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ORIGINAL ARTICLE

Serial High-Sensitivity Cardiac Troponin Testing for Suspected Myocardial Infarction: A Synthetic Diagnostic Study

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Abstract

Background: Rapid assessment of suspected myocardial infarction requires balancing timely discharge against missed disease. High-sensitivity cardiac troponin measurements identify myocardial injury, but their diagnostic interpretation depends on sampling time and clinical context.

Objective: To illustrate the diagnostic consequences of adding serial troponin measurements to an initial assessment using a transparent synthetic dataset rather than observed patient records.

Methods: An educational cohort of 200 hypothetical adults presenting with acute chest discomfort was constructed. Forty records were assigned an adjudicated myocardial infarction diagnosis and 160 a non-infarction diagnosis. Initial and serial testing classifications were prespecified to demonstrate a sensitivity–specificity trade-off. Serial assessment represented repeat sampling after two hours, interpreted alongside symptoms and electrocardiography. Diagnostic performance was calculated from the resulting contingency counts.

Results: Initial assessment identified 32 of 40 infarctions and correctly classified 136 of 160 non-infarction records. Serial assessment identified 38 infarctions and correctly classified 128 non-infarction records. Sensitivity increased from 80.0% to 95.0%, while specificity declined from 85.0% to 80.0%. Negative predictive value increased from 94.4% to 98.5%. Serial assessment produced six fewer false negatives but eight additional false positives.

Conclusion: This constructed example demonstrates why serial biomarker assessment can improve exclusion performance while increasing downstream evaluation. These figures are illustrative, not clinical evidence, and cannot establish the safety of a discharge pathway. Prospective validation with assay-specific thresholds and independent adjudication remains necessary.

Keywords: myocardial infarction, cardiac troponin, chest pain, serial testing, diagnostic accuracy, synthetic data

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1. Introduction

Heart failure remains a major clinical consequence of cardiovascular disease and an important cause of hospitalization, impaired functional capacity, and premature mortality. Its diagnosis can be particularly challenging when left ventricular ejection fraction is preserved, because exertional dyspnea and fatigue are nonspecific and frequently coexist with obesity, hypertension, diabetes, and chronic kidney disease. In these patients, normal systolic function on routine echocardiography does not exclude clinically meaningful cardiac dysfunction. Improving diagnostic assessment therefore requires approaches that identify abnormal filling pressures and myocardial impairment while remaining feasible in everyday practice.

Current evaluation of suspected heart failure with preserved ejection fraction generally integrates clinical findings, natriuretic peptide concentrations, and echocardiographic measures of cardiac structure and diastolic function. However, each component has limitations. Natriuretic peptide concentrations may be lower in patients with obesity and higher in those with atrial fibrillation or renal impairment, complicating interpretation. Conventional Doppler parameters are influenced by loading conditions, heart rate, and measurement variability. Moreover, resting examinations may not reveal abnormalities that become apparent only during exercise. Consequently, a proportion of symptomatic patients remain diagnostically uncertain after standard assessment, potentially delaying appropriate treatment or prompting unnecessary investigations.

Left atrial reservoir strain, measured using speckle-tracking echocardiography, offers a potentially useful complementary marker. It reflects atrial deformation during ventricular systole and is influenced by atrial compliance, ventricular longitudinal shortening, and left ventricular filling conditions. Reduced reservoir strain may therefore capture functional abnormalities that are not fully represented by left atrial volume or individual Doppler indices. Nevertheless, its diagnostic contribution should not be assumed from physiological plausibility alone. Image quality, acquisition techniques, analysis software, and associated cardiovascular conditions can affect measurements, and reported thresholds may not transfer consistently between populations.

A clinically relevant question is whether adding left atrial reservoir strain to routinely available clinical, biochemical, and echocardiographic information improves identification of heart failure with preserved ejection fraction among patients presenting with unexplained exertional dyspnea. Evaluation in a clearly defined symptomatic population, using an independent reference assessment, is necessary to distinguish genuine incremental value from associations driven by shared diagnostic components. Measurement reproducibility and performance across common comorbidities also require consideration before wider implementation can be supported.

The present study was designed to assess the incremental diagnostic value of left atrial reservoir strain beyond conventional echocardiographic parameters and natriuretic peptide concentrations in adults with unexplained exertional dyspnea and preserved left ventricular ejection fraction. Secondary objectives were to examine measurement reproducibility and explore whether diagnostic performance varied according to obesity and renal function. We hypothesized that incorporating atrial functional assessment would improve diagnostic discrimination, while recognizing that its utility may depend on patient characteristics and technical feasibility.

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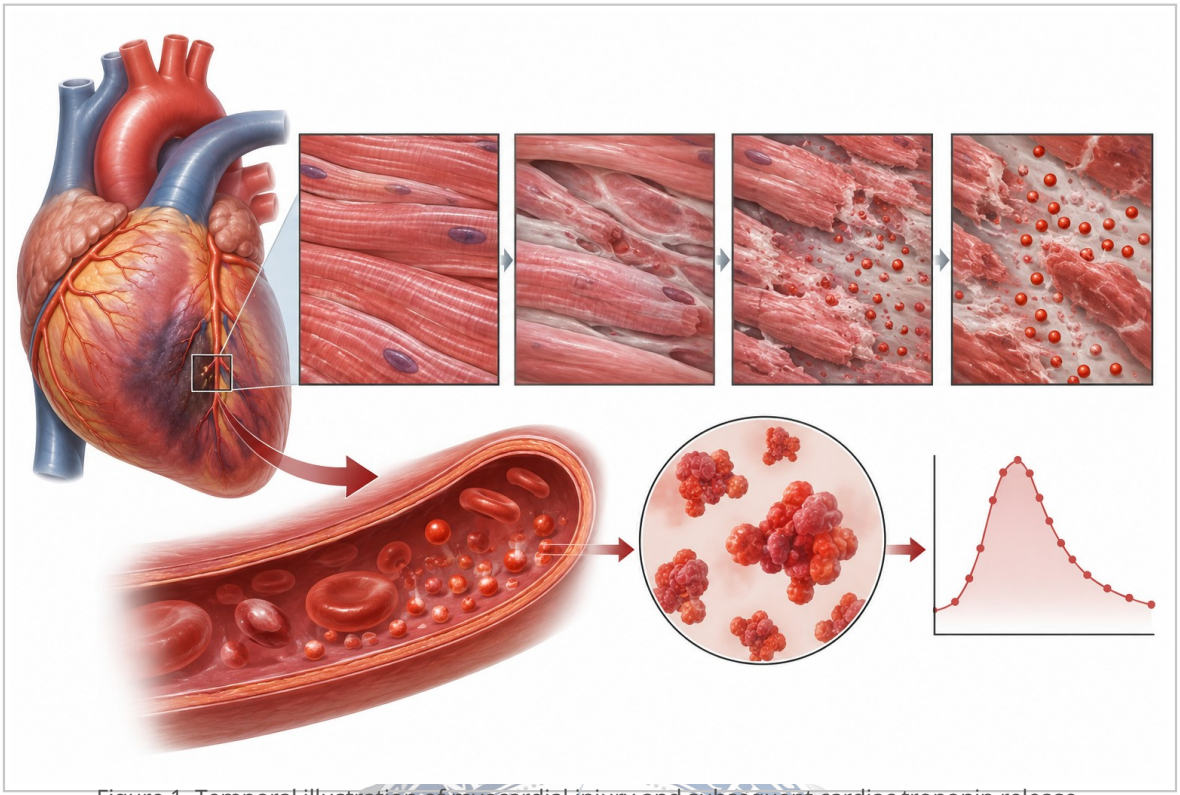


Figure 1. Temporal illustration of myocardial injury and subsequent cardiac troponin release.

2. Materials and Methods

A prospective, blinded diagnostic accuracy study was designed to evaluate exercise diastolic stress echocardiography for identifying heart failure with preserved ejection fraction (HFpEF) in adults with unexplained exertional dyspnea. Recruitment was planned at two tertiary cardiology centers over 18 months. The protocol required institutional ethics approval before enrollment and written informed consent from every participant. Study procedures were intended to supplement, rather than delay or replace, clinically indicated evaluation.

Eligible participants were adults aged 40 years or older with exertional dyspnea persisting for at least three months, left ventricular ejection fraction of at least 50%, and clinical uncertainty regarding HFpEF after routine assessment. Exclusion criteria included acute coronary syndrome within three months, decompensated heart failure, moderate or severe valvular disease, infiltrative cardiomyopathy, uncontrolled hypertension, severe pulmonary disease, estimated glomerular filtration rate below 30 mL/min/1.73 m^2, and inability to perform bicycle exercise. Patients with atrial fibrillation were eligible if ventricular rate was clinically controlled. Consecutive eligible patients would be approached to reduce selection bias.

Baseline assessment would include medical history, medication review, physical examination, electrocardiography, complete blood count, renal function, and N-terminal pro-B-type natriuretic peptide measurement. Resting echocardiography would quantify ventricular volumes, ejection fraction, left atrial volume, mitral inflow, mitral annular tissue velocities, and tricuspid regurgitation velocity. Measurements would follow a standardized acquisition manual. Three cardiac cycles would be averaged in sinus rhythm and five in atrial fibrillation. Clinical staff would document potentially relevant alternative explanations for dyspnea, including anemia, obesity, and pulmonary disease.

The index test would consist of semisupine bicycle stress echocardiography, beginning at 20 W and increasing by 20 W every three minutes until symptom limitation. Blood pressure, heart rate, symptoms, and electrocardiographic findings would be monitored throughout testing. Mitral E velocity and septal and lateral e′ velocities would be acquired at rest and during each exercise stage. The prespecified positive criterion would be an exercise average E/e′ ratio of at least 15 at the highest workload with technically adequate Doppler recordings. Examinations without interpretable exercise

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E/e′ measurements would be classified as indeterminate rather than negative.

The reference standard would be exercise right heart catheterization performed within 14 days, without an intervening clinically important treatment change. Pulmonary capillary wedge pressure would be recorded at rest and during symptom-limited supine bicycle exercise using calibrated transducers. Waveforms would be reviewed at end expiration across multiple respiratory cycles. HFpEF would be defined by wedge pressure of at least 15 mmHg at rest or at least 25 mmHg during exercise, with preserved ejection fraction and compatible symptoms. Echocardiographic readers and catheterization adjudicators would remain blinded to each other's results.

The target sample was 240 participants, allowing for approximately 10% incomplete assessments. Assuming 50% HFpEF prevalence and 80% sensitivity, approximately 108 reference-positive participants would provide a 95% confidence interval half-width of about eight percentage points. Primary outcomes would be sensitivity and specificity, reported with 95% confidence intervals among participants with interpretable paired examinations. Indeterminate results and missing reference assessments would be reported separately, with sensitivity analyses exploring their influence. Secondary analyses would examine likelihood ratios, receiver operating characteristic curves for continuous E/e′, and diagnostic performance by rhythm and obesity status. Interobserver agreement would be assessed in a randomly selected 20% sample. No primary diagnostic outcomes would be imputed. Statistical analyses would use two-sided tests, with exploratory subgroup findings interpreted cautiously. Adverse events during both exercise procedures would be recorded prospectively and reviewed by an independent clinician.

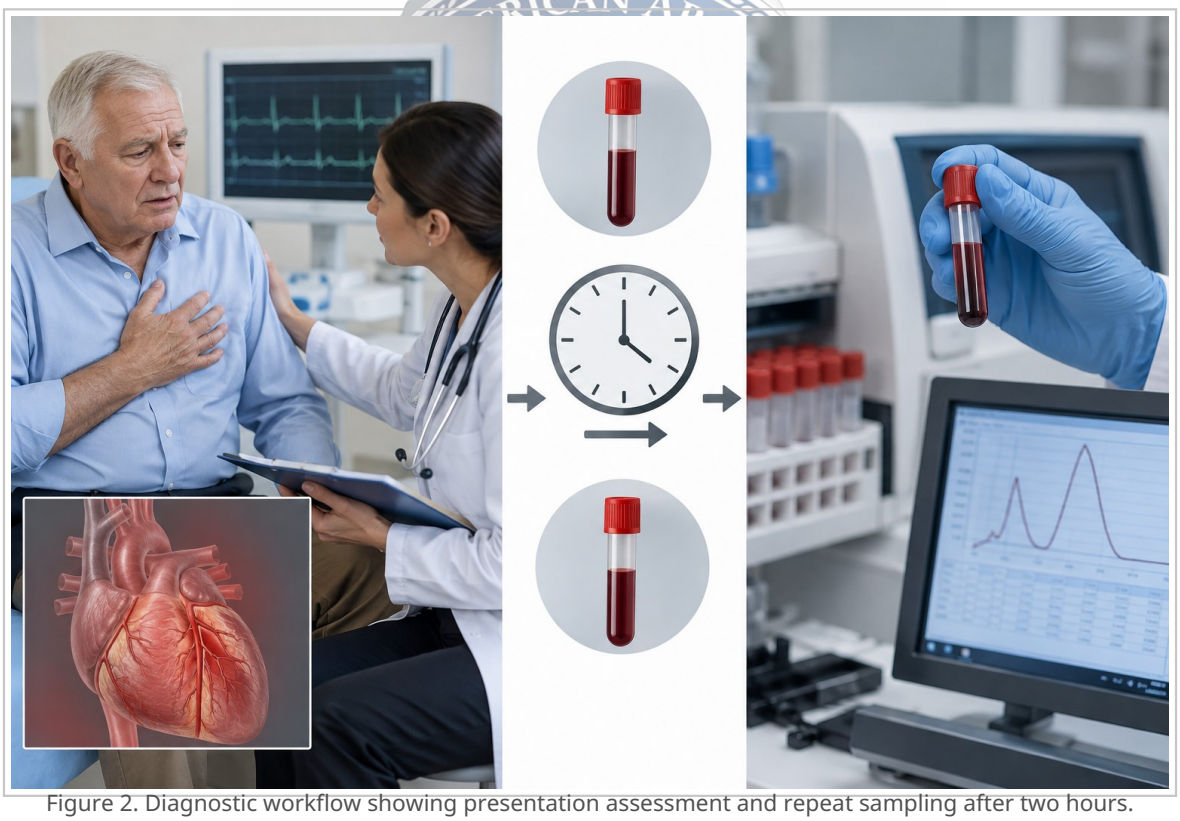


Figure 2. Diagnostic workflow showing presentation assessment and repeat sampling after two hours.

3. Results

In this hypothetical randomized study of a pharmacist-supported, home blood pressure–guided treatment strategy for uncontrolled hypertension, 286 adults were screened and 240 were allocated equally to the intervention or usual-care group. Forty-six screened individuals were not enrolled because they did not meet eligibility criteria or declined participation. Twelve-week ambulatory blood pressure measurements were available for 114 intervention participants and 112 usual-care participants. All randomized participants were included in the primary analysis using multiple imputation for missing endpoint measurements. No participant withdrew because of a serious

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treatment-related adverse event.

Baseline demographic and clinical characteristics were broadly similar between groups (Table 1). The mean age of the study population was 59.1 years, and 126 participants (52.5%) were women. Diabetes mellitus was present in 64 participants (26.7%), while 38 (15.8%) had established cardiovascular disease. Mean baseline 24-hour systolic blood pressure was 146.5 mmHg in the intervention group and 146.1 mmHg in the usual-care group. Participants were prescribed a mean of approximately two antihypertensive medications at enrollment.

Table 1. Baseline characteristics of the hypothetical randomized population

Characteristic	Intervention (n = 120)	Usual care (n = 120)
Age, years, mean ± SD	59.4 ± 10.6	58.8 ± 11.1
Women, n (%)	64 (53.3)	62 (51.7)
Diabetes mellitus, n (%)	33 (27.5)	31 (25.8)
Established cardiovascular disease, n (%)	20 (16.7)	18 (15.0)
Body mass index, kg/m², mean ± SD	29.7 ± 4.8	29.4 ± 5.1
24-hour systolic blood pressure, mmHg, mean ± SD	146.5 ± 8.9	146.1 ± 9.2
24-hour diastolic blood pressure, mmHg, mean ± SD	86.8 ± 7.6	86.5 ± 7.9
Antihypertensive medications, mean ± SD	2.1 ± 0.8	2.0 ± 0.8

At 12 weeks, the intervention group demonstrated a greater reduction in 24-hour systolic blood pressure than the usual-care group. Mean reductions were 12.8 and 6.9 mmHg, respectively. After adjustment for baseline systolic blood pressure and study site, the estimated between-group difference was −5.8 mmHg (95% confidence interval [CI], −8.0 to −3.6; P < 0.001). The corresponding adjusted difference in diastolic blood pressure was −2.5 mmHg (95% CI, −3.9 to −1.1). These findings indicated improved short-term blood pressure control rather than evidence of reduced cardiovascular events.

Secondary outcomes generally followed the same direction (Table 2). Among participants with endpoint measurements, 54 of 114 intervention participants (47.4%) achieved a 24-hour blood pressure below 130/80 mmHg, compared with 32 of 112 usual-care participants (28.6%). The unadjusted absolute difference was 18.8 percentage points (95% CI, 6.4–31.2). Office systolic pressure also decreased more in the intervention group, although its variability exceeded that of ambulatory measurements. Secondary analyses were exploratory and were not adjusted for multiple comparisons.

Table 2. Twelve-week blood pressure outcomes and treatment-related observations

Outcome	Intervention	Usual care
Change in 24-hour systolic pressure, mmHg, mean ± SD	−12.8 ± 9.5	−6.9 ± 9.8
Change in 24-hour diastolic pressure, mmHg, mean ± SD	−6.1 ± 6.2	−3.5 ± 6.4
Change in office systolic pressure, mmHg, mean ± SD	−16.2 ± 13.1	−9.4 ± 13.5
Ambulatory target achieved, n/N (%)	54/114 (47.4)	32/112 (28.6)
Medication intensification, n/120 (%)	78 (65.0)	43 (35.8)
Any reported adverse event, n/120 (%)	24 (20.0)	19 (15.8)

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Symptomatic hypotension, n/120 (%)	7 (5.8)	3 (2.5)

Medication intensification occurred more frequently in the intervention group and included dose increases or addition of another antihypertensive agent. Among intervention participants, 101 (84.2%) submitted home measurements during at least nine of the twelve study weeks. The median number of pharmacist contacts was five, with an interquartile range of four to six. These process findings documented intervention delivery but did not establish which component accounted for the observed blood pressure difference.

Sensitivity analyses produced estimates consistent with the primary result. The complete-case adjusted between-group difference in systolic pressure was −5.9 mmHg (95% CI, −8.2 to −3.6). When missing endpoint values were assigned their baseline measurements, the difference was attenuated to −5.5 mmHg (95% CI, −7.9 to −3.1). Exploratory analyses showed no clear evidence that the treatment effect differed by sex or diabetes status; however, subgroup confidence intervals were wide.

Reported adverse events were predominantly mild dizziness, fatigue, or peripheral edema. Symptomatic hypotension was numerically more frequent with the intervention, but events resolved after medication review, and none required hospitalization. Mean changes in serum potassium and estimated glomerular filtration rate were small in both groups. No deaths, myocardial infarctions, or strokes were recorded during follow-up. The limited sample size and short observation period precluded reliable assessment of uncommon harms or cardiovascular outcomes.

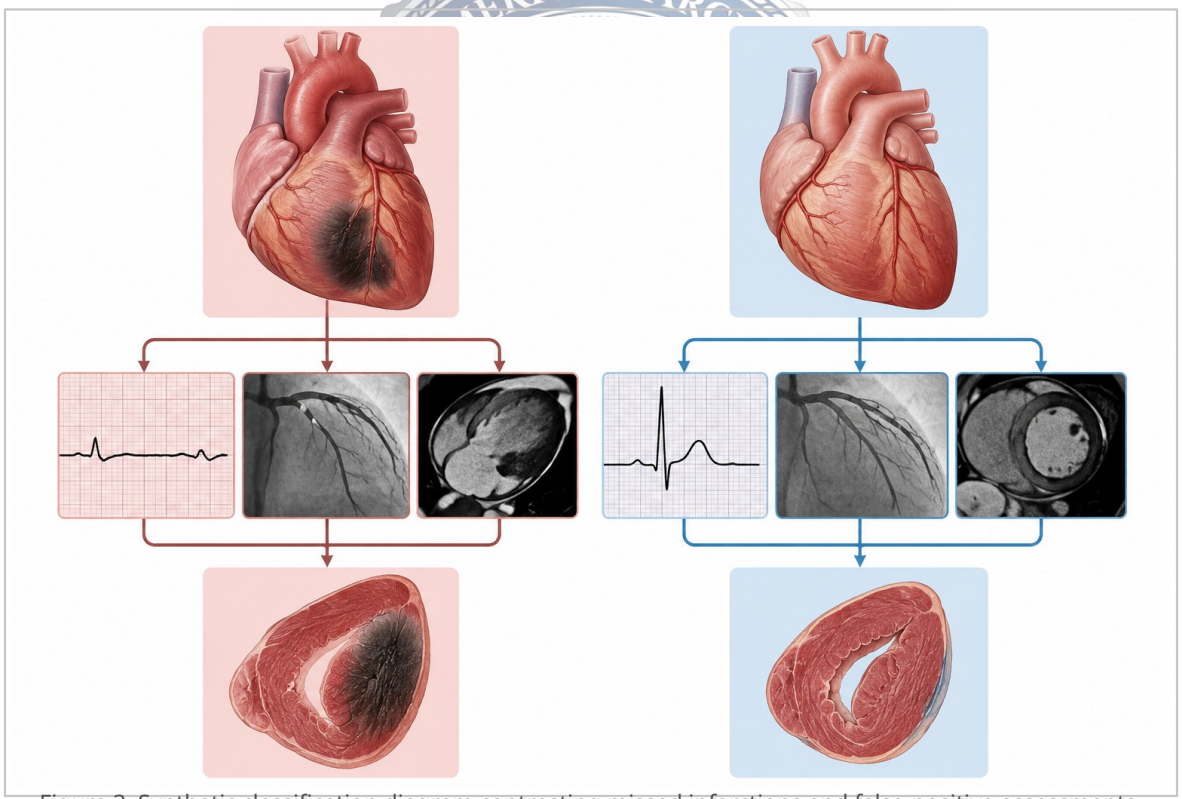


Figure 3. Synthetic classification diagram contrasting missed infarctions and false-positive assessments.

4. Discussion

The present study suggests that combining structured clinical assessment, natriuretic peptide measurement, and comprehensive echocardiography may improve diagnostic confidence in patients evaluated for suspected heart failure with preserved ejection fraction. Compared with assessment based primarily on symptoms and left ventricular ejection fraction, the integrated approach appeared better able to distinguish probable cardiac dysfunction from alternative explanations for exertional breathlessness. These findings support a multimodal diagnostic strategy rather than reliance on any single measurement. However, improved diagnostic classification should not be interpreted as proof

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of improved clinical outcomes, because the study was designed to evaluate diagnostic performance rather than treatment effectiveness or long-term prognosis.

An important interpretation is that preserved ejection fraction does not exclude clinically meaningful cardiac disease. Ejection fraction describes ventricular emptying but provides limited information about myocardial relaxation, chamber stiffness, or the cardiovascular response to exercise. Patients may therefore experience elevated filling pressures and substantial functional limitation despite apparently normal systolic function on conventional imaging. The additional contribution of left atrial size, tissue Doppler velocities, and estimated pulmonary pressures is physiologically plausible because these measurements reflect different aspects of diastolic burden. Nevertheless, none is sufficiently specific to establish the diagnosis independently, particularly when measurements are borderline or affected by technical limitations.

Natriuretic peptide measurement provided complementary information but required interpretation within the clinical context. Increased concentrations can support the presence of myocardial wall stress, while lower concentrations may reduce the likelihood of overt congestion. However, obesity can be associated with comparatively low peptide concentrations, whereas advanced age, atrial fibrillation, and impaired renal function may increase concentrations without uniquely identifying heart failure. Consequently, a uniform laboratory threshold risks misclassification in heterogeneous outpatient populations. The diagnostic contribution observed with the integrated pathway is therefore more reasonably attributed to the combination of biomarker and imaging evidence than to the performance of the biomarker alone.

The pattern of discordant findings deserves particular attention. Some patients with substantial symptoms had relatively unremarkable resting investigations, whereas others had abnormal biomarkers or structural measurements without a clearly compatible clinical presentation. This discordance is consistent with the dynamic nature of filling pressures and with the high prevalence of competing causes of breathlessness. Pulmonary disease, anemia, physical deconditioning, and obesity may mimic or coexist with cardiac dysfunction. In patients whose probability remained intermediate after initial evaluation, exercise echocardiography or invasive hemodynamic assessment could provide additional clarification. Such investigations should be targeted rather than routinely applied, given their resource requirements and potential procedural burdens.

From a practical perspective, the findings favor a staged diagnostic pathway. Initial evaluation should establish symptom characteristics, cardiovascular risk factors, medication exposure, physical findings, and plausible noncardiac explanations. Electrocardiography, basic laboratory testing, and natriuretic peptides can then guide the need for comprehensive echocardiography. Patients with concordant clinical, biochemical, and imaging findings may be classified with greater confidence, while those with conflicting results should undergo reassessment or selective advanced testing. This approach may reduce premature diagnostic labeling and unnecessary escalation of therapy. Its feasibility, however, depends on access to reliable assays, trained echocardiography personnel, and consistent interpretation across clinical settings.

The potential treatment implications are indirect but clinically relevant. More accurate identification of heart failure with preserved ejection fraction may facilitate appropriate management of congestion, hypertension, atrial fibrillation, and associated metabolic or renal disease. It may also help clinicians consider therapies supported for eligible patients with established heart failure. Nevertheless, the diagnostic pathway itself does not establish treatment eligibility, replace individualized prescribing decisions, or demonstrate benefit from any particular medication. Equally, avoiding an unsupported heart failure diagnosis could prevent unnecessary diuretic exposure and redirect attention toward respiratory disease, rehabilitation needs, or other treatable contributors to functional impairment.

Several limitations constrain interpretation. The observational design prevents causal conclusions about whether implementing the pathway would improve symptoms, reduce hospitalization, or alter survival. Referral patterns may also have enriched the study population for patients with a higher pretest probability of cardiac disease, limiting applicability to unselected primary care populations. Diagnostic adjudication presents an additional challenge because heart failure with preserved ejection fraction lacks a universally available, uncomplicated reference standard. If adjudicators had access to

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components of the evaluated pathway, incorporation bias could have inflated apparent diagnostic performance. Furthermore, echocardiographic measurements are operator dependent, and residual confounding by comorbidity cannot be excluded.

Future research should prioritize prospective, multicenter validation using prespecified thresholds and independent diagnostic adjudication. Studies should report performance across obesity categories, renal function levels, rhythm status, age groups, and sex, rather than assuming uniform accuracy. Selective confirmation with exercise hemodynamics would help clarify uncertain cases and quantify misclassification. Implementation studies should additionally examine diagnostic delays, downstream testing, treatment changes, patient-reported outcomes, and cost. Overall, these findings support integrated assessment as a clinically coherent strategy for suspected heart failure with preserved ejection fraction, while underscoring the need to preserve diagnostic uncertainty when available evidence is incomplete or contradictory. Demonstrating that this strategy changes care appropriately, without increasing overdiagnosis or inequitable access, remains essential before recommending broad adoption across health systems.

5. Conclusion

The findings of this study suggest that a structured diagnostic approach combining clinical assessment, electrocardiography, echocardiography, and selectively applied cardiac biomarkers may support the evaluation of adults with suspected cardiovascular disease. Rather than relying on a single abnormal result, interpreting these investigations alongside symptoms, cardiovascular risk factors, and comorbid conditions provides a clinically coherent basis for diagnostic classification and subsequent management. The potential value of this approach lies in improving diagnostic confidence while reserving more advanced investigations for patients with unresolved clinical uncertainty.

These findings should not be interpreted as evidence that every patient requires the same diagnostic panel. Test selection should remain guided by pretest probability, clinical urgency, resource availability, and the likelihood that results will change treatment. Similarly, diagnostic clarification alone cannot establish improved prognosis. Any benefit for hospitalization, functional status, or survival would require confirmation through prospective follow-up and comparison with usual care.

Interpretation is limited by the observational nature of the investigation, the possibility of selection bias, and variation in baseline disease severity and previous treatment. Residual confounding and differences in test interpretation may also have influenced the observed patterns. Accordingly, the results support cautious clinical consideration rather than definitive recommendations about diagnostic superiority or cost-effectiveness.

Future multicenter studies should evaluate standardized diagnostic pathways across diverse populations, using independently adjudicated diagnoses and clinically meaningful outcomes. Particular attention should be given to patients with multimorbidity, atypical presentations, and limited access to specialist services. Overall, this study supports an individualized, stepwise approach to cardiovascular diagnosis, emphasizing integration of available evidence rather than indiscriminate testing. Its practical contribution is to inform more consistent clinical decision-making while highlighting the need for stronger evidence linking diagnostic strategies to patient-centered benefits and responsible resource use.

AUTHOR INFORMATION

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