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Systematic review

Atypical presentations of myocardial infarction in patients with diabetes mellitus: diagnostic challenges and clinical outcomes; a systematic review

Mazi Mohammed Alanazi¹, Alaa Ghazi Alnabihi², Sarah Nabil Aloudah³, Lama Naif Mohammed Al Hadi⁴, Rayan Khalid Alyousef⁵, Abdullah Talal Ghandour⁶, Ahmed Abdulrahman Alosaimy⁷, Meshari Nasser Alotaibi⁸, Abdullah Abdulmalik Al Alshaykh⁹, Waleed Abdulrzag Aldbian¹⁰, Naif Mohammed Alotaibi¹¹

1. Saudi and Jordanian Board Emergency Medicine, Emergency Department, Head of Emergency Research Unit, First Health Cluster, Riyadh, Saudi Arabia. ORCID: 0009-0003-5836-8086.
2. Medical Intern, College of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia. Email: aalnubaihi@stu.kau.edu.sa.
3. Medical Intern, College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia. Email: 421210146@ksau-hs.edu.sa.
4. General Physician, Medicine Program, Batterjee Medical College, Aseer, Abha, Saudi Arabia. Email: Reallama@hotmail.com. Phone: 0532193651.
5. Medical Intern, College of Medicine, King Saud bin Abdulaziz University for Health Sciences (KSAU-HS), Riyadh, Saudi Arabia. Email: rayankhalid2002@gmail.com.
6. Medical Intern, College of Medicine, King Saud bin Abdulaziz University for Health Sciences (KSAU-HS), Riyadh, Saudi Arabia. Email: Abdullah_ghksa@hotmail.com.
7. Medical Intern, College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia. Email: osaimy26@gmail.com.
8. Medical Intern, College of Medicine, King Saud bin Abdulaziz University for Health Sciences (KSAU-HS), Riyadh, Saudi Arabia. Email: mesharialsager1@gmail.com.
9. Medical Intern, College of Medicine, King Saud bin Abdulaziz University for Health Sciences (KSAU-HS), Riyadh, Saudi Arabia. Email: abdullah.allshiekh@gmail.com.
10. Medical Intern, College of Medicine, King Saud bin Abdulaziz University for Health Sciences (KSAU-HS), Riyadh, Saudi Arabia. Email: waleedaldbian@gmail.com.
11. Medical Intern, College of Medicine, King Saud bin Abdulaziz University for Health Sciences (KSAU-HS), Riyadh, Saudi Arabia. Email: nalotaiby755@gmail.com.

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Abstract

Background: Diabetes mellitus complicates recognition of myocardial infarction through heterogeneous symptoms, comorbid illness, and delayed presentation. The relationship between diabetes and absence of chest pain differs between populations. This review examined presenting symptoms, diagnostic challenges, and associated clinical outcomes. **Methods:** we include ten articles, covering symptom comparisons, care seeking, diagnostic recognition, and prognosis. Eligible studies concerned adults with myocardial infarction or relevant acute coronary syndrome populations and publication through May 2026. Quantitative associations and qualitative findings were examined separately without statistical pooling. **Results:** Large registries associated diabetes with presentation without chest pain, although Swedish investigations reported similar frequencies of typical symptoms after adjustment. Breathlessness and fatigue featured prominently in several cohorts, with inconsistent differences across individual symptoms. A Swedish multicentre study reported median delays to first medical contact of 144 minutes with diabetes and 75 minutes without diabetes. In the Korean registry, two-year mortality among patients with diabetes was 29.5% with atypical presentation versus 11.4% with typical presentation. Broader coronary syndrome cohorts linked absent chest pain to missed initial recognition and less frequent evidence-based treatment. Definitions, adjustment strategies, overlapping registry populations, and observational designs limited causal interpretation. **Conclusion:** Diabetes-associated myocardial infarction presents in a broad symptom spectrum. Chest pain remains common, while its absence identifies a diagnostic vulnerability. Fast electrocardiography, contextual troponin interpretation, and symptom education warrant clinical attention.

Keywords: Diabetes mellitus; myocardial infarction; atypical presentation; chest pain; diagnostic delay.

Introduction

Diabetes mellitus is associated with increased coronary risk, creating a population in whom timely recognition of myocardial infarction is clinically important. An individual-participant analysis of 102 prospective studies reported approximately twice the risk of coronary heart disease among people with diabetes after adjustment for cardiovascular risk factors. This association establishes the importance of diabetes in cardiovascular assessment without establishing a uniform symptom pattern during an acute event (1). Swedish study found that cardiovascular outcomes varied according to the number of risk factors outside recommended ranges, emphasizing heterogeneity within the diabetic population (2).

Autonomic dysfunction provides a biological context for evaluating coronary presentations in

diabetes, although its prognostic association does not establish the mechanism of an individual patient's symptoms. In the ACCORD population, baseline cardiac autonomic neuropathy was associated with increased mortality after multivariable adjustment, reinforcing the clinical relevance of autonomic involvement (3). Diagnostic interpretation requires separation of acute myocardial injury from myocardial infarction, because an elevated cardiac troponin concentration alone does not establish an ischemic cause (4). The universal definition combines acute biomarker changes with evidence of myocardial ischemia, including clinical, electrocardiographic, imaging, or angiographic findings (4).

Chest pain guidance recognizes discomfort outside the chest and accompanying symptoms, including

breathlessness and fatigue, within the spectrum requiring evaluation for myocardial ischemia. Absence of classical central chest pain does not establish a noncardiac diagnosis or remove the need for appropriate risk assessment. The guideline discourages the routine designation of symptoms as atypical because that terminology is potentially misleading when communicating diagnostic probability (5).

Diagnostic vulnerability extends beyond symptom description to decisions about testing, observation, and hospital admission, as illustrated by emergency department research documenting missed acute cardiac ischemia. Pope and colleagues identified patients with infarction who were mistakenly discharged, showing that recognition failures occur within established emergency care systems (6). Diercks and colleagues documented a variation in timely electrocardiogram acquisition, connecting initial assessment processes with an important diagnostic step (7). The present review examined diabetes-associated symptom differences, diagnostic challenges, and clinical outcomes, with particular attention to the distinction between diabetes-specific evidence and broader coronary populations.

Methods

This review addressed adults with diabetes mellitus presenting with acute myocardial infarction and examined symptom patterns, diagnostic recognition, treatment delays, and outcomes. Reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses framework (Fig 1). Two authors independently conducted study selection, data extraction, and

methodological appraisal, resolving disagreements through discussion and consensus.

PubMed, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials were searched from inception through 31 May 2026. Searches combined controlled vocabulary, where available, with free-text terms for diabetes mellitus, myocardial infarction, acute coronary syndrome, chest pain, atypical presentation, painless presentation, dyspnea, diagnostic delay, and mortality. Synonyms within concepts were joined with OR, and disease concepts were combined with AND. A broad diabetes-and-infarction search supplemented symptom-focused searches to reduce dependence on inconsistent symptom terminology. Reference lists of relevant reports were examined for publications.

Eligible designs included observational cohorts, registry analyses, cross-sectional investigations, and qualitative studies describing acute symptom interpretation or care seeking. Studies required confirmed infarction or an acute coronary syndrome population with diabetes-related symptom information or relevant presentation-associated outcomes. Studies restricted to stable coronary disease, asymptomatic screening, isolated case reports, pediatric populations, and secondary reviews were excluded from the primary synthesis.

Duplicate records were removed before independent title and abstract screening. Eligible articles underwent independent full-text assessment against the eligibility criteria. Multiple publications from a shared registry were compared for recruitment periods, populations, and outcomes to identify overlapping data. Extraction covered publication details, setting, design, sample size,

diabetes definition, symptom ascertainment, presentation classification, delay definitions, diagnostic recognition, treatment, follow-up, and clinical endpoints. Adjusted estimates and confidence intervals were prioritized, with adjustment variables recorded. Unadjusted percentages were identified as descriptive comparisons, and mortality estimates from entire cohorts were separated from diabetes-specific estimates.

Methodological appraisal considered participant selection, symptom measurement, confounding, missing data, and outcome assessment using design-appropriate Joanna Briggs Institute checklists. Qualitative evidence was assessed for methodological congruity and representation of participants' experiences. A structured narrative synthesis grouped findings into symptoms, diagnostic and care-seeking challenges, and outcomes. Clinical heterogeneity and differences in outcome definitions precluded a pooled estimate. Qualitative findings were integrated as explanations of care-seeking experiences rather than estimates of prevalence.

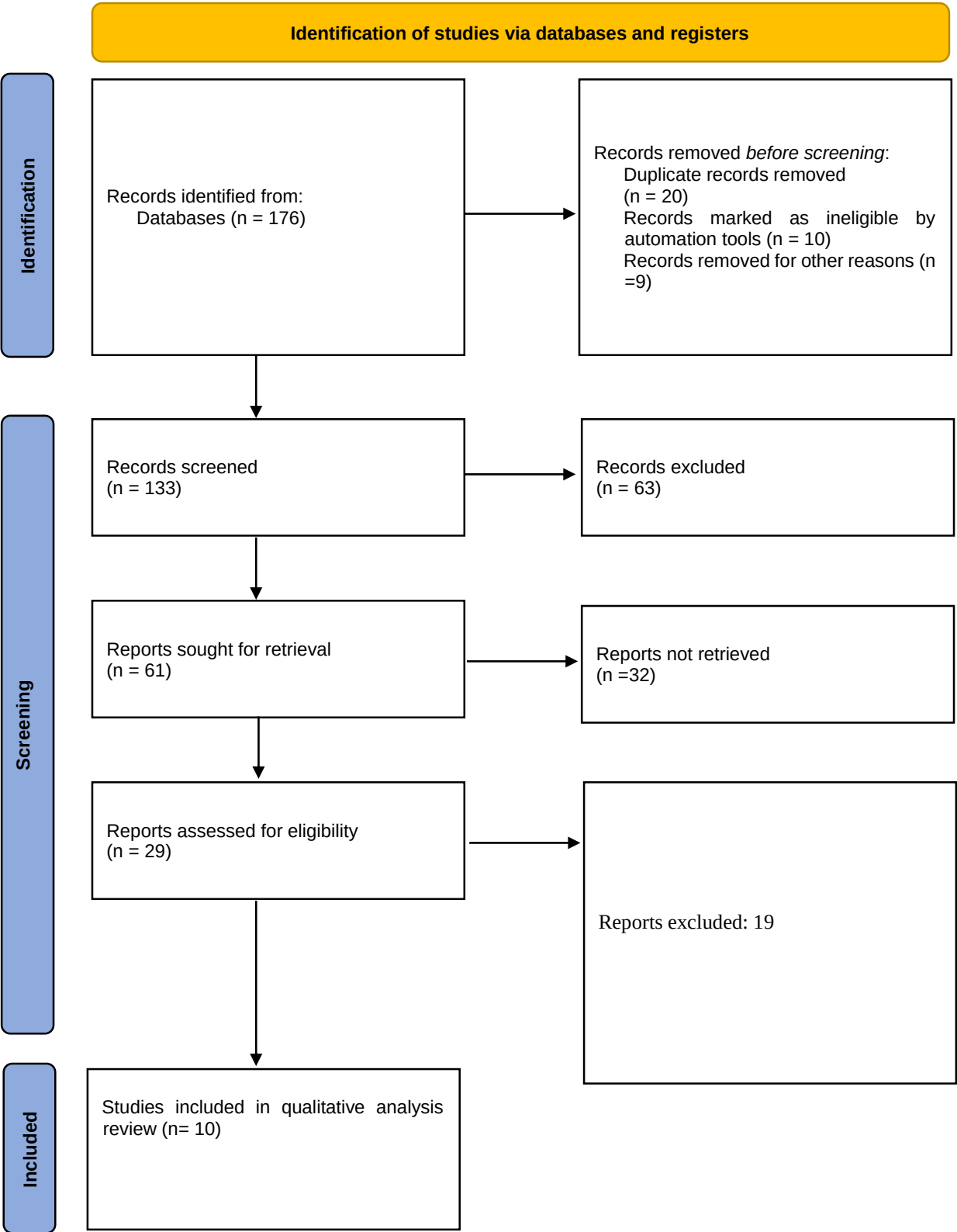


Figure 1: PRISMA flow chart

Results

Ten original studies contributed data spanning large registries, smaller symptom studies, and qualitative interviews, beginning with the United States registry analysis of 434,877 infarctions (8). The multinational GRACE analysis contributed broader acute coronary syndrome evidence concerning presentation without chest pain and failures of initial recognition (9). A smaller American study examined diabetes-associated symptom differences through patient interviews, providing complementary evidence beyond registry documentation (10).

In the United States registry, diabetes was independently associated with presentation without chest pain, with an adjusted odds ratio of 1.21 and 95% confidence interval of 1.19–1.23 (8). Within GRACE, 8.4% of participants presented without chest pain, and 23.8% of that subgroup were not initially recognized as having an acute coronary syndrome. These recognition figures describe the overall registry subgroup rather than patients with diabetes alone (9). DeVon and colleagues found less reported chest pain and more unusual fatigue among patients with diabetes, while longer diabetes duration was associated with greater breathing difficulty (10) (Table 1 & 2).

The Northern Sweden symptom analysis found typical presentations in 90.1% of patients with diabetes and 91.5% without diabetes, with no independent association between diabetes and atypical symptoms (11). A related registry analysis identified prehospital delays of at least two hours in 64% and 58%, respectively, atypical symptoms were associated with lower odds of prolonged delay,

challenging a universal assumption that nonclassic presentation necessarily delays care seeking (12).

Interviews with 15 patients with diabetes described a staged process of interpreting symptoms, recognizing illness, perceiving danger, and deciding to act (13). The Swedish multicentre survey reported median symptom-to-first-contact intervals of 144 minutes with diabetes and 75 minutes without diabetes, alongside more breathlessness, tiredness, and shoulder discomfort after adjustment (14).

The Chinese CAMI registry included 21,994 patients and identified diabetes as an independent predictor of atypical symptoms, with an adjusted odds ratio of 1.112 and 95% confidence interval of 1.034–1.196 (15). Persistent precordial pain was less frequent with diabetes, although nausea, breathlessness, and several other individual symptoms showed no statistically significant differences (15). The Korean registry analysis reported two-year mortality of 29.5% versus 11.4% among diabetic patients with atypical versus typical presentation, respectively (16). The German registry documented chest pain in 71.4% versus 79.7% and breathlessness in 55.1% versus 48.0% among patients with versus without diabetes, with attenuation of several associations after adjustment (17).

Across outcome studies, presentation without chest pain accompanied lower treatment receipt and worse prognosis, although these associations did not establish symptom-driven causation (8,9,16). Diabetes-specific mortality comparisons were most directly available from the Korean analysis, while the American and GRACE estimates represented broader populations (8,9,16). The data showed

heterogeneous symptom associations alongside recurring recognition and care-seeking difficulties, with chest pain remaining frequent and no single non-chest-pain symptom consistently characterizing all diabetic presentations (10–17).

Differences in study design and symptom measurement prevented interpreting the reported frequencies as interchangeable estimates in all study populations (8–17).

Table 1. Characteristics and interpretive limitations of the ten original reports

Study	Setting and design	Sample	Contribution and interpretive limitation
Canto, 2000	United States; infarction registry	434,877	Diabetes–symptom association and hospital outcomes; observational treatment comparisons (8).
Brieger, 2004	Multinational GRACE registry	20,881	Initial recognition and outcomes; mixed ACS population, with indirect applicability to diabetic infarction (9).
DeVon, 2008	United States; interview study	256	Diabetes-related symptoms and disease duration; convenience sampling and mixed ACS diagnoses (10).
Ängerud, 2012	Northern Sweden; population registry	4,028	First-infarction symptom classification; age restricted to 25–74 years (11).
Ängerud, 2013	Northern Sweden; population registry	4,266	Diabetes and prehospital delay; registry population overlapped the earlier symptom report (12).
Ängerud, 2015	Sweden; qualitative interviews	15	Symptom interpretation and decisions; explanatory findings rather than prevalence estimates (13).
Ängerud, 2016	Sweden; five-centre survey	694	Symptoms and first-contact delays; clinically stable participants able to complete questionnaires (14).
Fu, 2019	China; CAMI registry	21,994	Detailed symptom comparisons; residual confounding despite multivariable adjustment (15).
Lee, 2020	South Korea; KAMIR-NIH registry	11,159	Diabetes-by-presentation groups and two-year outcomes; observational prognostic associations (16).
Schmitz, 2024	Germany; population registry	5,900	First-infarction symptoms; several associations attenuated after adjustment (17).

Table 2. Selected quantitative findings and their applicable populations

Outcome	Comparison	Finding	Interpretation
Presentation without chest pain	Diabetes versus no diabetes	Adjusted OR 1.21; 95% CI 1.19–1.23	Diabetes-specific association within the American registry (8).
Initial diagnostic recognition	ACS without chest pain	23.8% initially unrecognized	Broader ACS estimate; not a diabetes-only result (9).
Typical symptoms	Diabetes versus no diabetes	90.1% versus 91.5%	No independent diabetes association in Northern Sweden (11).
Prehospital delay ≥ 2 hours	Diabetes versus no diabetes	64% versus 58%	Symptom onset to hospital arrival; distinct from first-contact delay (12).
Patient delay	Diabetes versus no diabetes	Median 144 versus 75 minutes	Symptom onset to first medical contact (14).
Atypical symptoms	Diabetes versus no diabetes	Adjusted OR 1.112; 95% CI 1.034–1.196	Modest association in CAMI (15).
Two-year mortality	Atypical versus typical presentation within diabetes	29.5% versus 11.4%	Unadjusted group rates; no causal attribution (16).
Breathlessness	Diabetes versus no diabetes	55.1% versus 48.0%	German registry symptom frequencies; crude comparison (17).

Discussion

The principal finding is a heterogeneous association between diabetes and infarction symptoms, accompanied by clinically important difficulties in recognition and timely care seeking. Large studies linked diabetes with absent or non-classic chest pain, while Swedish findings demonstrated that typical symptoms remained highly prevalent (8,11,15,17). These differences argue against teaching a fixed diabetic presentation and favor describing the range of symptoms alongside the individual's cardiovascular risk (10,11,14,17).

Interpretation requires attention to how investigators defined presentation and obtained symptom information, since registry categories and

detailed patient questionnaires measure different aspects of the same event (8,10,11,14). Age and comorbidity also matter, as adjustment attenuated several symptom associations in the German registry (17). Autonomic dysfunction remains biologically relevant, although its association with mortality in ACCORD does not prove that neuropathy caused the symptom differences reported in the included cohorts (3,17). Breathlessness therefore represents an important presenting complaint without serving as a diabetes-specific diagnostic marker (14,15,17).

Diagnostic assessment requires integration of symptoms, electrocardiography, and biomarkers rather than reliance on either pain classification or

an isolated positive troponin result (4,5). Wereski and colleagues demonstrated substantial overlap in presenting troponin concentrations across type 1 infarction, type 2 infarction, and myocardial injury, limiting discrimination from a single measurement (18). Neumann and colleagues supported risk assessment using initial high-sensitivity troponin concentrations together with serial changes and sampling intervals, reinforcing the value of structured interpretation (19). These diagnostic investigations provide contextual evidence rather than proof that a particular pathway improves outcomes specifically in diabetic patients without chest pain (18,19).

Acute presentations require separation from silent ischemia detected during elective screening, because these represent different clinical questions and populations (4,20). The initial DIAD investigation detected silent ischemia in 22% of 522 screened asymptomatic participants, establishing that symptom absence and demonstrable ischemia coexist in diabetes (20). The subsequent randomized DIAD outcome analysis did not demonstrate a significant reduction in cardiac death or nonfatal infarction from routine screening, so these findings do not justify equating broader acute symptom recognition with population screening (21).

Care-seeking behavior adds another layer beyond symptom physiology, as the qualitative evidence identified barriers involving perceived susceptibility and interpretation of bodily changes (13). The randomized trial by Dracup and colleagues found no overall reduction in prehospital delay from an individualized educational intervention, indicating that knowledge-focused strategies alone lack assured effectiveness (22). A practical research

priority is therefore testing repeated, context-sensitive education alongside accessible emergency pathways, with delay and clinical outcomes measured directly rather than inferred from improved awareness (13,22).

The mortality findings warrant caution because older age, comorbidity, infarct severity, and treatment differences complicate attribution of risk to presentation itself (8,9,16). Shared populations, inconsistent definitions, and selection of patients surviving to hospital assessment constrain generalizability and precision in the evidence base (8,11,12,14,17). Future prospective research requires standardized symptom definitions, explicit diabetes characterization, and separate measurement of patient delay, diagnostic delay, treatment delivery, and outcomes to clarify the mechanisms linking presentation with prognosis.

Conclusion

Myocardial infarction in patients with diabetes presents with symptom variation. Chest pain is common, while breathlessness, fatigue, and presentations without chest pain complicate recognition in important subgroups. Studies links nonclassic presentation with diagnostic difficulties, treatment differences, and poorer outcomes, with observational designs limiting causal conclusions. Diabetes accompanies longer care-seeking intervals in several populations, including studies without major differences in typical symptoms. Clinical assessment requires electrocardiography and interpretation of serial troponin results within the clinical context.

Abbreviations

ACCORD: Action to Control Cardiovascular Risk in Diabetes; ACS: acute coronary syndrome; CAMI: China Acute Myocardial Infarction; CI: confidence interval; DIAD: Detection of Ischemia in Asymptomatic Diabetics; GRACE: Global Registry of Acute Coronary Events; KAMIR-NIH: Korea Acute Myocardial Infarction Registry–National Institutes of Health; OR: odds ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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