Dogru MT, Simsek V, Demir V, Alp C, Kandemir H, et al. Influence of circadian blood pressure alterations on serum SCUBE-1 and soluble CD40 ligand levels in patients with essential hypertension. Am J Cardiovasc Dis 2019; 9(4): 42-8.
13. Yamak BA, Candemir M, Kızıltunç E, Özdemir HB, Gülbahar Ö, Şahinarslan A. Evaluating SCUBE-1 as predictive biomarker for hypertension-mediated organ damage: a comparative study. Rev Cardiovasc Med 2025; 26(1): 25832.
14. Yılmaz C, Gülen B, Sönmez E, Akbay D, Söğüt Ö, Özdemir S, et al. Serum SCUBE-1 levels and return of spontaneous circulation following cardiopulmonary resuscitation in adult patients. Avicenna J Med 2022; 12(3): 148-53.
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372.
16. Ali H. SCUBE in human diseases: a systematic review. Marmara Med J 2024; 37(2): 106-14.
17. Bolayır HA, Kıvrak T, Güneş H, Akaslan D, Şahin Ö, Bolayır A. The role of SCUBE1 in the development of late stent thrombosis presenting with ST-elevation myocardial infarction. Rev Port Cardiol (Engl Ed) 2018; 37(5): 375-81.
18. Kaul S, Methner C, Cao Z, Mishra A. Mechanisms of the "no-reflow" phenomenon after acute myocardial infarction: potential role of pericytes. JACC Basic Transl Sci 2023; 8(2): 204-20.
19. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J 2023; 44(38): 3720-826.
20. Tamis-Holland JE, Abbott JD, Al-Azizi K, Barman N, Bortnick AE, Cohen MG, et al. SCAI Expert Consensus Statement on the management of patients with STEMI referred for primary PCI. J Soc Cardiovasc Angiogr Interv 2024; 3(11): 102294.
21. Liao WJ, Wu MY, Peng CC, Tung YC, Yang RB. Epidermal growth factor-like repeats of SCUBE1 derived from platelets are critical for thrombus formation. Cardiovasc Res 2020; 116(1): 193-201.
22. Wu MY, Lin YC, Liao WJ, Tu CF, Chen MH, Roffler SR, et al. Inhibition of the plasma SCUBE1, a novel platelet adhesive protein, protects mice against thrombosis. Arterioscler Thromb Vasc Biol 2014; 34(7): 1390-8.
23. Sun W, Tang Y, Tai YY, Handen A, Zhao J, Speyer G, et al. SCUBE1 controls BMPR2-relevant pulmonary endothelial function: implications for diagnostic marker development in pulmonary arterial hypertension. JACC Basic Transl Sci 2020; 5(11): 1073-92.
24. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020; 41(4): 543-603.
25. Durante A, Mazzapicchi A, Baiardo Redaelli M. Systemic and cardiac microvascular dysfunction in hypertension. Int J Mol Sci 2024; 25(24): 13294.
26. Koike T, Imamura T, Tomoda F, Ohara M, Fujioka H, Kakeshita K, et al. Factors associating with non-dipping pattern of nocturnal blood pressure in patients with essential hypertension. J Clin Med 2023; 12(2): 570.
27. Bogner-Flatz V, Braunstein M, Ocker LE, Kusmenkov T, Tschoep J, Ney L, et al. On-the-scene hyaluronan and syndecan-1 serum concentrations and outcome after cardiac arrest and resuscitation. Mediators Inflamm 2019; 2019: 8071619.
28. Bro-Jeppesen J, Johansson PI, Hassager C, Wanscher M, Ostrowski SR, Bjerre M, et al. Endothelial activation/injury and associations with severity of post-cardiac arrest syndrome and mortality after out-of-hospital cardiac arrest. Resuscitation 2016; 107: 71-9.
29. Bronze L. SCUBE 1: a novel biomarker related to platelet activation and atherothrombosis. Rev Port Cardiol (Engl Ed) 2018; 37(5): 383-5.