

TIME TO REPERFUSION AND CLINICAL OUTCOMES IN ACUTE MESENTERIC ISCHEMIA: A SYSTEMATIC REVIEW

**TEMPO ATÉ A REPERFUSÃO E DESFECHOS CLÍNICOS NA ISQUEMIA
MESENTÉRICA AGUDA: UMA REVISÃO SISTEMÁTICA**

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ABSTRACT

Background: Acute mesenteric ischemia (AMI) is a life-threatening vascular emergency associated with persistently high mortality rates despite advances in imaging and revascularization strategies. Increasing evidence suggests that clinical outcomes are strongly influenced by the time interval between symptom onset, diagnosis, and definitive intervention, supporting the concept of a critical therapeutic window for intestinal viability.

Objective: To systematically evaluate the association between time to intervention (symptom-onset-to-reperfusion or diagnosis-to-surgery interval) and clinical outcomes in adult patients with acute mesenteric ischemia.

Methods: This systematic review was conducted in accordance with PRISMA 2020 guidelines. PubMed/MEDLINE, Embase, Scopus, and Cochrane Library were searched for studies published between January 2000 and December 2024. Observational studies evaluating time-related variables and reporting at least one relevant clinical outcome, including in-hospital or 30-day mortality, extent of bowel resection, need for reoperation, permanent total parenteral nutrition, or organ failure, were included. Methodological quality was assessed using the Newcastle–Ottawa Scale. Due to heterogeneity in time definitions and outcome reporting, a structured qualitative synthesis was performed.

Results: Ten observational studies met inclusion criteria. Across studies, delayed intervention was consistently associated with increased mortality and worse clinical outcomes. In particular, several observational studies within this synthesis reported higher mortality when intervention was delayed, with some identifying intervals of approximately six hours as clinically relevant and adjusted odds ratios in primary analyses indicating increased risk, with confidence intervals excluding unity when reported. Delays

were also associated with greater extent of bowel resection, higher likelihood of reoperation, and increased long-term dependence on parenteral nutrition. However, temporal definitions varied considerably across studies, precluding quantitative meta-analysis.

Conclusion: Time to intervention appears to be a key prognostic determinant in acute mesenteric ischemia. System-level strategies aimed at reducing diagnostic and therapeutic delays may have a greater impact on mortality reduction than isolated technical refinements in revascularization techniques.

Keywords: Acute Mesenteric Ischemia; Time-to-Intervention; Surgical Delay; Mortality; Revascularization.

RESUMO

Introdução: A isquemia mesentérica aguda (IMA) é uma emergência vascular potencialmente fatal, associada a taxas de mortalidade persistentemente elevadas, apesar dos avanços em métodos de imagem e estratégias de revascularização. Evidências crescentes sugerem que os desfechos clínicos são fortemente influenciados pelo intervalo de tempo entre o início dos sintomas, o diagnóstico e a intervenção definitiva, reforçando o conceito de uma janela terapêutica crítica para a viabilidade intestinal.

Objetivo: Avaliar sistematicamente a associação entre o tempo até a intervenção (intervalo entre início dos sintomas e reperfusão, ou entre diagnóstico e cirurgia) e os desfechos clínicos em pacientes adultos com isquemia mesentérica aguda.

Métodos: Esta revisão sistemática foi conduzida de acordo com as diretrizes PRISMA 2020. As bases PubMed/MEDLINE, Embase, Scopus e Cochrane Library foram pesquisadas em busca de estudos publicados entre janeiro de 2000 e dezembro de 2024. Foram incluídos estudos observacionais que avaliaram variáveis relacionadas ao tempo e relataram pelo menos um desfecho clínico

relevante, incluindo mortalidade intra-hospitalar ou em 30 dias, extensão da ressecção intestinal, necessidade de reoperação, nutrição parenteral total permanente ou falência de órgãos. A qualidade metodológica foi avaliada pela Escala de Newcastle-Ottawa. Devido à heterogeneidade nas definições de tempo e no relato de desfechos, foi realizada uma síntese qualitativa estruturada.

Resultados: Dez estudos observacionais preencheram os critérios de inclusão. Entre os estudos, a intervenção tardia esteve consistentemente associada a maior mortalidade e piores desfechos clínicos. Em particular, diversos estudos observacionais incluídos nesta síntese relataram maior mortalidade quando a intervenção foi retardada, com alguns identificando intervalos de aproximadamente seis horas como clinicamente relevantes, e razões de chances ajustadas nas análises principais indicando risco aumentado, com intervalos de confiança excluindo a unidade quando relatados. Os atrasos também foram associados a maior extensão de ressecção intestinal, maior probabilidade de reoperação e maior dependência de nutrição parenteral em longo prazo. No entanto, as definições temporais variaram consideravelmente entre os estudos, o que impossibilitou a realização de uma metanálise quantitativa.

Conclusão: O tempo até a intervenção parece ser um determinante prognóstico fundamental na isquemia mesentérica aguda. Estratégias em nível sistêmico voltadas à redução dos atrasos diagnósticos e terapêuticos podem ter impacto maior na redução da mortalidade do que refinamentos técnicos isolados nas técnicas de revascularização.

Palavras-chave: Isquemia Mesentérica Aguda; Tempo até a Intervenção; Atraso Cirúrgico; Mortalidade; Revascularização.

1. INTRODUCTION

Acute mesenteric ischemia (AMI) remains one of the most lethal abdominal emergencies in contemporary surgical practice. Despite advances in cross-sectional imaging, expansion of endovascular techniques, and improvements in critical care management, mortality rates remain unacceptably high, frequently exceeding 40–50% in hospital-based series. This persistent lethality suggests that outcomes may not depend solely on technological progress, but also on structural and temporal determinants within healthcare systems.

From a pathophysiological standpoint, AMI represents a time-dependent vascular emergency characterized by abrupt interruption or critical reduction of splanchnic blood flow. Sustained hypoperfusion leads to progressive cellular hypoxia, mucosal barrier disruption, bacterial translocation, and systemic inflammatory activation. Experimental and clinical evidence indicates that intestinal injury may evolve rapidly, with loss of tissue viability occurring within the first hours following arterial occlusion. Accordingly, time to reperfusion has emerged as a central prognostic variable, analogous to other time-sensitive conditions such as acute myocardial infarction and ischemic stroke.

Unlike these conditions, however, AMI lacks widely standardized care pathways or structured regional systems designed to ensure rapid diagnosis and intervention. Its initial clinical presentation is frequently nonspecific (typically characterized by abdominal pain disproportionate to physical findings, absence of early peritoneal signs, and laboratory abnormalities with limited specificity), contributing to substantial diagnostic delay. Furthermore, institutional factors such as delayed imaging, limited immediate access to specialized surgical teams, inter-hospital transfer, and variability in treatment strategy (open versus endovascular) may

further prolong the interval between symptom onset and definitive reperfusion.

Although multiple studies have identified clinical and laboratory predictors of mortality (including serum lactate, renal dysfunction, extent of bowel necrosis, ASA classification, and inflammatory indices), these parameters often reflect advanced stages of disease rather than early, modifiable determinants of outcome.

In parallel, contemporary literature has increasingly focused on comparisons between open surgical revascularization, hybrid techniques, and primary endovascular approaches. While some observational studies report improved outcomes with endovascular strategies in selected populations, it remains unclear whether these benefits derive from the technique itself or from earlier restoration of mesenteric perfusion in specialized centers.

Given these considerations, a systematic evaluation of time to intervention as an independent prognostic determinant in AMI is warranted. Clarifying the relationship between temporal delay and clinical outcomes may inform the development of optimized diagnostic algorithms and organizational strategies aimed at reducing preventable mortality in this highly lethal condition.

2. METHODS

2.1. Study Design

This systematic review was conducted in accordance with the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The protocol was defined prior to data extraction with the objective of evaluating the association

between time to intervention and clinical outcomes in adult patients with acute mesenteric ischemia (AMI).

2.2. Information Sources and Search Strategy

A comprehensive search was performed in PubMed/MEDLINE, Embase, Scopus, and Cochrane Library for studies published between January 1, 2000 and December 31, 2024 (date of last search).

Studies published in English, Portuguese, or Spanish were eligible.

The search strategy combined controlled vocabulary (MeSH and Emtree) and free-text terms related to AMI and time-dependent variables, including:

- “Acute Mesenteric Ischemia”
- “Mesenteric Artery Occlusion”
- “Non-occlusive Mesenteric Ischemia”
- “Time to Surgery”
- “Surgical Delay”
- “Time to Intervention”
- “Revascularization”
- “Mortality”
- “Bowel Resection”

- “Organ Failure”

Example of PubMed strategy:

("acute mesenteric ischemia" OR "mesenteric ischemia")

AND ("time to surgery" OR "surgical delay" OR "time to intervention"
OR "transfer")

AND ("mortality" OR "bowel resection" OR "organ failure" OR "clinical
outcomes" OR "revascularization")

No methodological filters were applied to maximize sensitivity. Reference lists of included studies were manually screened to identify additional relevant publications.

2.3. Eligibility Criteria

2.3.1. Inclusion Criteria

Studies were included if they met all of the following:

- Observational design (prospective or retrospective cohort studies, case-control studies, or national/multicenter database analyses);
- Adult population (≥ 18 years) diagnosed with AMI, regardless of etiology;
- Explicit evaluation of time-related variables (e.g., symptom-onset-to-intervention, admission-to-surgery, diagnosis-to-reperfusion, or inter-hospital transfer interval);

- Reporting at least one relevant clinical outcome, including in-hospital or 30-day mortality, extent of bowel resection, need for reoperation, organ failure, or permanent/prolonged total parenteral nutrition.

Systematic reviews and meta-analyses were used exclusively for contextual discussion and were not included in the primary synthesis.

2.3.2. Exclusion Criteria

- Case reports;
- Case series with fewer than 10 patients;
- Exclusively pediatric studies;
- Chronic mesenteric ischemia without acute event;
- Mesenteric ischemia secondary to trauma;
- Studies not allowing extraction or reasonable inference of time-related variables.

2.4. Study Selection

All retrieved records were exported to reference management software, and duplicates were removed. Two independent reviewers screened titles and abstracts according to predefined criteria. Potentially eligible studies underwent full-text review.

Disagreements were resolved by consensus; when necessary, a third reviewer adjudicated. Reasons for exclusion at the full-text stage were documented.

2.5. Data Extraction

Data were extracted independently by two reviewers using a standardized form. Extracted variables included:

- Author and year;
- Study design and sample size;
- Mean or median age;
- Etiology of AMI;
- Operational definition of time variable;
- Reported time interval (when available);
- Type of intervention (open, endovascular, hybrid);
- Mortality (in-hospital or 30-day);
- Extent of bowel resection;
- Reoperation (second-look laparotomy);
- Requirement for permanent/prolonged TPN;
- Independently reported prognostic factors.

When necessary, corresponding authors were contacted for clarification.

2.6. Risk of Bias Assessment

Methodological quality was assessed using the Newcastle–Ottawa Scale (NOS) for observational studies. Two reviewers independently scored studies across three domains: Selection (0–4), Comparability (0–2), and Outcome (0–3).

Studies were categorized as:

- 8–9 points: low risk of bias;
- 5–7 points: moderate risk;
- <5 points: high risk.

Disagreements were resolved by consensus.

2.7. Data Synthesis

Given the heterogeneity in operational definitions of time variables and variability in outcome reporting, quantitative meta-analysis was not performed.

A structured qualitative synthesis was conducted to identify consistent patterns of association between time to intervention and clinical outcomes.

Clinical and methodological heterogeneity precluded pooled effect estimation.

3. RESULTS

3.1. Study Selection

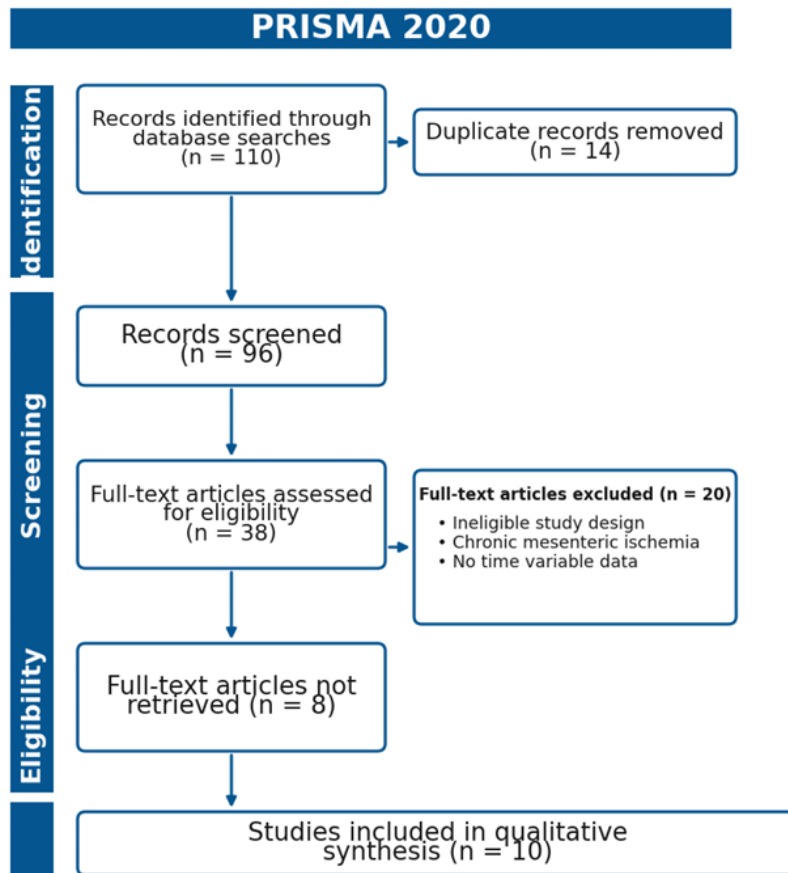
A total of 110 records were identified through electronic database searches. After removal of 14 duplicates, 96 records underwent title and abstract screening. Fifty-eight studies were excluded at this stage for not meeting eligibility criteria.

Thirty-eight full-text articles were assessed for eligibility. Eight reports could not be retrieved. Of the 30 full-text articles evaluated, 20 were excluded due to:

- Inadequate study design (case reports or case series with <10 patients);
- Chronic mesenteric ischemia without separate acute data;
- Secondary study design (systematic reviews or meta-analyses);
- Absence of analyzable time-related variables.

Ultimately, 10 observational studies were included in the qualitative synthesis. The study selection process is illustrated in **Figure 1**.

Figure 1. Characteristics of Included Studies



Characteristics of Included Studies

The 10 included studies consisted predominantly of retrospective cohort designs, including single-center institutional series and multicenter cohorts.

Sample sizes ranged from 30 to 2,410 patients. Most studies focused on arterial AMI (embolic or thrombotic), while a smaller subset evaluated non-occlusive mesenteric ischemia (NOMI) or mixed etiologies.

Operational definitions of time variables varied considerably and included:

- Symptom-onset-to-intervention interval
- Admission-to-surgery interval

Time from surgical consultation to laparotomy

A summary of methodological characteristics and main findings is presented in Table 1.

Table 1. Characteristics and Main Findings of Included Observational Studies

Author (Year)	Study Design	N	Etiology	Time Definition	Main Findings
Piton (2022)	Multicenter Cohort	2,410	NOMI	Time to diagnosis	Delayed diagnosis independently associated with increased mortality, especially

⚠ Esta tabela possui muitas colunas e foi cortada para impressão. Para visualizá-la completa, acesse o artigo original em: <https://revistatopicos.com.br/artigos/time-to-reperfusion-and-clinical-outcomes-in-acute-mesenteric-ischemia-a-systematic-review?noblockage>

3.2. Impact of Time to Intervention on Mortality

Across the included studies, delayed intervention was consistently associated with increased in-hospital or 30-day mortality.

Eltarawy et al. reported that surgical intervention performed more than 6 hours after consultation was independently associated with increased mortality (adjusted OR 3.7; 90% CI 1.1–12). The wide confidence interval suggests limited precision, likely due to small sample size. Although the study reported a 90% confidence interval rather than the conventional 95%, the lower bound remained above

unity, supporting a statistically significant association between surgical delay and mortality.

Piton et al., in a multicenter cohort of critically ill patients with non-occlusive mesenteric ischemia, identified delayed diagnosis as an independent predictor of mortality, particularly among patients presenting with shock, although no specific odds ratio for time delay was uniformly reported.

Overall, while no universal temporal threshold was established across studies, several investigations suggested that delays exceeding approximately 6 hours were associated with significantly worse outcomes.

3.3. Time to Intervention and Extent of Bowel Resection

Longer delays to laparotomy or revascularization were associated with increased intestinal necrosis and greater extent of bowel resection.

Paladino et al. and Acosta-Merida et al. reported that diagnostic or surgical delay correlated with increased resection length and higher rates of colonic involvement.

Delayed intervention was also associated with higher frequency of second-look laparotomy.

3.4. Long-Term Functional Outcomes

Nakao et al. demonstrated that symptom-onset-to-intervention intervals exceeding 6 hours were associated with increased risk of permanent total parenteral nutrition dependence among survivors.

In multivariable analysis, ascites was identified as an independent predictor of long-term TPN dependence (adjusted OR 11.6; $p < 0.01$), although the original study did not report the corresponding confidence interval. The absence of a reported confidence interval limits assessment of estimate precision.

Radiologic findings such as ascites and pneumatosis intestinalis were reported as markers of advanced ischemia and were associated with poorer functional recovery.

3.5. Laboratory Markers and Systemic Progression

Several studies described associations between renal dysfunction and increased mortality. Elevated inflammatory markers, including neutrophil-to-lymphocyte ratio, were identified as prognostic indicators, likely reflecting systemic progression of mesenteric hypoperfusion rather than early modifiable risk factors.

3.6. Methodological Quality

Methodological quality was assessed using the Newcastle–Ottawa Scale (NOS).

One study achieved 8–9 points and was classified as low risk of bias. The remaining nine studies scored between 6 and 7 points, corresponding to moderate risk of bias. No study was classified as high risk.

The most frequent limitations included retrospective design, incomplete adjustment for confounding variables, and heterogeneity in time-variable definitions. These factors precluded quantitative meta-analysis.

Detailed NOS scoring is presented in Table 2.

Table 2. Risk of Bias Assessment of Included Studies (Newcastle–Ottawa Scale)

Author (Year)	Selection (0–4)	Comparability (0–2)	Outcome (0–3)	Total Score (0–9)	Risk of Bias
Piton (2022)	4	2	3	9	Low
Eltarawy (2009)	3	2	2	7	Moderate
Nakao (2023)	3	2	2	7	Moderate

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4. DISCUSSION

Acute mesenteric ischemia (AMI) remains one of the most lethal vascular emergencies in general surgery, with reported mortality rates ranging from 40% to 70% despite advances in diagnostic imaging and revascularization strategies. The present review suggests that, although technical approaches have evolved (including endovascular and hybrid techniques), the interval to effective restoration of mesenteric perfusion remains consistently associated with clinical outcomes.

4.1. The Pathophysiological Dimension of Time

AMI follows a relatively predictable sequence of injury: initial mesenteric hypoperfusion, mucosal barrier disruption, bacterial translocation, transmural necrosis, and eventual abdominal sepsis with multiorgan failure. Experimental and clinical observations indicate that intestinal viability may deteriorate rapidly under sustained ischemia. However, in clinical practice, diagnostic recognition frequently occurs beyond this critical phase due to nonspecific presentation and low initial suspicion.

This mismatch between biological ischemic time and clinical recognition represents a fundamental challenge in AMI management.

4.2. Clinical Evidence and the Time–Outcome Relationship

Across the included studies, delayed intervention was consistently associated with increased in-hospital or 30-day mortality. Several observational cohorts included in this synthesis identified worse outcomes when intervention exceeded approximately six hours, although no universal threshold was established.

Additionally:

- Longer delays correlated with greater extent of bowel necrosis;
- Permanent total parenteral nutrition was more frequent following delayed reperfusion.

Collectively, these findings support a progressive relationship between treatment delay and worsening prognosis rather than a strict temporal cutoff.

4.3. The Concept of a “Mesenteric Therapeutic Window”

Integrating pathophysiological and clinical evidence, we propose the conceptual framework of a ‘Mesenteric Therapeutic Window,’ a critical interval between onset of hypoperfusion and effective reperfusion during which intestinal viability remains potentially reversible.

This interpretative framework shifts emphasis from a purely technical perspective toward a temporal and organizational paradigm, highlighting that the timing of reperfusion may be as relevant as the method employed.

4.4. Organizational Implications

Structural and system-level factors, such as delayed inter-hospital transfer, likely contribute to this dimension of delay. These findings support the development of streamlined diagnostic pathways, rapid access to contrast-enhanced computed tomography, early surgical consultation, and potential regionalization strategies.

Similar to myocardial infarction and ischemic stroke, AMI may benefit from structured systems aimed at minimizing time to definitive intervention.

4.5. Technique Versus Time

Although some observational studies suggest improved outcomes with endovascular or hybrid strategies, these comparisons remain subject to selection bias. Hemodynamically unstable patients and those with established necrosis are frequently managed with open surgery, limiting direct equivalence between techniques.

Therefore, while technical strategy may influence perioperative morbidity, timeliness of reperfusion appears to be a major and potentially modifiable prognostic determinant.

4.6. NOMI and the Challenge of Reversibility

Non-occlusive mesenteric ischemia presents additional complexity. These patients often require vasopressor support, which may exacerbate mesenteric hypoperfusion and further narrow the window for reversibility. Early recognition and hemodynamic optimization are therefore critical.

4.7. Biomarkers and the Limitations of a Reactive Model

Renal dysfunction and inflammatory indices were associated with increased mortality; however, these markers likely reflect advanced systemic involvement rather than early, modifiable determinants. This reinforces the need for early suspicion and rapid diagnostic confirmation before irreversible necrosis occurs.

4.8. Limitations

This review is limited by the retrospective nature of most included studies and significant heterogeneity in the operational definition of “time.” Variability among symptom-onset, admission-to-intervention, and diagnosis-to-reperfusion intervals precluded quantitative meta-analysis and limits the establishment of a universal temporal threshold.

4.9. Final Synthesis

AMI should be understood as a time-dependent emergency. While technological advances have expanded therapeutic options, systematic reduction of diagnostic and therapeutic delay appears fundamental and may be more impactful than isolated technical refinements alone.

5. CONCLUSION

Acute mesenteric ischemia remains one of the most lethal surgical emergencies, with outcomes strongly influenced by the timeliness of mesenteric reperfusion. The present systematic review demonstrates a consistent association between delayed intervention and adverse clinical outcomes, including increased mortality, greater extent of bowel resection, and unfavorable long-term functional consequences.

Observational evidence indicates that delays exceeding early intervention intervals (often around six hours in individual studies) may be associated with increased mortality risk, as reflected in adjusted odds ratios with confidence intervals excluding unity when reported in primary studies.

Although advances in endovascular and hybrid techniques have expanded therapeutic options, the speed of effective reperfusion appears to remain the dominant prognostic determinant. Therefore, acute mesenteric ischemia should be approached as a time-dependent emergency requiring not only technical expertise but also optimized institutional coordination and streamlined diagnostic pathways.

Future prospective, multicenter investigations using standardized temporal definitions and robust multivariable modeling are

necessary to refine intervention thresholds and strengthen time-based management strategies.

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