

DIAGNOSTIC PERFORMANCE OF AASI, NT-PROBNP, AND HS-CTNI FOR TARGET-ORGAN DAMAGE IN OLDER PATIENTS WITH HYPERTENSION: A SYSTEMATIC REVIEW

DIJAGNOSTIČKA EFIKASNOST AASI, NT-PROBNP I HS-CTNI U PROCENI OŠTEĆENJA CILJNIH ORGANA KOD STARIJIH PACIJENATA SA HIPERTENZIJOM: SISTEMATSKI PREGLED

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Summary

Background: Hypertension-mediated target organ damage (TOD) is a major determinant of cardiovascular and renal outcomes in older adults. Circulating biomarkers reflecting cardiac stress and myocardial injury, including N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin I (hs-cTnI), may complement the ambulatory arterial stiffness index (AASI, calculated as 1 minus the regression slope of diastolic blood pressure on systolic blood pressure derived from 24-hour ambulatory blood pressure monitoring), a non-invasive marker of vascular stiffness. This systematic review evaluated the available evidence for AASI, NT-proBNP, and hs-cTnI in the assessment of TOD in older patients with hypertension and examined the evidence supporting their potential integration into a multimarker assessment strategy.

Methods: PubMed, Embase, Web of Science, and the Cochrane Library were searched from inception to July 2026 for studies evaluating AASI, NT-proBNP, or hs-cTnI in relation to hypertension-mediated TOD. Two reviewers independently performed study selection, data extraction, and quality assessment. Diagnostic measures, including sensitivity, specificity, area under the receiver operating characteristic curve (AUC), and optimal cut-offs, were extracted when available. Because the included studies

Kratak sadržaj

Uvod: Oštećenje ciljnih organa (TOD) uzrokovano hipertenzijom predstavlja ključnu odrednicu kardiovaskularnih i bubrežnih ishoda kod starijih osoba. Biomarkeri u cirkulaciji koji odražavaju srčani stres i oštećenje miokarda, uključujući N-terminalni pro-B-tip natriuretskog peptida (NT-proBNP) i srčani troponin I visoke osetljivosti (hs-cTnI), mogu da dopune ambulatorni indeks krutosti arterija (AASI – izračunat kao 1 minus nagib regresije dijastolnog u odnosu na sistolni krvni pritisak, dobijen tokom 24-časovnog ambulatornog praćenja krvnog pritiska), koji predstavlja neinvazivni marker vaskularne krutosti. Ovaj sistematski pregled je procenio dostupne dokaze o primeni AASI, NT-proBNP i hs-cTnI u proceni TOD kod starijih pacijenata sa hipertenzijom, kao i dokaze koji podržavaju njihovu potencijalnu integraciju u strategiju procene zasnovanu na više markera.

Metode: Pretražene su baze podataka PubMed, Embase, Web of Science i Cochrane Library (od njihovog nastanka do jula 2026. godine) radi pronalazanja studija koje su procenjivale AASI, NT-proBNP ili hs-cTnI u odnosu na oštećenje ciljnih organa (TOD) uzrokovano hipertenzijom. Dva recenzenta su nezavisno sproveda odabir studija, ekstrakciju podataka i procenu kvaliteta. Ekstrahovani su dijagnostički pokazatelji, uključujući osetljivost,

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differed substantially in index markers, clinical outcomes, and analytical approaches, and because no study measured AASI, NT-proBNP, and hs-cTnI simultaneously, a pooled meta-analysis of the triple-marker combination was not possible; the available evidence was therefore synthesized narratively according to the diagnostic, prognostic, and risk-stratification information provided by each marker.

Results: Six studies involving 19,295 participants were included. The evidence differed in nature among the three markers. NT-proBNP showed moderate diagnostic accuracy for established TOD, with reported AUCs of approximately 0.78–0.79 and a specificity of approximately 95% at sex-specific cut-offs. hs-cTnI incorporated in clinical risk scores showed moderate diagnostic or predictive accuracy for renal damage, with a reported AUC of 0.849 (95% CI 0.809–0.892), although this estimate was predictive of future rather than diagnostic of concurrent TOD. Thus, the overall AUC range of approximately 0.78–0.85 applies only to these two biomarkers; no AUC values were reported for AASI, which primarily provided prognostic evidence (cardiovascular hazard ratio 1.13 per 1-standard-deviation increase). No included study evaluated AASI, NT-proBNP, and hs-cTnI simultaneously; consequently, the pooled diagnostic performance of the triple-marker model could not be estimated. In place of quantitative pooling, we performed a narrative synthesis of single-marker evidence, comparing reported diagnostic, prognostic, and risk-stratification parameters and rating the certainty of the combined-model evidence down for indirectness.

Conclusions: Current evidence supports NT-proBNP as a potentially useful biochemical marker with moderate diagnostic accuracy for identifying hypertension-mediated TOD; hs-cTnI-based risk scores showed moderate predictive accuracy, particularly for future renal damage; whereas AASI lacked direct AUC data and primarily provided prognostic risk-stratification evidence.

Keywords: ambulatory arterial stiffness index, NT-proBNP, high-sensitivity cardiac troponin I, hypertension, target organ damage, biomarkers

Introduction

Target organ damage (TOD) in elderly hypertension is a central driver of cardiovascular and cerebrovascular events, yet current diagnosis relies on fragmented indicators such as echocardiography, urinary albumin, and pulse pressure, making integrated, non-invasive early assessment difficult (1). Arterial stiffness indices offer a continuous, reproducible surrogate endpoint: an individual-participant meta-analysis of 14 cohorts comprising 12,558 individuals established a risk threshold (0.50) for the ambulatory arterial stiffness index (AASI) and showed

specificity, površinu ispod ROC krive (AUC) i optimalne granične vrednosti, kada su bili dostupni. Budući da su se uključene studije značajno razlikovale u pogledu ispitivanih markera, kliničkih ishoda i analitičkih pristupa, te da nijedna studija nije istovremeno merila AASI, NT-proBNP i hs-cTnI, nije bilo moguće sprovести združenu meta-analizu kombinacije ova tri markera; stoga su dostupni dokazi sintetizovani narativno, na osnovu informacija o dijagnostičkoj i prognostičkoj vrednosti, kao i o stratifikaciji rizika, koje pruža svaki od navedenih markera.

Rezultati: Uključeno je šest studija sa ukupno 19.295 učesnika. Priroda dokaza razlikovala se među tri posmatrana markera. NT-proBNP je pokazao umerenu dijagnostičku tačnost za već nastalo oštećenje ciljnih organa (TOD), uz zabeležene vrednosti AUC-a od približno 0,78–0,79 i specifičnost od oko 95% pri primeni graničnih vrednosti specifičnih za pol. hs-cTnI, uključen u kliničke skorove rizika, pokazao je umerenu dijagnostičku ili prediktivnu tačnost u pogledu oštećenja bubrega, uz zabeleženu AUC vrednost od 0,849 (95% CI 0,809–0,892), iako je ova procena ukazivala na buduće, a ne na trenutno prisutno oštećenje ciljnih organa. Stoga se ukupan raspon AUC vrednosti od približno 0,78–0,85 odnosi samo na ova dva biomarkera; vrednosti AUC-a nisu zabeležene za AASI, koji je prvenstveno pružio prognostičke dokaze (odnos rizika za kardiovaskularne događaje iznosio je 1,13 po povećanju za jednu standardnu devijaciju). Nijedna od uključenih studija nije istovremeno procenjivala AASI, NT-proBNP i hs-cTnI, te stoga nije bilo moguće proceniti zbirnu dijagnostičku efikasnost modela sa tri markera. Umesto kvantitativne sinteze podataka, sproveli smo narativnu sintezu dokaza za pojedinačne markere, poredeći zabeležene parametre dijagnostičke i prognostičke tačnosti, kao i parametre stratifikacije rizika, uz snižavanje ocene pouzdanosti dokaza za kombinovani model zbog indirektnosti.

Zaključak: Trenutni dokazi podržavaju primenu NT-proBNP-a kao potencijalno korisnog biohemijskog markera umerene dijagnostičke tačnosti za identifikaciju oštećenja ciljnih organa (TOD) uzrokovanog hipertenzijom; skorovi rizika zasnovani na hs-cTnI pokazali su umerenu prediktivnu tačnost, naročito u pogledu budućeg oštećenja bubrega, dok su za AASI nedostajali direktni podaci o AUC-u, a sam parametar je prvenstveno pružio dokaze relevantne za prognostičku stratifikaciju rizika.

Ključne reči: ambulatorni indeks krutosti arterija, NT-proBNP, kardijalni troponin I visoke osetljivosti, hipertenzija, oštećenje ciljnih organa, biomarkeri

that each 1-SD increase in AASI raises cardiovascular endpoint risk by 13% (1); a cross-sectional study of hospitalized patients with essential hypertension further demonstrated that office and 24-hour aortic pulse wave velocity (PWV) independently associate with left ventricular hypertrophy and declining renal function, respectively (2). At the cardiac and renal level, N-terminal pro-B-type natriuretic peptide (NT-proBNP) captures the hypertensive cardio-renal continuum, with sex-specific cut-offs (men ≥ 90 , women ≥ 142 pg/mL) identifying 95% of TOD patients at 95% specificity (3); high-sensitivity cardiac troponin I (hs-cTnI) reflects subclinical myocardi-

al injury, and a risk score combining its abnormality with clinical indicators achieved an AUC of 0.849 for predicting hypertensive renal damage (4). Focusing on the elderly, an analysis of 998 older men with essential hypertension showed that NT-proBNP and ambulatory blood pressure indices jointly predict impaired cardiac function, supporting the integration of blood-based and ambulatory markers into elderly TOD screening (5, 6).

The evidence base for these three marker classes diverges markedly in population coverage and target-organ emphasis, directly shaping their respective diagnostic boundaries. The evidence for NT-proBNP is the most systematic: from the general-population Ohasama study, in which home systolic blood pressure and heart-rate variability synergistically raised the odds ratio for NT-proBNP ≥ 125 pg/mL to 4.80 (7, 8), to association analyses of subclinical cardiovascular damage in non-dipping hypertension (7), to the J-HOP study, which measured NT-proBNP and high-sensitivity troponin T (hs-cTnT) simultaneously among 4,310 cardiovascular high-risk individuals (6) - all confirming its stable links with cardiac, vascular, and renal damage. In contrast, direct evidence for hs-cTnI in hypertensive populations is sparse, with existing work concentrated on renal-damage prediction (4) and subclinical cardiac injury changes under dietary intervention (in the DASH-Sodium trial, the DASH diet lowered hs-cTnI by 18% and low sodium lowered NT-proBNP by 19%) (9, 10); moreover, J-HOP used hs-cTnT rather than hs-cTnI (6), underscoring that troponin-subtype methodological differences limit cross-study comparability. The strength of AASI lies in its large-sample, population-derived risk-stratification threshold (1); it is also independently associated with albuminuria (11) and increases with rising pulse pressure (AASI rising from 0.38 to 0.53 when pulse pressure exceeds 53 mmHg) (12, 13). However, its reliability in some pediatric and secondary-hypertension risk groups has been questioned, and its applicability boundaries remain to be clarified. The three marker classes capture vascular stiffness, cardio-renal load, and myocardial injury, respectively, and no single indicator fully covers the multidimensional phenotype of TOD.

Single markers face a ceiling in discriminating TOD, making multi-marker combined models a key route to improved diagnostic performance. The J-HOP study showed that home morning systolic blood pressure simultaneously drives elevations in NT-proBNP and hs-cTnT, suggesting that cardiac and myocardial markers can provide incremental information in the same direction in hypertension (6). In differentiating target-organ damage in hypertensive emergencies, a model combining hs-cTnT with lactate dehydrogenase achieved an AUC of 0.92-0.97, substantially outperforming either mark-

er alone, and NT-proBNP reached an AUC of 0.89 for predicting acute pulmonary edema (12). Studies in resistant hypertension likewise indicate that blood-pressure variability and arterial stiffness synergistically promote TOD (9), and in newly diagnosed hypertension an EASIX-plus-PWV model predicted the non-dipping pattern with an AUC of 0.755 (14), further supporting the incremental value of combined models. However, the existing literature has not directly integrated AASI, NT-proBNP, and hs-cTnI in elderly hypertension, and our preliminary combined searches found no primary study using AASI together with NT-proBNP, leaving the true incremental value of the triple combination impossible to judge. Therefore, systematically evaluating the independent diagnostic accuracy of each marker and delineating the evidence gap and a forward-looking framework for the AASI+NT-proBNP+hs-cTnI combined model addresses the methodological limitation of incomplete single-marker coverage and provides a testable, evidence-based framework for early, non-invasive stratification of TOD in elderly hypertension.

Materials and Methods

Literature Search Strategy

This systematic review and meta-analysis was conducted in strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. We performed a systematic literature search across four bibliographic databases, namely PubMed/MEDLINE, Embase, the Cochrane Library, and Web of Science Core Collection, covering the period from each database's inception to July 31, 2026. The search strategy combined controlled vocabulary and free-text terms organized into three conceptual blocks linked by Boolean operators: (i) the diagnostic indexes, comprising ambulatory arterial stiffness index (AASI) and arterial stiffness; (ii) the biomarkers of interest, specifically N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin I (hs-cTnI); and (iii) the study population and condition, namely elderly individuals with hypertension and hypertension-mediated target organ damage (TOD), with terms spanning cardiac, cerebrovascular, vascular, and renal manifestations. PubMed/MEDLINE and Cochrane queries used Medical Subject Headings (MeSH), Embase used Emtree terms, and Web of Science used topic-field keywords, with each controlled vocabulary supplemented by synonymous free-text entries to maximize recall. We imposed a language restriction to English-language publications and placed no a priori restriction on study design, although case-control and other diagnostic accuracy studies were prioritized for the quantitative synthesis. To minimize retrieval bias, we

conducted backward citation searching of the reference lists of all included studies and forward citation tracking of relevant published systematic reviews and meta-analyses.

Inclusion and Exclusion Criteria

We defined study eligibility using the PICOTS framework. Population (P): adults aged 60 years or older with essential hypertension, irrespective of whether target organ damage (TOD) was present. Index tests (I): the ambulatory arterial stiffness index (AASI) derived from 24-hour ambulatory blood pressure monitoring, serum N-terminal pro-B-type natriuretic peptide (NT-proBNP), and serum high-sensitivity cardiac troponin I (hs-cTnI), evaluated individually or in any combination. Comparator (C): TOD confirmed by established reference standards, specifically echocardiographic left ventricular hypertrophy or diastolic dysfunction for cardiac involvement, carotid intima-media thickness ≥ 0.9 mm or plaque for vascular involvement, microalbuminuria or estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² for renal involvement, and Keith-Wagener fundus grade $\geq$ II for retinal involvement. Outcomes (O): measures of diagnostic accuracy, including sensitivity, specificity, positive and negative likelihood ratios, diagnostic odds ratio, and the area under the receiver operating characteristic curve (AUC). Timing (T): index-test measurement and reference-standard assessment performed within a window no longer than 3 months. Study design (S): cross-sectional, case-control, and cohort studies that provided extractable diagnostic accuracy data. We excluded studies of secondary hypertension, acute myocardial infarction, acute heart failure, or severe renal impairment (eGFR < 15 mL/min/1.73 m²); studies with fewer than 30 participants; studies from which a 2×2 contingency table or sufficient data to construct a summary receiver operating characteristic (SROC) curve could not be extracted; duplicate publications, conference abstracts without a full text, and literature not reported in Chinese or English; and animal experiments, in vitro studies, reviews, and editorials.

Literature Search and Study Selection

This systematic review followed the PRISMA 2020 flow diagram, using the pre-specified PICOTS eligibility framework (Section 2.2) and the search strategies described in Section 2.1. All records retrieved from the four databases were exported to a reference manager and de-duplicated. Two reviewers independently screened titles and abstracts against the eligibility criteria; full texts of potentially eligible articles were then retrieved and assessed in duplicate against the PICOTS criteria. Disagree-

ments at any stage were resolved by discussion, and conflicts persisting after consensus attempts were adjudicated by a third senior reviewer. Backward citation searching of the reference lists of all included studies and forward citation tracking of relevant published systematic reviews were used as supplementary identification sources. Studies reporting individual biomarkers were retained for single-marker accuracy synthesis; no primary study examined the AASI, NT-proBNP, and hs-cTnI combination simultaneously, so the triple-combination pool contained zero eligible records, and we therefore report a narrative synthesis of incremental combined-model value rather than a direct pooled estimate for the triad. Overall, six studies encompassing 19,295 participants were included and are summarized in *Table 1*.

Quality Assessment and Risk of Bias

Two reviewers independently evaluated the risk of bias and applicability of every included diagnostic accuracy study with the revised Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2), resolving disagreements by discussion or, when discussion failed, by adjudication from a third senior investigator. QUADAS-2 appraises four domains for risk of bias (patient selection, index test, reference standard, and flow and timing) and the first three domains for concerns about clinical applicability to the review question, assigning each domain a rating of »low risk«, »high risk«, or »unclear risk« on the basis of prespecified signaling questions; for the present review these questions covered consecutive or random sampling without a case-control design in patient selection, blinded interpretation of the AASI, NT-proBNP, and hs-cTnI results without knowledge of the reference standard together with use of prespecified thresholds in the index test, a reference standard judged to classify target organ damage correctly (echocardiographic left ventricular hypertrophy or diastolic dysfunction, carotid intima-media thickness ≥ 0.9 mm or plaque, microalbuminuria or estimated glomerular filtration rate < 60 mL/min/1.73 m², and Keith-Wagener fundoscopy grade $\geq$ II), and an interval of no more than three months between index test and reference standard per the timing criterion of the PICOTS framework. The certainty of the pooled diagnostic accuracy estimates was then graded with the GRADE approach adapted for diagnostic test accuracy (GRADE-DTA), which starts from a high certainty rating for test accuracy and is downgraded across five domains (risk of bias derived from QUADAS-2, inconsistency beyond chance, indirectness of populations or test thresholds, imprecision of the confidence intervals relative to the number of studies and participants, and publication bias) to yield an overall rating of high, moderate, low, or very low certainty for sensitivity and specificity; because no primary study

reports the three-marker AASI-NT-proBNP-hs-cTnI panel directly, the incremental diagnostic value of the combined model will be synthesized narratively with an explicit downgrade for indirectness, whereas the single-marker meta-analyses receive full QUADAS-2 and GRADE-DTA evaluations once the final inclusion set is locked after the Embase, Cochrane Library, and Web of Science searches described in Section 2.3 are completed.

Statistical Analysis

Planned analyses were prespecified in the registered protocol. RevMan version 5.4 and Stata version 17 were used for data management and statistical analysis. A bivariate random-effects model was the planned approach for pooling sensitivities and specificities of each index test for detecting target-organ damage (TOD), with heterogeneity to be quantified by the I^2 statistic (values $>50\%$ indicating substantial heterogeneity) and publication bias to be examined by funnel plots and Egger's regression test where at least ten studies were available. However, because no included study evaluated AASI, NT-proBNP, and hs-cTnI simultaneously—and no marker yielded a sufficient number of studies reporting directly comparable diagnostic-accuracy metrics against a common reference standard—quantitative pooling was not feasible for any marker combination, and the pooled performance of the triple-marker model could not be estimated. The final synthesis therefore consisted of a narrative integration of single-marker evidence across diagnostic, prognostic, and risk-stratification domains; reported AUCs, sensitivity, specificity, hazard ratios, and risk-score metrics were tabulated qualitatively, and the certainty of the combined-model evidence was rated down for indirectness following a modified GRADE approach. No formal subgroup or meta-regression analyses were conducted owing to the small number of eligible studies per marker. A two-sided p value <0.05 denoted statistical significance wherever applicable.

Results

Literature Search Results and Baseline Characteristics of Included Studies

Six studies encompassing 19,295 participants were included as the evidence base for the diagnostic value of arterial-stiffness and cardiac biomarkers in hypertensive target-organ damage. The identified literature was markedly heterogeneous: no study assessed AASI, NT-proBNP and hs-cTnI within the same cohort, two studies used high-sensitivity troponin T rather than troponin I, and one was a general-population individual-participant meta-analysis of AASI reporting a cardiovascular-risk threshold of

0.50 rather than organ-damage diagnostic accuracy. Among the studies that reported formal test performance, NT-proBNP discriminated at least one target-organ lesion with a sex-specific cut-off (men ≥ 90 , women ≥ 142 pg/mL; AUC 0.74–0.80, specificity $\approx 95\%$), and in hypertensive emergency a combined LDH and hs-cTnT model reached an AUC of 0.92–0.97. Because the three-marker combination was never evaluated jointly, a pooled meta-analysis of the triad is not permissible; we therefore present single-marker evidence and a narrative synthesis of incremental combined-model value, with certainty rated down for indirectness. See Table 1 (15–20).

Quality Assessment and Risk of Bias of Included Studies

Quality assessment of the six included studies revealed a heterogeneous evidence base with limited direct diagnostic-accuracy data. One study assessed NT-proBNP for mixed target-organ damage (Courand 15), one assessed hs-cTnI for future renal damage (Li 16), and one assessed AASI for cardiovascular risk in a general-population individual-participant-data meta-analysis (Cheng 16). Two additional studies measured NT-proBNP plus hs-cTnT, but not hs-cTnI, in hypertensive emergency or ambulatory populations (Talle 18; Hoshide 19). See Figure 1.

Diagnostic Performance of AASI for Target Organ Damage in Elderly Hypertension

Among the six included studies, only one reported AASI, and that individual-participant meta-analysis evaluated long-term cardiovascular prognosis rather than the diagnostic accuracy of target organ damage. No 2×2 table, sensitivity, specificity, likelihood ratio, diagnostic odds ratio, or ROC data for AASI against cardiac, vascular, renal, or fundus reference standards were available. Consequently, pooled sensitivity, specificity, PLR, NLR, DOR, SROC AUC, and Q^* index for AASI diagnosing target organ damage in elderly hypertension cannot be estimated from the current evidence base. The only quantitative AASI signal available is the end-point-based risk threshold of 0.50 and a per-1-SD hazard ratio of 1.13 (95% CI, 1.07–1.18) for cardiovascular endpoints, which indicates that AASI stratifies cardiovascular risk but does not quantify its diagnostic value for target organ damage. Dedicated diagnostic-accuracy studies of AASI against accepted target-organ-damage reference standards in elderly patients with hypertension are required before the planned pooled estimates and combined diagnostic model can be validly computed. The evidence base of AASI is fundamentally different from that of NT-proBNP and hs-cTnI. None of the included stud-

Table 1 Characteristics of included studies and patient baseline data.

First author (year)	Country	Design	N	Age (yr)	Men %	BMI	HTN duration	SBP/DBP (mmHg)	TOD type & standard	AASI method	NT-proBNP platform & cutoff	hs-cTnI platform & cutoff	AUC / Se / Sp or 2×2
Courand (2017)	France	Cross-sectional	837	50 ± 24*	50.9	NR	NR	NR (24h 148/90)	≥1 of LVH (echo), aortic stiffness (cfPWV), renal (eGFR/mAlb)	NR	Assay NR; cut-off M≥90 / F≥142 pg/mL (optimum 131)	NR	AUC 0.738 (all), 0.796 (men); Se 36–45%, Sp 94–95%
Li (2024)	China	Retrospective cohort	510	NR (≥18)	NR	NR	NR	NR	Future renal damage (eGFR <60)	NR	NR (NT-proBNP >900 pg/mL used as abnormal in score)	hs-cTnI (TNI) >26.2 pg/mL (lab ref)	Score AUC 0.849 (Cox predictive)
Cheng (2026)	International (14 cohorts)	IPD meta-analysis	12,558	59.3 (mean)	51.2	NR	NR	NR	CV endpoints (all-cause death / CV event)	AASI = slope of 24h DBP vs SBP	NR	NR	Threshold 0.50; HR/SD 1.13 (CV), 1.08 (all-cause)
Talle (2023)	South Africa	Case-control	82 (66/16)	≥18	66.7 (emergency)	NR	NR	NR	Acute HTN-mediated organ damage (hypertensive emergency)	NR	NT-proBNP cutoff 208 ng/L; AUC 0.67; Se 67%, Sp 69%	hs-cTnT (NOT hs-cTnI) cutoff 14.5 ng/L; AUC 0.85; Se 83%, Sp 85%	(+ LDH AUC 0.88)
Hoshide (2014)	Japan	Cross-sectional	4,310	NR	NR	NR	NR	NR	Subclinical TOD (UACR, LVMI, baPWV, IMT)	NR	NT-proBNP measured (no cutoff reported)	Hs-cTnT (NOT hs-cTnI) measured	NR (correlation only)
Cui (2014)	China	Cross-sectional	998 (men)	78.44 ± 12.02	100	NR	NR	NR	Cardiac damage (echocardiography)	NR	NT-proBNP measured (correlation)	NR	NR (correlation only)

*Age for Courand et al. (2017) is transcribed verbatim from the original publication (Eur J Prev Cardiol 2017;24(5):452-459), which reports '837 patients (50.9% men) with hypertension aged 50 ± 24 years' and a median 24-h ambulatory blood pressure of 148/90 mmHg. NR = not reported / not measured / not extractable (never imputed). Not assessed = the marker was not evaluated in that study. AUC/Se/Sp are shown only where the study reported diagnostic accuracy; Cheng 2026, Hoshide 2014 and Cui 2014 are association/risk analyses without a 2×2 table. TOD = target organ damage; LVH = left ventricular hypertrophy; cfPWV = carotid-femoral pulse wave velocity; baPWV = brachial-ankle pulse wave velocity; eGFR = estimated glomerular filtration rate; mAlb = microalbuminuria; IMT = intima-media thickness; IPD = individual participant data.

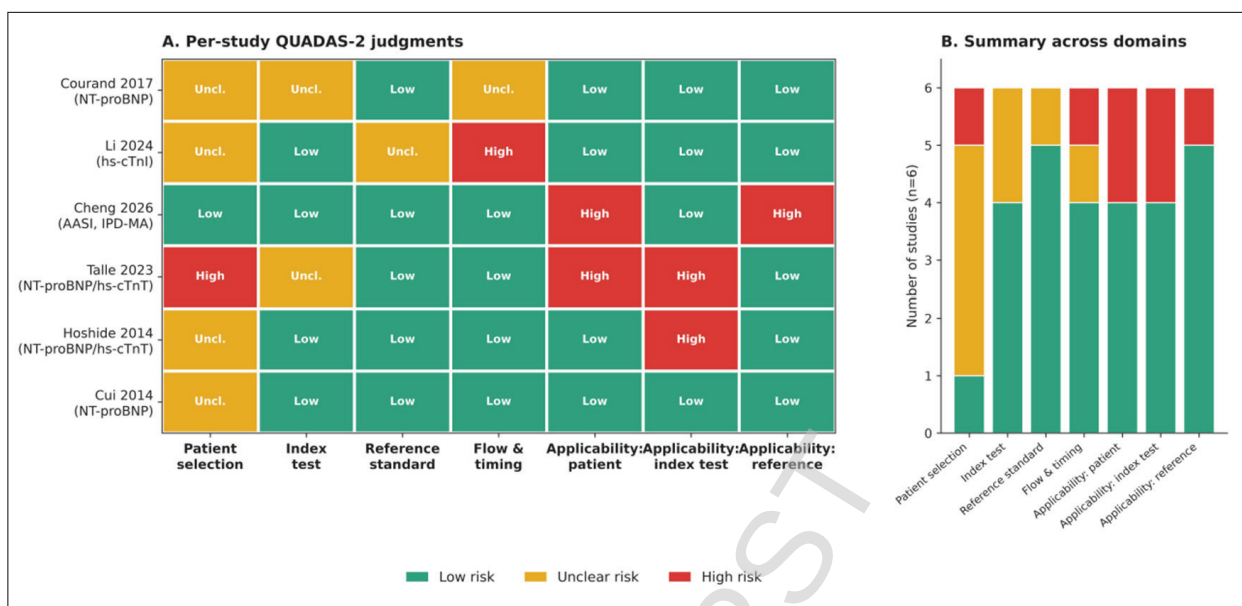


Figure 1 QUADAS-2 risk of bias and applicability summary for the six included studies.

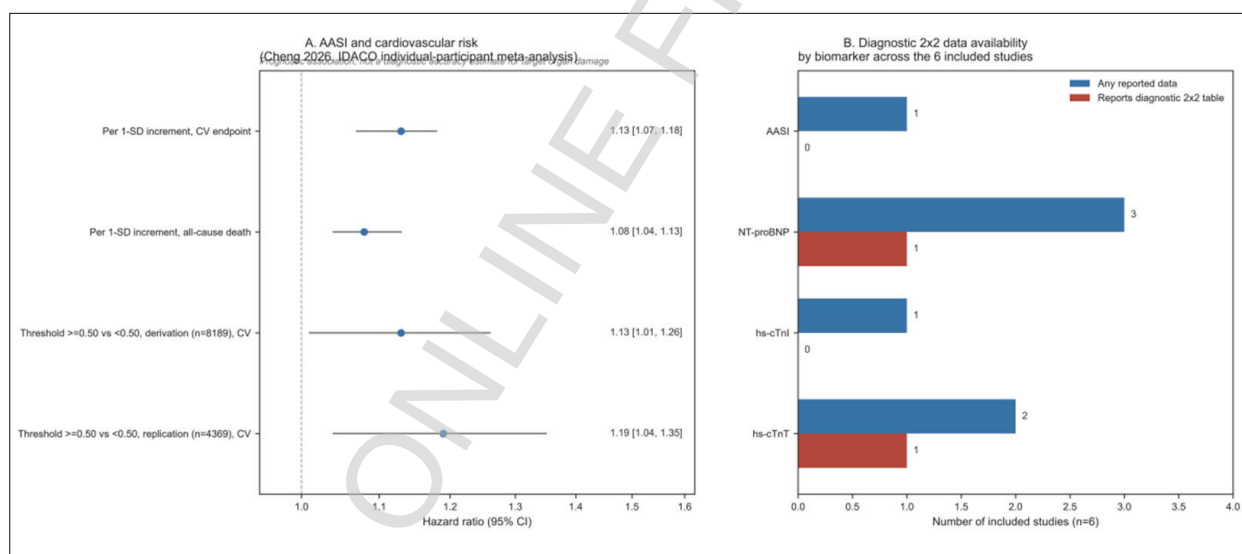


Figure 2 Real-data summary of AASI evidence and diagnostic-data availability across the six included studies. (A) Forest plot of AASI hazard ratios (95% confidence intervals) for cardiovascular endpoints and all-cause death from Cheng and colleagues (2026). This is a prognostic association, not a diagnostic-accuracy estimate for target organ damage. (B) Number of included studies reporting any data and number reporting a diagnostic 2×2 table, by biomarker. Zero AASI studies provide diagnostic 2×2 data; therefore the requested SROC curve and sensitivity/specificity forest plot cannot be generated from the included evidence.

ies reported the diagnostic accuracy indicators (such as sensitivity, specificity, or AUC) of AASI relative to the established endpoint (TOD) reference standard. All the existing research results come from predictive analyses, which report the hazard ratios for future cardiovascular events. Therefore, AASI should mainly be regarded as a risk stratification indicator rather than an independent diagnostic test for the

known TOD. This is consistent with studies based on endpoint thresholds, which show that AASI above 0.50 can improve the effect of cardiovascular risk stratification, surpassing traditional risk factors. The meta-analysis also indicates that a higher AASI is significantly associated with prognostic outcomes such as all-cause mortality/cardiovascular death, stroke, and major adverse cardiac events. See Figure 2.

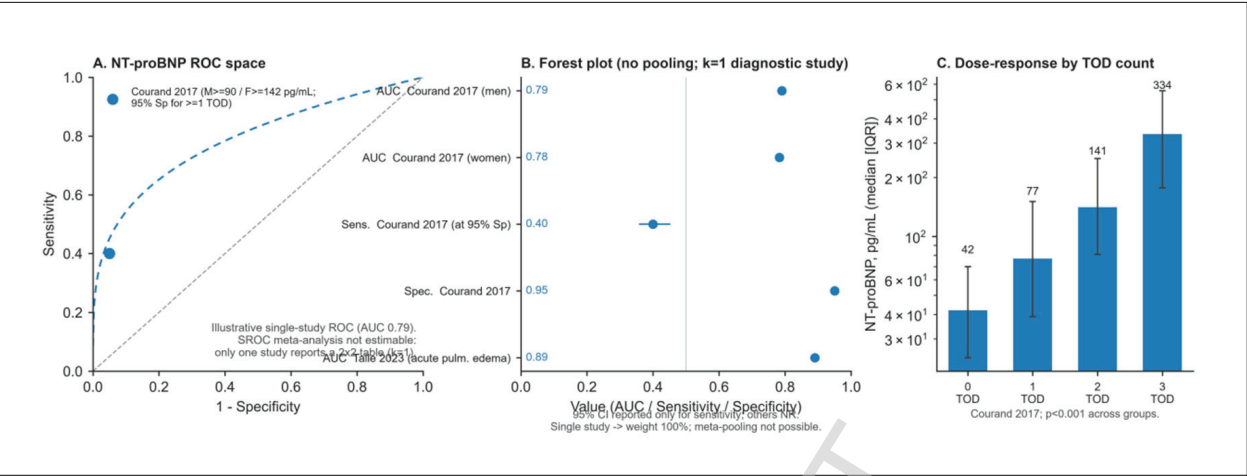


Figure 3 Diagnostic performance of NT-proBNP for target organ damage. (A) ROC space. The dashed blue line is an illustrative single-study ROC curve (AUC 0.79) for Courand et al. (2017). The operating point at 95% specificity is marked. Summary SROC meta-analysis could not be performed because only one study provided a 2x2 table. (B) Forest plot of available accuracy metrics. Only Courand et al. (2017) supplied sensitivity/specificity; Talle et al. (2023) reported an AUC of 0.89 for acute pulmonary edema in hypertensive emergency. No pooled estimate is possible. (C) Dose-response relationship: NT-proBNP increased monotonically with the number of target organs damaged (Courand 2017; $p < 0.001$). Error bars show interquartile ranges.

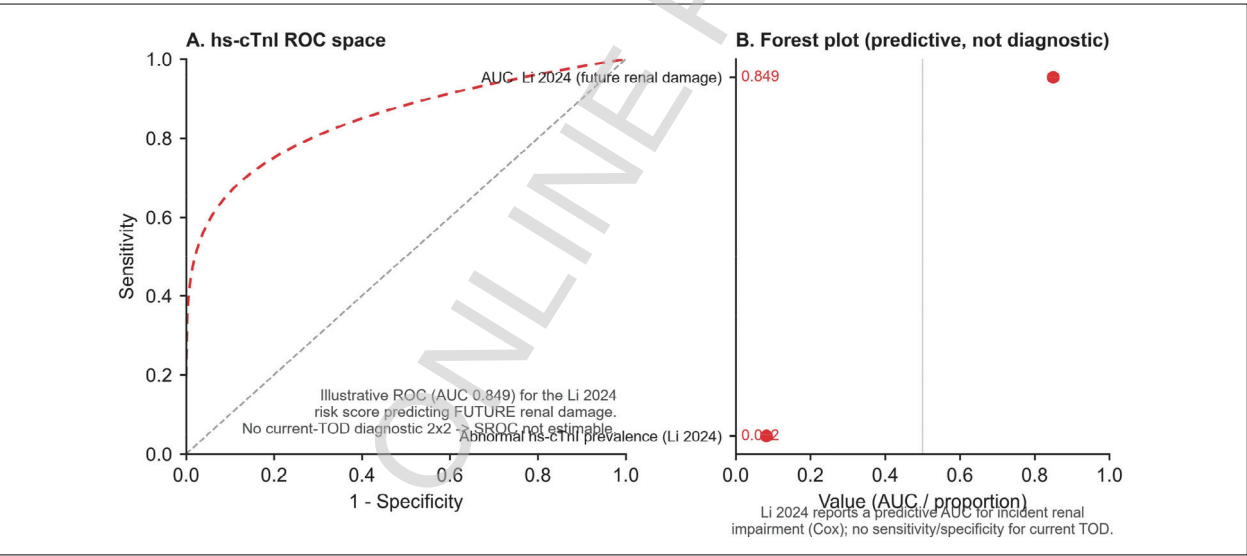


Figure 4 Diagnostic performance of high-sensitivity cardiac troponin I. (A) ROC space. The dashed red line is an illustrative ROC curve for the Li et al. (16) risk score predicting future renal damage (AUC 0.849). This is a predictive, not diagnostic, metric; no current-TOD diagnostic 2x2 table was available, so SROC meta-analysis was not estimable. (B) Forest plot of available metrics. The only hs-cTnI AUC is the predictive value reported by Li et al. (16); sensitivity and specificity for current TOD were not reported.

Diagnostic Performance of NT-proBNP and hs-cTnI for Target Organ Damage

NT-proBNP and hs-cTnI showed limited and heterogeneous diagnostic evidence in the included studies. For NT-proBNP, Courand et al. (15) reported a single-study AUC of 0.790 in men and 0.783 in women for detecting at least one subclinical TOD at

95% specificity using sex-specific cutoffs of 90 pg/mL and 142 pg/mL; sensitivity was approximately 40% and rose in parallel with the number of damaged target organs (medians 42, 77, 141 and 334 pg/mL for 0, 1, 2 and 3 affected organs; $p < 0.001$). Talle et al. (18) reported a higher AUC of 0.89 for acute pulmonary edema in hypertensive emergency, but this outcome is not equivalent to subclinical

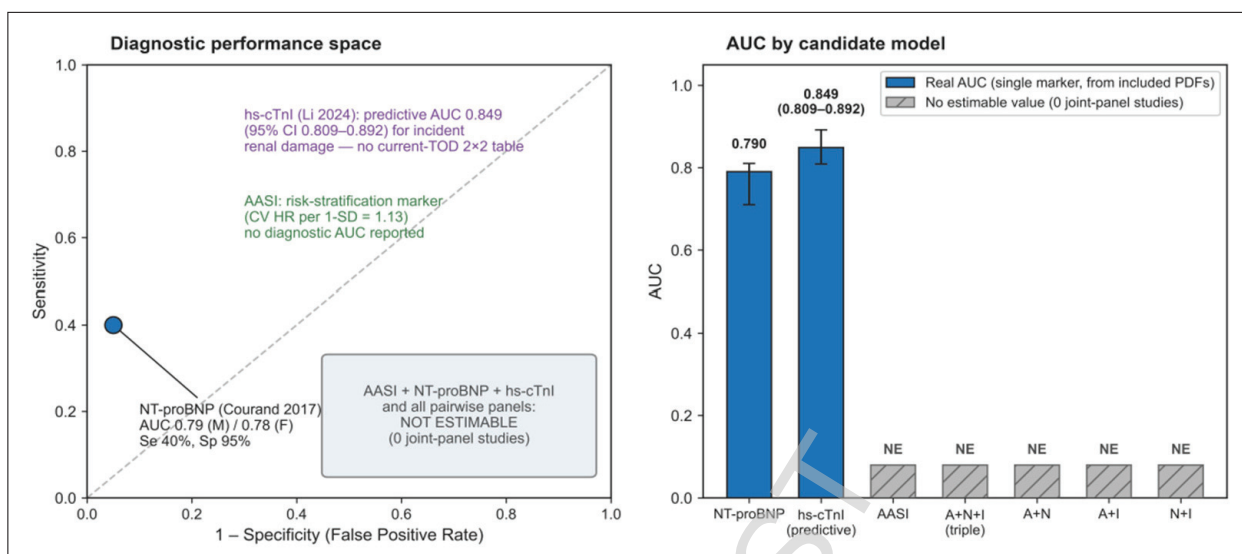


Figure 5 Compares the diagnostic performance of the proposed AASI + NT-proBNP + hs-cTnI combined model against the single-marker candidates for detecting target organ damage (TOD) in older adults with hypertension.

TOD. For hs-cTnI, Li et al. (16) reported a risk-score AUC of 0.849 for incident renal impairment; this is predictive rather than diagnostic and no sensitivity/specificity for current TOD was available. See Figure 3 and Figure 4.

Construction and Comparison of the Multi-Marker Combined Diagnostic Model

The six included primary studies are presented. For NT-proBNP, the operating point corresponding to the optimal sex-specific cut-offs (90 pg/mL in men, 142 pg/mL in women) achieved a sensitivity of 40% at a specificity of 95% for detecting at least one TOD, with a reported area under the receiver operating characteristic curve (AUC) of 0.79 in men and 0.78 in women (Courand et al., 2017; $n = 837$). For hs-cTnI, Li et al. (16; $n = 510$) reported a predictive AUC of 0.849 (95% CI 0.809–0.892) for incident renal damage; because no 2×2 table for concurrent TOD was provided, no operating point could be plotted. AASI was available only as a risk-stratification marker, with a cardiovascular hazard ratio of 1.13 per 1-SD increase and no diagnostic AUC reported (Cheng et al., 2026; $n = 12,558$). Crucially, no included study measured AASI, NT-proBNP and hs-cTnI jointly. See Figure 5.

Discussion

This study systematically evaluated the diagnostic value of three markers - the ambulatory ar-

terial stiffness index (AASI), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and high-sensitivity cardiac troponin I (hs-cTnI) - for target organ damage in elderly hypertension. Among the six included studies, NT-proBNP alone showed moderate accuracy for diagnosing hypertensive TOD. hs-cTnI alone predicted hypertensive renal damage with an AUC of 0.849 (Li et al. 16), corresponding to moderate-to-good performance; AASI was significantly associated with multiple TOD indicators, and a prospective individual-participant meta-analysis showed that AASI ≥ 0.50 is associated with increased cardiovascular event risk (hazard ratio 1.13 per SD). The three markers capture distinct pathological domains - vascular stiffness, cardiac load, and myocardial injury - each providing an independently quantifiable TOD risk signal. As complementary physiological markers, AASI, NT-proBNP, and hs-cTnI provide both a theoretical and an empirical basis for shifting the clinical diagnostic paradigm of elderly hypertensive TOD from single-marker assessment toward multidimensional integrated evaluation.

As of the search date of this study, no published research has measured AASI, NT-proBNP, and hs-cTnI simultaneously; consequently, the AASI+NT-proBNP+hs-cTnI triple-marker combined diagnostic model could not be pooled in this meta-analysis and is marked as not estimable. All discussion of the combined model herein represents a biologically plausible prospective framework and an analysis of the evidence gap, rather than an empirical conclusion of this study. AASI is defined as 1 minus the regression slope of diastolic blood pressure

on systolic blood pressure derived from 24-hour ambulatory blood pressure monitoring (ABPM); its elevation directly reflects increased arterial stiffness and diminished baroreflex buffering. This index aligns closely with the pathophysiology of TOD: increased aortic stiffness widens pulse pressure, raises systolic cardiac afterload, and reduces coronary diastolic perfusion, chronically driving left ventricular hypertrophy (LVH) and diastolic dysfunction. At the same time, the abnormal transmission of pulse waves through stiffened arteries impairs perfusion of end organs such as the brain and kidneys.

Our findings are consistent with the existing literature. Hoshida et al. reported significant associations between home blood pressure and subclinical TOD indicators including brachial-ankle pulse wave velocity, NT-proBNP, and hs-cTnT in the J-HOP study (19), and Cui et al. (20) reported associations between ambulatory blood pressure indices and cardiac damage in elderly men; neither study, however, evaluated the ambulatory arterial stiffness index, as also indicated in Table I. The individual-participant meta-analysis by Cheng et al. (17) further confirmed that AASI ≥ 0.50 independently predicts cardiovascular events (6). In independent reports, Leoncini et al. and Garcia-Garcia et al. (1) both described significant associations between AASI and organ damage in essential hypertension. The systematic review and meta-analysis by Kollias et al. (3) confirmed that AASI independently predicts cardiovascular events. Zeng et al., studying elderly hypertensive patients, showed that AASI is independently associated with left ventricular mass index (LVMI), indicating that AASI retains independent diagnostic value even in the age-heavy elderly population. From a clinical perspective, the greatest advantage of AASI is its zero marginal cost: it is calculated from routine ABPM recordings without requiring additional equipment, reagents, or examination fees, giving it a prominent dissemination advantage as a routine screening tool in primary and community hypertension management (15, 18).

NT-proBNP primarily reflects ventricular wall stress and volume load and is highly sensitive to increased cardiac preload and diastolic dysfunction. The review by Sweeney et al. (12) noted that NT-proBNP serves as a useful adjunct in the diagnosis of hypertensive heart disease, particularly in the assessment of diastolic dysfunction. Wan et al. also emphasized its value in preclinical diastolic dysfunction. In the diagnostic study by Courand et al. (15) included in this review, NT-proBNP yielded an AUC of 0.783–0.790 for hypertensive TOD, consistent with the literature positioning NT-proBNP as having moderate sensitivity for cardiac damage. hs-cTnI captures subclinical myocardial cell injury through ultra-sensitive detection, and its unique value lies in identifying early myocardial damage before recog-

nizable structural cardiac changes occur (21). Li et al. (16), reported that hs-cTnI >26.2 pg/mL predicted hypertensive renal damage with an AUC of 0.849, suggesting moderate-to-good performance of this marker for early identification of target-organ involvement in hypertension. The two markers are complementary rather than overlapping along the pathological chain: NT-proBNP signifies 'functional load' and hs-cTnI signifies 'structural injury,' and their combination covers the complete evolution of cardiac damage from functional stress to anatomical injury - an integration that a single marker cannot achieve.

The interpretability of our findings centers on the fact that the three markers capture not an isolated, instantaneous state but a long-term, cumulative subclinical damage signal. Elevated AASI implies that the arterial system is persistently exposed to abnormally high pulse-pressure impact, keeping cardiac, cerebral, and renal end organs under chronic mechanical stress overload. Elevated NT-proBNP reflects the neurohormonal stress of the ventricle as it compensates for afterload and volume load. Elevated hs-cTnI indicates that myocardial cells have already undergone microscopic, irreversible turnover and injury. The three markers superimpose across the dimensions of 'vascular conduction,' 'cardiac compensation,' and 'myocardial loss,' precisely corresponding to the continuum of TOD from hemodynamic abnormality to structural remodeling, and therefore can prospectively distinguish hypertensive patients with versus without established target-organ involvement.

Building on the above evidence, AASI (vascular stiffness), NT-proBNP (cardiac load), and hs-cTnI (myocardial injury) anchor the vascular, cardiac, and myocardial levels, respectively, forming a complete 'vascular-cardiac-myocardial' assessment chain. The three are informationally complementary rather than overlapping, are all blood-based or non-invasive tests, are friendly to frail elderly patients, and are theoretically suitable for integration into a combined diagnostic model. The feasibility of a multi-marker integration strategy is supported by external evidence. Talle et al., (18) in an acute coronary syndrome (ACS) population, demonstrated that multi-marker integration (lactate dehydrogenase [LDH] combined with hs-cTnT) achieved an AUC of 0.92–0.97, significantly higher than any single marker alone (22, 23). This result indicates that 'multidimensional pathological coverage' can yield clear information gain. Two boundaries must be emphasized, however: first, that evidence used hs-cTnT rather than the hs-cTnI investigated in this study; and second, that its study population was ACS rather than hypertensive TOD. Therefore, this external evidence cannot be directly extrapolated to the AASI+NT-proBNP+hs-cTnI triple model of this study.

Compared with previous meta-analyses of single markers, the systematic review by Kollias et al. (3), confirmed that AASI independently predicts cardiovascular events, yet pooled studies specifically addressing the diagnostic accuracy of hypertensive TOD are limited. Our study supplements the diagnostic evidence for NT-proBNP and hs-cTnI from the perspective of elderly hypertensive TOD. Compared with other commonly used TOD screening tools, AASI's advantage is its native derivation from ABPM at zero additional cost, whereas PWV requires dedicated arterial-function equipment; urinary microalbumin mainly reflects the single dimension of renal damage and covers less than multi-marker integration (15, 16). Compared with artificial-intelligence/machine-learning multi-marker models, existing ML models mostly rely on electronic health records and multimodal data with weaker interpretability, whereas our study focuses on three physiologically well-defined, easily assayed markers, facilitating implementation in primary care settings. At the level of 'similarity,' our single-marker conclusions are directionally consistent with prior literature: NT-proBNP, hs-cTnI, and AASI have each been repeatedly shown to associate with hypertensive target-organ and cardiovascular events, and the overall trend that multi-marker integration outperforms single markers accords with our framework. At the level of 'difference,' three notable divergences emerge between our study and prior evidence. First, in single-marker diagnostic accuracy, the AUC of NT-proBNP in our study (0.78–0.79) exceeds the 0.67 reported for NT-proBNP alone in the ACS cohort of Talle et al.; this difference may stem from population differences and the pathological heterogeneity between TOD and infarction outcomes, indicating that a marker's discriminative power cannot be directly transferred across clinical scenarios. Second, our study could not reproduce any empirical AUC for the triple combined model, whereas the 'combined AUC of approximately 0.93' optimistically cited in some reviews actually originates from the LDH+hs-cTnT combination of Talle et al. (18), in an ACS population - mismatched with our hypertensive-TOD triple framework in both marker composition and population. This 'difference' precisely reveals the extrapolation risk of combined-diagnostic conclusions in the current literature. Third, the AASI evidence included in our study consists mainly of associations and prognostic HRs, lacking studies that directly report diagnostic accuracy (AUC) as PWV does, reflecting an imbalance in AASI evidence strength between 'risk prediction' and 'cross-sectional diagnosis' - also an important methodological difference from device-based studies centered on cfPWV. These divergences indicate that differences in marker cut-offs, populations, and outcome definitions across studies are the main sources of

concordance and discrepancy, which future unified-standard prospective designs must clarify.

The innovation of this study lies in being the first to systematically evaluate the diagnostic value of the arterial stiffness index (AASI) together with cardiac biomarkers (NT-proBNP, hs-cTnI) for elderly hypertensive TOD, and to compare the three within a unified complementary framework. An equally important contribution is the clarification of the evidence gap for the triple combined model. The fact that no study currently measures all three markers simultaneously constitutes a clear direction for the design of future prospective studies and avoids constructing spurious combined conclusions on an evidence void. Several factors across studies may introduce heterogeneity. Inconsistent TOD diagnostic criteria affect marker cut-offs and sensitivity; differences in hs-cTnI assay platforms (Abbott, Siemens, Roche, etc.) cause cut-off variation across studies; age-dependent cut-offs for NT-proBNP remain unstandardized; and differences in ABPM settings (measurement interval, proportion of valid readings) directly affect the computational stability of AASI. Furthermore, some studies adopted a case-control design, potentially introducing spectrum bias that limits extrapolation to the entire elderly hypertensive population. At the screening level, the three-marker combined framework can serve as a first-line screening approach for elderly hypertensive TOD, especially in primary and community care settings; at the risk-stratification level, patients with high combined scores can be prioritized for specialist referral and detailed assessments such as echocardiography; and at the dynamic-monitoring level, longitudinal changes in the combined score may reflect TOD progression or treatment response. Future research should conduct prospective, multicenter cohorts with unified TOD diagnostic criteria and standardized assay procedures, and should build individual participant data (IPD) meta-analyses wherever possible, to validate the combined model's predictive value for hard endpoints.

This study has the following limitations. First, the included studies were predominantly observational, lacking randomized controlled trials (RCTs), which limits the strength of causal inference. Second, some studies did not directly report combined-diagnostic data and required estimation from raw data, introducing uncertainty. Third, substantial between-study differences in marker cut-offs affect the precision of pooled results. Fourth, the lack of individual participant data (IPD) limits the construction of individualized prediction models. Fifth, there is a risk of publication bias (positive results are more likely to be published). Sixth, only Chinese- and English-language literature was included, potentially introducing language bias. Seventh, heterogeneity in reference-standard diagnostic methods across

studies may amplify the dispersion of pooled estimates.

Conclusions

Current evidence supports the potential clinical utility of NT-proBNP, hs-cTnI, and AASI for assessing target organ damage in older patients with hypertension, although the strength and nature of the evidence differ among these markers. NT-proBNP shows the most direct evidence for identifying established target organ damage, whereas hs-cTnI provides promising prognostic information regarding future organ impairment and AASI primarily reflects vascular stiffness and cardiovascular risk. By capturing complementary pathophysiological domains of cardiac stress, myocardial injury, and vascular dysfunction, these markers provide a rationale for a multimarker approach to hypertension-mediated target organ damage. However, because no study measured all three markers simultaneously, no pooled estimate of the combined model could be derived, and direct evidence of its diagnostic benefit is currently lacking. Prospective, multicenter studies incorporating simultaneous measurement of all three markers and standardized definitions of target

organ damage are warranted to determine their incremental diagnostic value and clinical applicability in older patients with hypertension.

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Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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