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Systematic review

Barriers to Timely Intramuscular Epinephrine Administration for Anaphylaxis in Emergency Departments: A Systematic Review

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Abstract

Background: Anaphylaxis is a life-threatening emergency which requires prompt intramuscular epinephrine administration and its use in emergency care still below guideline recommendations. **Methods:** PubMed, Web of Science, and Scopus were systematically searched for original studies examining barriers to timely intramuscular epinephrine administration in emergency departments and acute care settings. Two reviewers independently screened records, extracted data, and assessed risk of bias using tools appropriate to each study design: the JBI Checklist, NOS, RoB 2, MMAT, and ROBINS-I. Results were synthesized narratively. **Results:** Twenty-three studies were included: 11 physician knowledge surveys, 11 patient cohort studies, and one simulation study. Clinician barriers included difficulty recognizing anaphylaxis, errors in dose and route selection, and concerns about adverse effects. Older age and the absence of cutaneous symptoms were associated with lower rates of epinephrine administration. Reported organizational barriers included

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inadequate training, prolonged observation protocols, and deficiencies in discharge practices. Clinicians often reserved epinephrine for severe reactions, contrary to recommendations for its use in all cases of anaphylaxis. Intramuscular administration rates ranged from 16.9% to 60.8%, with treatment omitted in more than 40% of patients in most cohorts. **Conclusion:** Barriers to timely intramuscular epinephrine administration involve clinical recognition, treatment decisions, patient characteristics, and care procedures. Strategies to reduce delays and omissions should combine targeted education, clinical pathways, and changes to emergency care systems.

Keywords: Anaphylaxis; Epinephrine; Intramuscular Injection; Emergency Department; Barriers.

Introduction

Anaphylaxis is a severe systemic allergic reaction that progress rapidly after exposure to a trigger, such as food, medication, or venom, and may be fatal.¹ The impact worldwide is hard to miss or ignore. Yearly incidence runs 50 to 112 cases per 100,000, and lifetime prevalence ranges from 0.3% on the low end to over 5% on the high end.² The incidence of anaphylaxis-related emergency department visits has been rising, with a notable 101% increase observed in the United States between 2005 and 2014,³ highlighting the growing clinical and public health importance of this condition.

Intramuscular epinephrine is recommended as the first-line treatment for anaphylaxis.¹ Its administration rapidly reverse the cardiovascular and respiratory manifestations of the reaction and is the only intervention that reliably halts progression.⁴ Delay epinephrine, and the consequences are clear. Patients face more severe illnesses, a higher risk of the reaction coming back, and a higher mortality outcome.⁵ The guidelines are explicit, and early epinephrine is a proven lifesaver. Yet many studies show that paramedics and emergency staff still do not use it nearly enough.⁶

Clinician-related factors include knowledge gaps in recognizing anaphylaxis, uncertainty about indications, incorrect dosing and administration routes, and fear of adverse effects.⁵ System-level obstacles such as variability in protocols, limited access to auto-injectors, and inadequate training further compound the problem.⁷

Given that timely epinephrine administration is the cornerstone of anaphylaxis management, identifying and understanding these barriers is essential for developing effective interventions. This systematic review therefore aims to synthesize the available evidence on the factors that impede the timely administration of intramuscular epinephrine for anaphylaxis in emergency and acute care settings.

Methods

This systematic review follows the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards for open, comprehensive, and standardized reporting of the review process.⁸

Literature Search Strategy

We searched PubMed, Web of Science (WoS), and Scopus to identify original research on barriers to timely intramuscular epinephrine administration for anaphylaxis in emergency settings. The search

was performed from 2015 to the date of inception and limited to English-language publications. Search terms combined free-text keywords and, where applicable, controlled vocabulary (MeSH terms in PubMed) across five key areas: anaphylaxis, epinephrine/adrenaline, intramuscular administration, emergency department/acute care, and barriers/factors influencing timely use. Boolean operators (AND, OR) and database-specific syntax were used throughout. The full search strings for each database are provided in the Supplementary File.

Terms such as "delay", "omission", "barrier", and "undertreat" targeted studies on impediments to timely administration. "Knowledge", "awareness", "diagnos", "recognit", "protocol", "guideline", and "adherence" captured clinician--,system--, and protocol-related factors. Truncation () captured variant word endings (delay, delayed, delaying; diagnosis, diagnostic, diagnosing). To limit retrieval to primary studies, the PubMed search excluded reviews, systematic reviews, and meta-analyses; however, we hand-searched the reference lists of these articles for additional relevant studies.

Study Selection and Eligibility Criteria

We included original research studies that examined barriers, predictors, or factors influencing the timely administration of intramuscular epinephrine for anaphylaxis in emergency department or acute care settings. Eligible study designs comprised randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, qualitative studies, mixed-methods studies, registry-based studies, and quality improvement studies. We excluded case reports, case series, editorials, letters, commentaries, conference abstracts, narrative reviews, systematic reviews, and meta-analyses, although the latter were screened for additional references. Animal studies,

laboratory-based studies, and studies with insufficient methodological detail or unavailable full text were also excluded.

Participants/Population

Studies involving patients of any age presenting with anaphylaxis in emergency departments or other acute care settings, or healthcare professionals involved in the emergency management of anaphylaxis, were eligible.

Intervention/Exposure

We included studies evaluating factors, barriers, predictors, or influences affecting the timely administration of intramuscular epinephrine. This encompassed clinician-related factors (knowledge gaps, diagnostic uncertainty, confidence), patient-related factors (atypical presentations, age), and healthcare system-related factors (workflow, protocol availability, training).

Comparators

The implicit comparator was timely/guideline-adherent intramuscular epinephrine administration versus delayed or omitted administration. We did not require a traditional intervention-versus-control comparison.

Outcomes

The primary outcome was delayed or omitted intramuscular epinephrine administration, including time to administration and adherence to guidelines. Secondary outcomes included clinician knowledge and confidence regarding anaphylaxis management, protocol implementation, and other factors influencing epinephrine use.

Following the systematic database searches, all identified records were exported into EndNote reference management software. Duplicate entries were removed using automated functions, and the

remaining records were manually verified to confirm accuracy. Two independent reviewers subsequently screened titles and abstracts against the predetermined eligibility criteria. Full-text reports of studies considered potentially relevant during this initial phase were retrieved and re-evaluated by the same two reviewers for final inclusion. Any exclusions made at the full-text stage were systematically recorded, with reasons categorized according to predefined criteria (inappropriate study design, irrelevant population, ineligible intervention or comparator, treatment duration below the required threshold, missing or incomplete outcome data, or non-English language publication).

When discrepancies arose between the two reviewers during the screening phases, they were resolved through deliberation and agreement. If no consensus could be achieved, an independent third reviewer made the final determination.

Data Items and Data Extraction

Two reviewers independently extracted data using a standardized form prepared for this review. Any disagreements were settled through discussion or by consulting a third reviewer. We collected information on study characteristics (design, country, setting, duration), population details (for patient studies: sample size, age, gender, anaphylaxis criteria, triggers, severity, organ systems involved, prior anaphylaxis, auto-injector prescription, arrival mode, triage, comorbidities; for healthcare professional studies: role, experience, training, specialty), and outcome measures (delay definition, time to IM epinephrine, administration rates, omitted or delayed doses, inappropriate route use, and guideline adherence). Barriers were grouped into three categories: clinician-related (knowledge gaps, diagnostic uncertainty, incorrect dosing, fear of side effects), patient-related

(atypical presentation, no skin symptoms, age, reaction severity), and system-related (protocols, workflow, training, resources). For each barrier and predictor, we recorded descriptions, how they were measured, frequency or prevalence, effect estimates (OR, RR, HR, beta coefficients with 95% CIs and p-values), and whether associations were statistically significant. We planned a narrative synthesis of the findings, and considered meta-analysis where data were sufficiently homogenous. Where information was missing, we recorded it as not reported.

Risk of Bias Assessment

For analytical cross-sectional studies, the revised JBI Critical Appraisal Tool was used. This tool comprises eight key questions to assess the risk of bias. It evaluates whether the inclusion criteria were clearly defined and whether the study subjects and setting were described in detail. The tool also assesses whether the exposure and outcome (or condition) were measured using objective, standard, valid, and reliable criteria, and whether confounding factors were identified and accounted for in the design or analysis. The final item ensures the use of appropriate statistical analysis. Based on their responses to these eight questions, studies were classified as having a low, moderate, or high risk of bias.⁹

The Newcastle–Ottawa Scale (NOS) was used to assess the quality and risk of bias in cohort designs. Three key elements are tested: selection, comparability, and outcome (for cohort studies) or exposure (for case-control studies). The NOS uses a star rating system with a maximum score of 9 stars. Studies are then classified according to quality, with scores of seven to nine stars indicating high quality, four to six stars reflecting moderate quality, and fewer than four stars suggesting low quality.¹⁰

The risk of bias in the included studies was assessed using the Cochrane RoB 2 tool for randomized trials. This instrument evaluates five domains in randomized controlled trials: the randomization process, deviations from the intended intervention, missing outcome data, outcome measurement, and selective reporting. Each domain is judged as low, some concerns, or high risk of bias, and the overall study rating is then determined from these assessments.¹¹

In addition to the Mixed Methods Appraisal Tool (MMAT), which was used to assess the methodological quality of the single mixed-methods study included in this review. The MMAT is a critical appraisal tool designed to appraise the methodological quality of qualitative, quantitative, and mixed-methods studies concurrently. It consists of two initial screening questions to determine whether the study has clear research questions and whether the collected data allow them to be addressed. Following the screening questions, the tool includes five core quality criteria for each of the five study design categories: qualitative, randomized controlled trials, non-randomized studies, quantitative descriptive studies, and mixed-methods studies. For the mixed-methods study included in this review, both quantitative descriptive and mixed-methods criteria were applied. Each criterion was rated as "Yes," "No," or "Can't tell," and an overall quality score was calculated as the percentage of criteria met.¹²

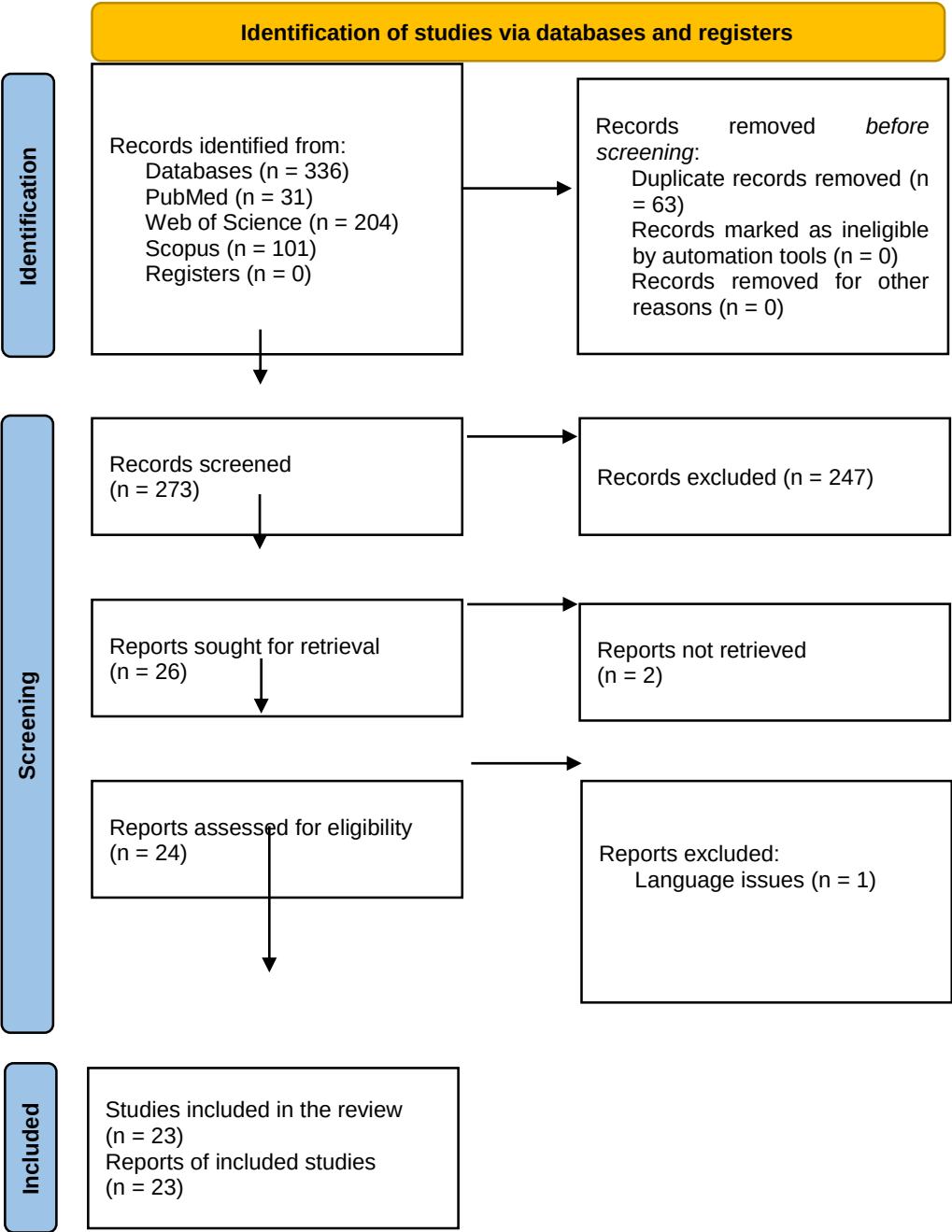
Finally, the ROBINS-I tool (Risk Of Bias In Non-randomized Studies of Interventions) was used to assess the quality of the non-randomized intervention studies. It examines seven domains of bias: confounding, participant selection, classification of the intervention, deviations from the intended intervention, missing data, outcome measurement, and selection of the reported result. Each domain is judged as low, moderate, serious, or

critical risk of bias, and the overall study rating is then assigned based on these domain-level assessments.¹³

Results

PRISMA Flow Diagram

A systematic search of PubMed, Web of Science, and Scopus yielded 336 records. After removing 63 duplicate records, 273 unique records were screened by title and abstract. Of these, 247 records were excluded as they did not meet the eligibility criteria. The remaining 26 full-text reports were sought for retrieval, and two of them were not successfully obtained. Following full-text assessment, only 1 report was excluded due to language issues. Consequently, 23 studies met the inclusion criteria and were included in the systematic review (**Figure 1**).



As shown in **Table 1**, the 23 studies included in this systematic review spanned diverse designs, settings, and populations across multiple countries, with most published between 2015 and 2025. The evidence base was split between physician knowledge surveys (11 studies) and patient cohort studies (11 studies), with one simulation-based study. Studies originated from North America, Europe, Türkiye, and the Asia-Pacific region, providing broad geographic representation. Physician surveys predominantly assessed knowledge of anaphylaxis diagnosis and epinephrine administration among various healthcare professionals, including emergency physicians, pediatricians, family physicians, residents, and nurses. Patient cohort studies evaluated actual epinephrine administration patterns, barriers, and outcomes in emergency department and hospital settings. The geographic distribution reveals substantial contributions from Türkiye (4 studies) and the Asia-Pacific region (7 studies), with fewer studies from other European countries and North America. This heterogeneity in study design, population, and setting reflects the multifaceted nature of barriers to timely epinephrine administration, ranging from individual clinician knowledge gaps to systemic issues in healthcare delivery.

Patient cohorts across the included studies demonstrated consistent patterns in the presentation and management of anaphylaxis (**Table 2**). Food allergens were the predominant trigger in pediatric populations, while drugs emerged as the leading cause in adults and older patients. Cardiovascular and respiratory symptoms were the most frequently documented organ system involvements, though cutaneous manifestations remained common across all age groups. Severity distribution varied considerably

across studies, with proportions of severe anaphylaxis ranging from 17% to 84% depending on the setting and inclusion criteria. Notably, studies consistently reported low rates of prior epinephrine auto-injector prescriptions, suggesting inadequate secondary prevention. Older patients had higher rates of cardiovascular comorbidities and were more likely to present with severe reactions yet paradoxically received less epinephrine. The finding that patients with previous anaphylaxis history had higher pre-hospital epinephrine use indicates that prior education and auto-injector availability may improve timely treatment, though significant gaps persist even in this higher-risk population.

Table 3 presents three major categories of barriers that emerged across the studies: clinician-related, patient-related, and healthcare system-related factors. Clinician-related barriers included knowledge deficits in diagnosing anaphylaxis, particularly when cutaneous symptoms were absent, and uncertainty about the correct epinephrine dose and route of administration. Patient-related barriers, including atypical presentations, older age, and the absence of skin symptoms, were consistently associated with lower epinephrine administration rates. Healthcare system barriers encompassed prolonged observation protocols, limited access to autoinjectors, and inadequate training programs. The most robust predictors of epinephrine administration were the presence of respiratory symptoms, younger age, and a history of prior anaphylaxis. Older patients consistently received less epinephrine despite higher comorbidity burden and severe reaction rates. Venom-induced anaphylaxis cases were significantly less likely to receive epinephrine compared to other triggers, even after severity adjustment. The studies demonstrated that training and education were consistently associated with better knowledge of

correct epinephrine use, though knowledge decay over time remained a persistent challenge. Many studies reported alarmingly low rates of epinephrine use, with omission rates frequently exceeding 40% even in confirmed anaphylaxis cases.

The detailed barrier analysis reveals recurrent themes across studies that explain persistent underuse of epinephrine (See **Table 4**). Knowledge gaps in recognizing anaphylaxis without cutaneous symptoms represented a critical barrier to timely IM epinephrine administration to help these cases, with several studies showing that clinicians frequently missed cardiovascular or gastrointestinal presentations of anaphylaxis when skin findings were absent. Dosing errors and incorrect route selection were common, with many clinicians preferring intravenous or subcutaneous administration over the recommended intramuscular route. Fear of adverse effects, particularly in older patients with cardiovascular comorbidities, emerged as a significant concern, though studies consistently demonstrated that intramuscular epinephrine remained safe in this population. Training deficits were pervasive across all healthcare professional groups, with nurses and auxiliary staff showing consistently lower knowledge levels than physicians. The impact of training was evident in studies comparing trained and untrained groups, in which training significantly improved correct route selection and auto-injector knowledge. However, knowledge decay over time was documented in multiple studies, suggesting that initial training alone is insufficient without regular reinforcement. Healthcare system barriers, including prolonged observation protocols, lack of clinical pathways, limited availability of autoinjectors, and inadequate discharge practices, further compounded individual clinician-level barriers. These findings collectively indicate that

effective improvement strategies must address multiple levels simultaneously through education, protocol standardization, and system-level interventions.

Risk of Bias Assessment

JB1 Checklist Appraisal Tool: Cross-Sectional Studies

The JBI assessment of the ten cross-sectional studies revealed good overall methodological quality, with scores ranging from 7 to 8 out of 8 (**Table 5**). All ten studies clearly defined inclusion criteria, used standardized diagnostic criteria from established guidelines (NIAID/FAAN, NIH, Resuscitation Council UK, or WAO) as reference standards, employed structured and pretested questionnaires for exposure measurement, measured outcomes using objective scoring systems, and provided detailed descriptions of study subjects and settings. The main limitation across eight of the ten studies was the lack of strategies to deal with confounding factors. Only Wijekoon et al. (2021) and Campbell et al. (2016) performed multivariable regression analyses or subgroup analyses to control for potential confounders, such as training level, professional background, and years of experience. The remaining eight studies relied solely on bivariate comparisons (chi-square tests, t-tests, Mann-Whitney U tests, ANOVA), which may have influenced the interpretation of associations between professional characteristics and knowledge, as unmeasured or unadjusted confounders were not controlled for. The lack of formal reliability testing of questionnaires beyond face validity is another limitation, though this is common in knowledge assessment surveys. Response rates ranged from 64% to 91.5%, with most studies achieving rates above 70%, supporting the representativeness of the samples. Despite

these limitations, the consistent use of standardized criteria, clear study descriptions, and appropriate statistical analyses supports the validity of the findings from these cross-sectional studies. The high methodological quality across most studies provides confidence that the identified knowledge gaps and barriers to timely epinephrine administration are valid and not substantially influenced by methodological flaws.

NOS Assessment: Retrospective Cohort & Chart Review Studies

As presented in **Table 6**, the NOS assessment of the eight retrospective cohort and case-control studies showed overall good methodological quality, with scores ranging from 6 to 9 out of 9. All studies achieved full marks for selection criteria, including representativeness of cohorts, appropriate selection of comparison groups, clear ascertainment of exposure, and demonstration that outcomes were not present at baseline. Outcome assessment was consistently robust across all studies, with objective measures from medical records, pharmacovigilance databases, or standardized chart reviews, adequate follow-up periods for outcome occurrence, and complete follow-up of cohorts. The comparability domain was the main area of variation. Wang et al. (2017) and Francuzik et al. (2020) received full marks (2/2) for controlling for important confounders through multivariate regression and propensity score matching, respectively.

In contrast, Ho et al., 2024; Xing et al., 2018; Dubus et al., 2018; Cohen et al., 2018; and Kawano et al., 2017 received 1/2 stars because they did not perform comprehensive multivariable adjustment for potential confounders, such as comorbidities, severity, or trigger type. Krmpotic et al. (2019) received 6/9 stars, with no stars for comparability, as it was a single-arm descriptive cohort without a

comparator group, and the small sample size (n=12) precluded multivariable analysis. Despite this limitation, the study provides valuable descriptive data on severe anaphylaxis in pediatric patients. The high methodological quality across most studies provides confidence that their findings regarding barriers to timely epinephrine administration are valid and not substantially influenced by selection bias or measurement error. The main limitation across studies remains inadequate control for confounding in observational designs, though the consistency of findings across different settings and populations supports the overall conclusions.

RoB-2 Assessment

In **Figure 2**, the two randomized trials included in this systematic review demonstrated low risk of bias across all five domains of the Cochrane RoB-2 tool. Sharma et al. (2019) used adequate randomization with allocation concealment in a double-blind, placebo-controlled design, with normal saline infusions used to maintain blinding across treatment groups. The trial was prospectively registered (NCT01284855), and outcomes were reported transparently. Outcome measurement was robust, with severe antivenom-related anaphylaxis defined using NIAID/FAAN criteria and documented as serious adverse events through standardized forms reviewed by multiple investigators and ethics committees. All patients who received at least 1 dose of antivenom were included in the analysis, with no missing outcome data. Pape et al. (2025) used random selection of physicians from multiple hospitals and specialties. All 95 participants received the same standardized intervention, and complete outcome data were available for all participants. Outcomes were objectively measured using standardized criteria, including video recordings of autoinjector use timing. All pre-specified outcomes were reported transparently, including detailed breakdowns of

incorrect responses. The only caveat for Sharma et al. (2019) is that the nested analysis of severe anaphylaxis cases (n=13) had limited statistical power, but this does not affect the risk-of-bias assessment of the trial methodology itself. The absence of prospective trial registration in Pape et al., 2025 is a minor limitation, but the clear definition of outcomes and transparent reporting suggest this is unlikely to have introduced bias. Overall, these high-quality trials provide valid and robust evidence that can be confidently included in the systematic review without downgrading for risk of bias.

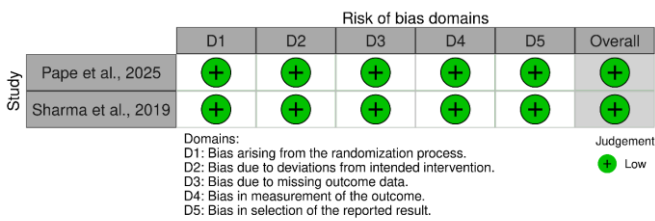


Figure 2: Risk of Bias Assessment of the Randomized Controlled Trial (RoB-2) (n = 2)

Mixed Methods Appraisal Tool: Mixed Methods Study

As shown in **Table 7**, the Hamadi & Casale (2024) study demonstrated moderate methodological quality overall, scoring 60% on the overall quality rating. The study demonstrated clear research questions and appropriate use of two data sources to address them. The EMR component was methodologically strong, with representative sampling, appropriate measurements, complete data capture, and appropriate statistical analysis. The survey component had limitations regarding representativeness and non-response bias, as the voluntary nature of the FARE survey may have introduced self-selection bias, and the study did not report response rates or compare respondents to non-respondents. The mixed-methods integration

was the weakest aspect, as the study presented survey and EMR data separately, without explicit integration, combined analysis, or exploration of how the two datasets inform each other. Despite these limitations, the study provides valuable insights into how COVID-19 influenced patient behavior and the clinical management of anaphylaxis, and the two data sources complement each other in addressing the research question. The moderate quality rating suggests that findings should be interpreted with consideration of the methodological limitations, particularly regarding the survey component and the limited integration of the mixed methods design.

ROBINS-I Assessment

The two non-randomized intervention studies assessed with the ROBINS-I tool demonstrated a moderate overall risk of bias (**Figure 3**). Lee et al. (2018) evaluated a revised clinical pathway for anaphylaxis management. They showed moderate risk of bias primarily due to potential confounding from temporal trends, as the pre-post design without concurrent controls meant that patient characteristics, ED staffing, or other changes between the two periods could have influenced outcomes independently of the pathway revision. The authors did not perform multivariable adjustment for potential confounders, and important co-interventions that may have changed between periods were not reported. However, the study benefited from clearly defined intervention groups, objective outcome measurement from electronic medical records, complete data for primary outcomes, and appropriate use of run chart analysis to track admission rates over time. Price et al. (2023) evaluated in situ simulation for anaphylaxis management and reported a moderate risk of bias, primarily due to the lack of control for participant characteristics such as years of experience, prior training, or professional

background that could have influenced performance outcomes. The study had several strengths, including a clearly defined intervention, objective outcome measurement of time to adrenaline, direct observation of medication errors, complete data for primary outcomes, and transparent reporting of all outcomes. Both studies were judged to have low risk of bias across the remaining ROBINS-I domains, including selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results. Despite the moderate risk of bias, both studies provide valuable evidence that can inform clinical practice, with Lee et al. (2018) demonstrating that clinical pathway revision significantly reduced admission rates without increasing return visits, and Price et al. (2023) identifying medication errors and latent safety threats during simulated anaphylaxis management.

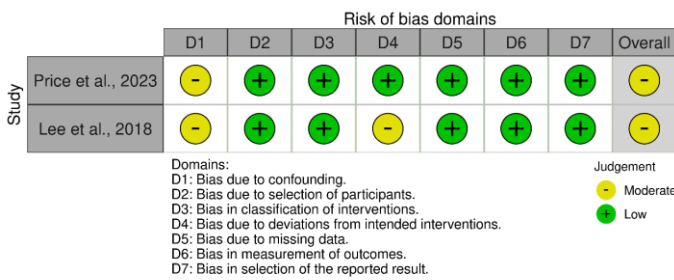


Figure 3: Risk of Bias Assessment of the Non-Randomized Quality Improvement Study (n = 2)

Discussion

Anaphylaxis remains a life-threatening emergency where timely intramuscular epinephrine administration is the single most critical intervention. Despite consistent guideline recommendations spanning decades, this systematic review demonstrates that underuse, delayed administration, and incorrect dosing of epinephrine persist across diverse healthcare

settings and professional groups. The review synthesized findings from 23 studies conducted in multiple countries, including physician knowledge surveys, patient cohort studies, and simulation-based evaluations, to identify the factors contributing to this persistent gap between evidence and practice. The findings reveal that barriers operate at multiple levels: clinician-related factors such as knowledge deficits and diagnostic uncertainty; patient-related factors, including atypical presentations and age; and healthcare system factors, ranging from inadequate training to limited access to cognitive aids and autoinjectors. A particularly striking pattern emerged across studies showing that clinicians often reserve epinephrine for severe reactions, despite guidelines recommending immediate use in all cases of anaphylaxis. This practice, combined with the consistent observation that senior physicians often perform worse than junior colleagues, suggests that knowledge decay and outdated training contribute substantially to suboptimal care.

Clinician-Related Barriers to Timely Epinephrine Administration

Among the findings of this study, clinician-related barriers to timely epinephrine administration appeared to contribute to this issue in emergency departments. Knowledge deficits among healthcare professionals represent the most consistently identified barrier to timely intramuscular epinephrine administration across the included studies. Multiple surveys demonstrated that, despite high recognition of adrenaline as the first-line treatment, significant gaps persisted in its practical application. Bülbül et al. (2024) found that while 93.7% of family physicians knew adrenaline was first-line, only 61.8% correctly identified the adult dose.^{Error! Bookmark not defined.} Similarly, Lauraa et al., 2019 reported that although 99% of pediatricians chose adrenaline as first-line, only 73%

selected the intramuscular route and 55% knew the correct dose.^{Error! Bookmark not defined.} This pattern was consistent across different healthcare settings and professional groups, with physicians in tertiary hospitals, primary care settings, and pediatric emergency departments all demonstrating similar knowledge-practice gaps. The discrepancy between knowing the drug and knowing how to administer it correctly appears to be a recurring theme that undermines guideline adherence.

These findings align with a cross-sectional study from Saudi Arabia, which found that only 5.2% of non-critical care physicians correctly identified all anaphylaxis clinical scenarios. While 42.8% recognized epinephrine as first-line, only 24.3% knew the correct dose and 24.9% the correct route.¹⁴ Similarly, a nationwide Turkish study of 400 primary care physicians reported that although 86.5% correctly identified epinephrine as first-line, only 74.0% knew the correct dose and 53.0% the appropriate concentration, revealing substantial knowledge deficiencies.¹⁵ The consistent pattern across countries suggests that knowledge-practice gaps are not confined to specific healthcare systems but represent a global challenge in anaphylaxis education.

More specifically, diagnostic uncertainty emerged as a major clinical barrier. Several studies documented that clinicians frequently missed anaphylaxis when cutaneous symptoms were absent or when presentations were atypical. Pimentel-Hayashi et al. (2020) found that while 96.4% of physicians diagnosed anaphylaxis with cutaneous symptoms, only 59.2% recognized anaphylaxis without cutaneous symptoms.^{Error! Bookmark not defined.} Cohen et al., 2018 reported that misdiagnosed patients had significantly lower rates of breathing difficulties (47.8% vs. 64.8%) and wheezing (11.7% vs. 31%), suggesting that clinicians rely heavily on respiratory symptoms to trigger the

diagnosis.^{Error! Bookmark not defined.} This pattern was also observed in venom-induced anaphylaxis, where Francuzik et al. (2020) demonstrated that absence of skin symptoms correlated with more severe reactions yet paradoxically led to lower epinephrine use.^{Error! Bookmark not defined.} The tendency to reserve epinephrine for classic presentations with respiratory or cutaneous involvement suggests that clinicians may not fully appreciate the heterogeneous nature of anaphylaxis, particularly its cardiovascular and gastrointestinal presentations.

Incorrect route selection and dosing errors were consistently documented across multiple studies, with a troubling preference for intravenous administration in some settings. Wang et al. (2017) found that only 16.9% of patients received epinephrine by the recommended intramuscular route, with 43.5% receiving an intravenous bolus and 31.5% receiving subcutaneous injections.^{Error! Bookmark not defined.} The intravenous route was strongly associated with supratherapeutic dosing, with 94.1% of intravenous bolus doses exceeding recommended limits. This pattern was similarly observed in pediatric populations, where Xing et al. (2018) reported that only 23% of children received intramuscular epinephrine, with 31% receiving an intravenous bolus.^{Error! Bookmark not defined.} The persistence of subcutaneous administration, despite clear guidelines recommending intramuscular injection for its superior absorption, suggests that some clinicians continue to rely on outdated practices. These findings indicate that knowledge of the correct route and dose may be less well retained than knowledge of the drug itself, representing a critical gap in practical clinical skills.

The safety data from the wider literature reinforces the importance of correct route selection. Campbell et al. (2015) demonstrated that the risk of overdose and adverse cardiovascular events is significantly

higher with intravenous bolus epinephrine administration compared with intramuscular administration, with all overdoses occurring when epinephrine was given intravenously.¹⁶ Analysis of their data showed adverse cardiovascular events occurred in 10% of IV bolus doses compared with 1.3% of IM doses (odds ratio 8.7, 95% CI 1.8-40.7). These findings from the broader literature reinforce the safety profile of intramuscular epinephrine and support the need for education to discourage inappropriate IV bolus use in anaphylaxis.

In addition to fear of adverse effects, particularly cardiovascular complications, appears to influence clinician decision-making. Campbell et al. (2016) reported that providers rated manual epinephrine injection as having a significantly higher risk of dosing errors than autoinjectors, and this perception may contribute to underuse.^{Error! Bookmark not defined.} However, the evidence suggests that intramuscular epinephrine is safe even in high-risk populations. Kawano et al. (2016) found that among patients receiving intramuscular epinephrine, cardiovascular complications were rare in both older (1/31, 3.2%) and younger (1/186, 0.5%) patients, with no significant difference between groups. Despite this, older patients were significantly less likely to receive epinephrine (36.1% vs. 60.8%), suggesting that perceived cardiovascular risk may be a disproportionate concern.^{Error! Bookmark not defined.} This reluctance appears to be driven by concern for side effects rather than evidence of harm, particularly given that intramuscular administration has a favorable safety profile even in patients with cardiac risk factors.

A particularly concerning finding was that physicians with more years of experience often performed worse than junior colleagues. Pape et al. (2025) found that board-certified physicians were 79% less likely to select the correct therapy than residents.^{Error! Bookmark not defined.} Lauraa et al., 2019

reported that physicians with less than five years of experience were significantly more likely to choose the intramuscular route (83% vs. 52%) and recognize gastrointestinal symptoms as part of anaphylaxis (60% vs. 35%).^{Error! Bookmark not defined.} Bülbül et al., 2024 similarly found that physicians with less professional experience demonstrated better knowledge of first-line treatment, correct route, and correct site of adrenaline administration.^{Error! Bookmark not defined.} This inverse relationship between experience and knowledge suggests that newer graduates may have received more contemporary training, while senior physicians may have outdated knowledge from earlier guidelines that recommended subcutaneous adrenaline. This finding has important implications for continuing medical education, as it suggests that knowledge decay over time is a substantial problem that requires active remediation rather than passive learning. A nationwide study of Turkish primary care physicians similarly found that clinical experience alone did not predict better performance, while regular educational activity and recent training were significantly associated with higher knowledge scores.¹⁵

Patient-Related Barriers to Timely Epinephrine Administration

Age emerged as a significant predictor of epinephrine administration, with older patients consistently receiving less treatment despite more severe reactions. Ho et al. (2024) documented that intramuscular epinephrine was administered to 46.5% of children, 37.3% of adults, and only 29.8% of older adults, with the disparity most pronounced in moderate reactions, where only 14.3% of older adults received epinephrine compared to 55.3% of children.^{Error! Bookmark not defined.} Kawano et al., 2016 observed a linear decline in epinephrine use with increasing age, from 57.9% in patients aged 17–29 years to only 16% in those over 70 years.^{Error! Bookmark not defined.}

not defined. This age-related disparity persisted even after accounting for severity, suggesting that clinicians may be more cautious in older patients due to concerns about comorbidities or adverse effects. The reluctance to treat older patients is particularly concerning given that they have higher rates of severe reactions, cardiovascular comorbidities, and hospitalization.

These findings are corroborated by a growing body of literature on anaphylaxis in older people. A recent single-center cohort study from a large Midwestern academic medical center found that older adults (≥ 65 years) were more likely than younger adults to experience severe anaphylactic reactions, particularly those triggered by medications or contrast dyes, and had more cardiovascular symptoms and underlying heart or lung disease.¹⁷ Despite arriving by ambulance more often, older adults were significantly less likely to receive epinephrine from EMS providers after adjusting for comorbidities and other factors, with age identified as the strongest predictor of severe anaphylaxis.¹⁷

Likewise, Khalaf et al. (2025), using data from the Cross-Canada Anaphylaxis Registry across five emergency departments, found that epinephrine use was less frequent in elderly patients (30.0%) and that elderly patients had higher intensive care unit admission rates compared to non-elderly adults. These consistent findings across multiple settings indicate that older adults may not only be at higher risk of poor outcomes from anaphylaxis but may also be less likely to receive timely or appropriate treatment.¹⁸

The absence of cutaneous symptoms consistently predicted lower epinephrine administration rates. Francuzik et al., 2020 found that patients with venom-induced anaphylaxis without skin symptoms received epinephrine less often, and this pattern

was associated with more severe reactions.^{Error! Bookmark not defined.} Xing et al., 2018 reported that 96.4% of physicians diagnosed anaphylaxis with cutaneous symptoms, compared to only 59.2% without skin involvement, representing a substantial diagnostic gap.^{Error! Bookmark not defined.} Krmpotic et al., 2019 described two fatal cases where patients had immediate recognition of anaphylaxis and access to epinephrine, yet the drug was not administered until after cardiorespiratory arrest.^{Error! Bookmark not defined.} These findings indicate that cutaneous symptoms remain the primary trigger for diagnosis, and when they are absent, clinicians may fail to recognize or treat anaphylaxis appropriately.

Reaction severity influenced epinephrine use in ways that deviate from guideline recommendations. Dubus et al. (2018) demonstrated that epinephrine was used in 84.8% of severe (Grade III) reactions. However, only 22.3% of moderate (Grade II) reactions received epinephrine, with an odds ratio of 19.05.^{Error! Bookmark not defined.} This suggests that clinicians reserve epinephrine for the most severe presentations, contrary to guidelines that recommend epinephrine for all anaphylaxis regardless of severity. The consequence is that patients with moderate reactions, who might otherwise progress to severe reactions or experience biphasic reactions, may not receive the only treatment that can halt progression. This pattern was also observed in pediatric populations, where Ho et al. (2024) found that severity-based hesitancy was most pronounced in moderate reactions, with only 14.3% of older adults receiving epinephrine compared to 55.3% of children.^{Error! Bookmark not defined.}

Comorbidities affected both the likelihood of receiving epinephrine and the treatment approach. Kawano et al., 2016 reported that older patients had more cardiac risk factors (6.5% vs. 0.3%),

including prior myocardial infarction (4.1% vs. 0%), yet received less epinephrine.^{Error! Bookmark not defined.} Francuzik et al., 2020 found that patients with cardiovascular disease had a higher risk of severe venom-induced anaphylaxis, but did not receive more aggressive treatment.^{Error! Bookmark not defined.} The presence of comorbidities appears to create a treatment paradox where patients at highest risk of complications receive the least aggressive therapy, possibly due to clinician concerns about medication safety in these populations.

Healthcare System-Related Barriers to Timely Epinephrine Administration

Across multiple studies, training was consistently associated with better knowledge and practice, yet many healthcare professionals had not received adequate training. Özmen et al. (2015) found that only 50.6% of healthcare professionals had received anaphylaxis training, and among those trained, 41.7% had received training more than 2 years ago.^{Error! Bookmark not defined.} Ateş & Sahiner, 2022 reported that 65.6% of health professionals had received adrenaline training, but this means over a third had received none.^{Error! Bookmark not defined.} Kaya & Alaylar (2024) found that despite 89.4% claiming prior training, only 4.7% correctly identified all diagnostic criteria, suggesting that the training received was either inadequate or poorly retained.^{Error! Bookmark not defined.} The observation that knowledge decay occurs over time, with those trained more recently performing better, indicates that one-time training is insufficient and that regular refresher education is necessary.

A systematic review and meta-analysis on community use of epinephrine for anaphylaxis identified low prescription rates of epinephrine autoinjectors and lack of stock epinephrine in schools as major barriers to use.¹⁹ This finding aligns with the system-level barriers identified in our

review, particularly regarding discharge practices and follow-up care. The same review concluded that pre-hospital use of epinephrine in anaphylaxis remains suboptimal, indicating that barriers extend beyond the emergency department setting.

The availability and accessibility of cognitive aids and equipment significantly affected performance. Price et al. (2023) found that medication errors occurred in 30% of simulations, and all administration errors occurred when a weight-based cognitive aid was not used. The cognitive aid was used in only 56% of simulations, indicating that availability alone does not guarantee utilization. The same study identified latent safety threats including unfamiliarity with trolley contents, missing equipment, and difficulty locating resources.^{Error! Bookmark not defined.} This suggests that system-level problems, such as inadequate equipment organization, contribute to errors that may be misattributed to individual clinician knowledge gaps.

Clinical pathways and protocols demonstrated substantial impact when implemented effectively. Lee et al. (2018) showed that reducing the recommended observation period from 8 to 4 hours through a revised clinical pathway reduced admission rates by nearly 60% (from 58.2% to 25.3%) without increasing return visits. This intervention, combined with provider education and discharge with an autoinjector in hand, demonstrates that system-level changes can significantly improve care.^{Error! Bookmark not defined.} However, Cohen et al., 2018 found that guideline revision alone was insufficient to improve correct diagnosis (37% vs. 39%) or epinephrine use (56% vs. 54%), suggesting that passive dissemination of guidelines without active implementation strategies is unlikely to change practice.^{Error! Bookmark not defined.}

The impact of clinical pathways is supported by a recent study from a large pediatric hospital that implemented an Anaphylaxis Clinical Pathway across all clinical settings. Following implementation, the average time from patient presentation to the first dose of epinephrine decreased from 84 minutes to 45 minutes, with increased use of epinephrine as initial treatment and a 50% decrease in the use of adjunct oral steroids.²⁰ This demonstrates that standardizing management through clinical pathways, in conjunction with multidisciplinary stakeholder engagement, can lead to sustained improvements in care delivery.

Discharge practices and follow-up care consistently fell short of guideline recommendations. Lee et al. (2018) achieved 85.4% of discharged patients leaving with an epinephrine autoinjector in hand through an active intervention, but baseline rates in other studies were much lower.^{Error! Bookmark not defined.} Dubus et al., 2018 reported that only 31.7% of patients received autoinjector prescriptions and 44.2% received allergist referrals upon discharge.^{Error! Bookmark not defined.} Wijekoon et al. (2021) found that 50% of medical graduates did not know that follow-up care was needed after anaphylaxis.^{Error! Bookmark not defined.} Ho et al. (2024) documented that only 15.3% of patients received allergist referrals, with rates varying from 52.2% in children to 1.8% in older adults.^{Error! Bookmark not defined.} This represents a substantial gap in secondary prevention, as patients discharged without autoinjectors or follow-up are at risk for future episodes without adequate protection.

Acquisto et al. (2023) found that, despite guidelines recommending that patients with anaphylaxis be prescribed epinephrine autoinjectors, carry them, and be referred to an allergist, there are multiple barriers to EAI administration, including obtaining the medication, keeping it available, recognizing

when to use it, and administering it appropriately.²¹ This reinforces the finding that discharge prescription alone does not guarantee appropriate use, and education is equally important.

Availability of resources and equipment varied across settings. Hamadi & Casale (2024) found that during the COVID-19 pandemic, 71% of patients avoided seeking medical care, and 38% had epinephrine available but chose not to use it. This indicates that beyond clinical knowledge, patient behavior and healthcare access affect epinephrine use.^{Error! Bookmark not defined.} Özmen et al. (2015) reported that only 3% of healthcare professionals had ever prescribed an epinephrine autoinjector, even though 48.8% were aware of it.^{Error! Bookmark not defined.} This gap between knowledge and prescription suggests that system-level factors, such as lack of autoinjector availability or complex prescription processes, contribute to underuse.

Implications for Clinical Practice

The consistent finding across studies that knowledge does not reliably translate into practice suggests that education alone is insufficient to address barriers to epinephrine administration. The observation that clinicians reserve epinephrine for severe reactions, despite guidelines recommending universal use, indicates a fundamental misunderstanding of the role of epinephrine as the only treatment that can halt anaphylaxis progression. Practical training that emphasizes the safety of intramuscular epinephrine, particularly in older patients, should be prioritized. The finding that senior physicians often perform worse than their junior colleagues suggests that continuing medical education must address knowledge decay through regular refresher courses rather than one-time training.

The gap between diagnosis and treatment is particularly concerning. Misdiagnosis rates exceeded 60% in some studies, and patients without skin symptoms were consistently underdiagnosed. Improving recognition of anaphylaxis without cutaneous symptoms should be a priority for educational interventions. Clinical decision support tools, such as the cognitive aids evaluated by Price et al. (2023), may help bridge this gap by reducing cognitive load and standardizing dose calculations.

Strengths and Limitations

This systematic review synthesized evidence from 23 studies across multiple countries and healthcare settings, providing a comprehensive overview of barriers to timely epinephrine administration. The inclusion of both physician survey studies and patient cohort studies allows triangulation of findings, with consistent patterns observed across different methodologies. However, the predominantly cross-sectional nature of the included studies limits the ability to establish causal relationships. Publication bias may exist, as studies showing negative findings may be less likely to be published. The geographical distribution of studies, with overrepresentation from certain regions, may limit generalizability. The focus on emergency department and acute care settings means that findings may not apply to prehospital or outpatient settings. Additionally, the studies included focused on barriers rather than interventions, limiting the ability to conclude effective solutions.

Conclusion

This systematic review demonstrates that delayed or omitted intramuscular epinephrine administration in anaphylaxis remains common despite clear guideline recommendations. Barriers operate at clinician, patient, and system levels, with

diagnostic uncertainty, incorrect dosing, fear of adverse effects, and undertreatment of older patients as prominent factors. The consistent finding that physicians reserve epinephrine for severe reactions represents a critical practice gap requiring urgent attention. The safety of intramuscular epinephrine, even in older patients with cardiovascular comorbidities, is well established. System-level interventions, including clinical pathways, cognitive aids, and regular practical training, show promise in improving adherence. Future research should evaluate implementation strategies that address multiple barriers simultaneously.

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