

COMMENT

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Percutaneous versus surgical treatment of acute cholecystitis

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Abstract

A recent meta-analysis by Fanchulli et al. concluded that cholecystectomy (CC) is associated with lower mortality and readmission than percutaneous cholecystostomy (PC) for acute cholecystitis, but this interpretation is limited by confounding by indication to management. The pooled evidence in this article consists predominantly of observational cohorts where crude or minimally adjusted comparisons are vulnerable to case-mix imbalance; even the CHOCOLATE randomised trial, which supports laparoscopic cholecystectomy in selected high-risk but eligible patients (ASA III–IV, age ≥ 70 or comorbidity, excluding peritonitis/septic shock), does not validate interchangeability across the broader PC and CC populations synthesised in unadjusted meta-analyses. Future evidence synthesis should prioritise adjusted estimates, stratification by Tokyo severity/ASA class, and, where feasible, individual participant data meta-analysis; clinically, CC remains preferred for appropriate surgical candidates, whereas PC should be reserved as a bridge or salvage strategy in selected high-risk patients.

Keywords Acute cholecystitis, Percutaneous cholecystostomy, Cholecystectomy, Confounding by indication, Residual confounding, CHOCOLATE trial, Tokyo guidelines 2018

I read with great interest the systematic review and meta-analysis by Fanchulli et al. [1] and the accompanying commentary by Chen [2]. While the authors correctly emphasise the established role of early cholecystectomy in appropriate surgical candidates, several methodological issues limit the causal interpretation of their pooled mortality and readmission estimates.

1. The core problem—confounding by indication and CHOCOLATE context.

The fundamental challenge is confounding by indication: in routine practice, percutaneous cholecystostomy (PC) is selectively allocated to patients with higher surgical risk, more severe physiological derangement, or

unfavourable local inflammatory conditions (e.g., gangrenous cholecystitis, severe adhesions) that make immediate surgery hazardous, whereas cholecystectomy (CC) is performed in patients deemed suitable for definitive surgical intervention [3–7]. This non-random treatment allocation creates systematic baseline imbalances that crude or minimally adjusted pooled comparisons cannot eliminate. The CHOCOLATE trial [8]—the only adequately powered randomised comparison—demonstrated that laparoscopic cholecystectomy, compared with percutaneous catheter drainage, reduced serious complications, reinterventions, recurrent biliary events, and rehospitalisations in selected high-risk but eligible patients (ASA III–IV, age ≥ 70 or significant comorbidity, excluding those with diffuse peritonitis or septic shock where PC may be the only viable option). Crucially, CHOCOLATE's strict inclusion criteria (no ASA V, no peritonitis, informed consent feasible) mean its findings support CC in a defined subgroup of high-risk patients,

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but do not validate the assumption of interchangeability across the heterogeneous observational cohorts pooled by Fanchulli et al.

2. Quantitative illustration of bias in unadjusted pooling.

To illustrate the potential magnitude of bias, consider a hypothetical scenario: suppose PC patients have a baseline 30-day mortality risk of 20% (reflecting severe comorbidity, ASA IV–V, immunosuppression), whereas CC patients—selected for operability—have a baseline risk of 8%. If PC achieves a 25% relative risk reduction (true treatment effect), observed PC mortality would be 15% ($20\% \times 0.75$). If CC achieves a 50% relative risk reduction (superior treatment effect), observed CC mortality would be 4% ($8\% \times 0.50$). An unadjusted pooled comparison would yield an apparent odds ratio of approximately 0.23, favouring CC (4% vs. 15%), which might be misinterpreted as a large treatment effect. However, after adjusting for baseline risk (e.g., via propensity score matching or multivariable regression incorporating comorbidity indices, ASA class, and Tokyo severity grade), the true treatment effect might be OR ~1.0 or even favour PC in specific high-risk strata. This numeric example demonstrates that crude pooled estimates from observational studies with profound case-mix imbalance can produce spuriously large apparent treatment effects that do not reflect causal superiority.

3. Explicit methodological recommendations.

To mitigate these biases and strengthen causal inference, future systematic reviews should implement the following sensitivity and subgroup analyses:

1. RCT-only synthesis: Separately pool randomised trials (primarily CHOCOLATE) to isolate evidence least susceptible to confounding by indication.
2. Adjusted observational estimates: Prioritise studies reporting propensity score-matched comparisons, multivariable regression-adjusted hazard ratios, or instrumental variable analyses; exclude or downweight crude unadjusted estimates.
3. Stratification by Tokyo severity and ASA class: Conduct subgroup meta-analyses within severity grades (Grade I/II vs. Grade III) and ASA strata (ASA I–II vs. III vs. IV–V), as both strongly influence treatment allocation and prognosis [11].
4. Meta-regression by risk of bias: Perform meta-regression to assess whether pooled effect sizes are driven by lower-quality retrospective cohorts with high selection bias versus prospective studies with rigorous covariate adjustment.
5. Individual participant data meta-analysis: Where feasible, obtain individual-level data to enable harmonised adjustment for baseline covariates (age, comorbidity burden, organ dysfunction

scores, Tokyo grade) and more robust exploration of treatment-effect heterogeneity across clinically relevant patient subgroups.

These analytic strategies would clarify whether apparent mortality/readmission differences reflect true treatment effects or residual confounding [9, 10].

4. Clinical conclusion and practical guidance.

In clinical practice, cholecystectomy remains the preferred treatment for patients who are appropriate surgical candidates, consistent with international guidelines and the positive findings of CHOCOLATE in selected high-risk but eligible patients. Conversely, percutaneous cholecystostomy should be considered primarily as a bridge to interval cholecystectomy or as a salvage strategy in critically ill patients (ASA V, severe septic shock, prohibitive comorbidity) for whom immediate surgery poses unacceptable perioperative risk [3, 11]. Comparative effectiveness research in this domain must rigorously account for confounding by indication through advanced statistical adjustment, trial-level stratification, and transparent reporting of baseline risk profiles. Only then can pooled mortality and readmission estimates inform evidence-based treatment allocation rather than reflect pre-existing differences in patient severity.

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Data availability

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Declarations

Ethical approval and consent to participate

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Consent for publication

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Competing interests

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