

ASSOCIATION OF PRE-EXISTING MEDICAL CONDITIONS AND PHARMACOTHERAPY WITH SURGICAL OUTCOMES IN ADULTS: A SYSTEMATIC REVIEW WITH META-ANALYSIS OF INFECTIOUS COMPLICATIONS AND NARRATIVE SYNTHESIS OF CARDIOVASCULAR AND METABOLIC OUTCOMES

Youssef Mohamed Fawzi Moustafa Ahmed¹, Haya Mohammed M.T Saffarini², Alaa Abbas Mohamed Ali Ellaithi³, Hiba Naveed Ilahi⁴, Sumaiya Rafique⁵, Faiza Zafar⁶, Nimra Javed⁷, Bisher Alanis⁸, Owais Mudassir⁹, Khamis Ibrahim Matar Abujarad¹⁰, Ahmed Mohamed Daleh Hassan¹¹, Ahmed Mohamed Saleh Hassan¹²

¹Mbbs Student, Gulf Medical University

²Gulf Medical University

³University of Science and Technology

⁴MBBS Student, Islamabad Medical and Dental College, Akbar Niazi Teaching Hospital

⁵Gulf Medical University

⁶MBBS Student, Islamabad Medical and Dental College

⁷House Officer, Services Hospital Lahore

⁸Medical University of Lublin

⁹Post Graduate Resident, Cardiac Surgery, PIMS Islamabad

¹⁰Urologist, Urology Department, Saqr Hospital, Ras Al-Khaimah-UAE

¹¹Emergency Physician, Emergency Department

¹²Emergency physician. emergency department saqr hospital Ras alkaimah-UAE

¹yoyo1122003@gmail.com, ²hayasaff29@gmail.com, ³alaa.ellaithi@gmail.com,

⁴hibanaveed9@gmail.com, ⁵sumaiyarafique8390@gmail.com, ⁶faizazafar484@gmail.com,

⁷nimrajaved.ch@outlook.com, ⁸bisheralanis@gmail.com, ⁹awais_noor2008@yahoo.com,

¹⁰khamis.abujarad@ehs.gov.ae, ¹¹ahmed.saleh@ehs.gov.ae, ¹²ahmed.saleh@ehs.gov.ae

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Abstract

Background:

The patient-related factors are considered to have a great impact on surgical outcomes, such as medical conditions and perioperative pharmacotherapy. Among them, perioperative hyperglycemia has become a risk factor that may be modified, and with the help of it, the postoperative morbidity, especially the infectious ones, increased. Nevertheless, there are inconsistent findings on its effects in general in the differing surgical groups.

Objectives:

The objective of this study was to critically assess the impact of already existing medical conditions and pharmacotherapy on the surgical outcomes in adult patients including quantitative meta-analysis of the relationships between perioperative hyperglycemia and postoperative infectious complications, and a narrative synthesis of cardiovascular and metabolic outcomes.

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Youssef Mohamed Fawzi
Moustafa Ahmed

Methods:

The systematic review was done according to PRISMA 2020 recommendations based on PubMed, Scopus, and Web of Science. Studies with adult patients who underwent major surgery were included and reported postoperative complications. The meta-analysis involved six studies that had similar definitions of perioperative hyperglycemia as well as infectious outcomes. A random-effects model (DerSimonian-Laird method) was used to pool odds ratios (ORs) with 95% confidence intervals (CIs) and weighted by the inverse variance. The I^2 was used to measure heterogeneity. Other studies assessing cardiovascular, metabolic and pharmacotherapy related outcomes were narratively synthesized.

Results:

1,247 records were identified and 14 studies met the inclusion criteria and 6 studies were included in the meta-analysis. Perioperative hyperglycemia was also found to have a significant impact on postoperative infectious complications, pooled random-effects OR of 2.45 (95% CI 1.89-3.18; $p < 0.001$). The fixed-effect model yielded similar results (OR = 2.22, 95% CI 1.86–2.65). The heterogeneity was not high ($I^2 = 15.7\%$) so the results of the studies were similar. The results were robust as shown by sensitivity analysis. Narrative synthesis showed that pre-existing cardiovascular diseases, metabolic dysregulation, and pharmacotherapy, such as anticoagulants, corticosteroids and immunosuppressive agents were also linked with adverse postoperative outcomes.

Conclusion:

Perioperative hyperglycemia is an important and a consistent predictor of postoperative infectious complications in surgical adult patients. Moreover, pre-existing illnesses and pharmacotherapy also pose an increased risk of surgery. The results indicate the need to consider perioperative risk assessment and optimization, especially glycemic control, in order to enhance the surgical outcomes.

INTRODUCTION

Surgery is an essential part of healthcare in the contemporary world, but still, the postoperative complications are a major burden that can lead to morbidity, mortality, and healthcare expenditures worldwide. The occurrence of adverse events like surgical site infections (SSI), cardiovascular events, and metabolic disturbances is common in a variety of surgical populations despite the improvement of surgical techniques and perioperative care [16,17]. The occurrence of these complications is dependent on a complicated interplay of patient-related factors, such as underlying medical conditions, physiological changes during the perioperative period, and pharmacological interventions.

Surgical site infections are a significant healthcare system burden among postoperative

complications, which results in extended hospital stay, increased cost, and readmission and mortality [7,27]. Many studies have found that there are various risk factors connected to SSIs such as comorbidities of the patient, obesity, complexity of the operations, and perioperative management practices [13,17,28]. Nevertheless, the comparative role of changeable metabolic causes and especially postoperative hyperglycemia is still a topic of research.

Perioperative hyperglycemia has become a matter of growing importance as a determinant of postoperative outcomes not only among patients with diabetes but also among individuals who do not have a history of a metabolic disease [11,21]. Elevated glucose levels are also known to suppress immune functions, interfere with leukocyte functioning, and wound healing, which makes a person more prone to infection [2,18]. A number

of observational studies have shown a stable relationship between hyperglycemia and higher occurrence of postoperative infections in various surgical specialties such as general surgery, orthopedic surgery and breast surgery [1,2,25,29]. Further, intraoperative and postoperative hyperglycemia have been found to be independent predictors of adverse outcome that glycemic control during the perioperative time is the key to improving patient prognosis [14,32].

Although despite the growing body of evidence, the literature still has critical constraints. The definitions of hyperglycemia, the time at which glucose is measured and the reporting of the outcome differ significantly in many studies, making the findings of these studies inconsistent and therefore making it difficult to compare the results of different studies. Moreover, the majority of studies concentrate on the individual risk factors alone, without considering the effects of comorbidity and pharmacotherapy. This disconnect in analysis has impeded the creation of an integrated perspective on how metabolic, cardiovascular, and pharmacological influences can interact to affect surgical outcomes.

Simultaneously, preexisting cardiovascular disease has been continuously linked to the enhanced risk of perioperative events, such as myocardial injury, arrhythmias, and postoperative mortality [4,19]. Even though predicting risk models like the Revised Cardiac Risk Index are commonplace, they may not be accurate predictors owing to the variability in the population of patients and surgical complexity [19,22]. In the same fashion, pharmacological treatment, like anticoagulants, corticosteroids, and immunosuppressive agents, pose other risks, such as bleeding issues, poor wound healing, and an increased risk of infection [3,10,26]. These aspects make the perioperative management even more complicated and emphasize the importance of risk assessment strategies tailored to each individual.

The last world-changing events, such as the COVID-19 pandemic, have only highlighted the susceptibility of surgical patients to the adverse outcome due to the existence of systemic illness and infection [6]. In turn, global recommendations have highlighted the need to

use evidence-based approaches to the prevention of infection and perioperative optimization, especially when it comes to high-risk patient groups [31]. Nonetheless, there is still a gap in the implementation of these recommendations in clinical practice, in part because the evidence base underpinning such recommendations varies.

Since these constraints exist, it is evident that a thorough assessment should be conducted that combines quantitative and qualitative data to gain a clearer insight into the factors that determine the surgical outcomes. In particular, a narrow meta-analysis of perioperative hyperglycemia and its correlation with postoperative infectious complications should be conducted to give a more accurate risk assessment. Simultaneously, these findings need to be placed in a broader synthesis of cardiovascular and metabolic outcomes and the effects of pharmacotherapy to situate it in the broader context of perioperative risk.

Thus, the aim of the current research is to critically evaluate the impact of pre-existing health issues and drug treatment on surgical outcome in adult patients. To measure the relationship between perioperative hyperglycemia and postoperative infectious complications, a meta-analysis is carried out, whereas cardiovascular and metabolic outcomes, and effects of pharmacotherapy are synthesized in narrative. This combination strategy is aimed to offer a more in-depth and clinically applicable perception of what factors lead to the negative surgical outcomes.

Methods:

This meta-analysis and systematic review was done within the framework of the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. The study was not registered in the PROSPERO database. An extensive literature review of PubMed, Scopus, and Web of Science database from inception to December 2024 was carried out. Medical Subject Headings (MeSH) terms and search keywords were used as the search strategy, i.e., perioperative hyperglycemia, surgical outcomes, postoperative complications, infections, comorbidities, and pharmacotherapy. To narrow down search, the use of Boolean operators (AND/OR) allowed the

search to be narrowed down and reference lists of included studies were screened manually to find more relevant publications.

A PICO framework was used to define the study selection criteria. The sample (P) was comprised of adult patients who were undergoing significant surgical operations. The exposure (I) included perioperative hyperglycemia, pre-existing medical conditions, or pharmacotherapy. The comparator (C) comprised normoglycemic patients or those without exposures. Postoperative complications (O) were the outcomes, with the primary focus on the infectious outcome (surgical site infections and composite infection measures). The criteria used to include studies were that they should have adult populations, should have reported relevant postoperative outcomes and have adequate data to estimate the effect like odds ratios or extract raw event data. Both prospective and retrospective types of observational studies were eligible. Articles were not included when they were based on pediatric populations, did not provide extractable data, were review articles, case reports, conference abstracts or reported irrelevant outcomes.

Two reviewers independently screened the titles and abstracts and then conducted a full-text screening of eligible studies. Any disagreements were sorted out by discussion to build consistency in the decisions of inclusion. The extraction of data was done in a standardized manner, and the following characteristics of the study were captured; author, year of publication, study design, patient population, and type of surgery, exposure definition, outcome measures, and reported effect estimates. Where odds ratios were not directly provided, they were determined using available raw data.

The outcome of interest was mainly postoperative infectious complications, such as surgical site infections, deep infections, and composite infection outcomes. The synthesis of secondary outcomes (such as cardiovascular complications, metabolic disturbances, and pharmacotherapy-related effects) was performed as a narrative synthesis because of differences in reporting and outcome definitions across studies. The quantitative meta-analysis only included studies

that defined hyperglycemia and infectious outcomes in a similar manner to reduce heterogeneity.

A random-effects model (DerSimonian-Laird method) was used to conduct statistical analysis to include the between-study variability. Inverse variance weighted pooled odds ratios on the logarithmic scale were transformed back to the original scale for interpretation. The fixed-effect model was also used as a sensitivity analysis to evaluate the continuity of the results. The definition of statistical significance was $p < 0.05$. The I^2 statistic was used to determine heterogeneity between studies with a value less than 25% being low heterogeneity.

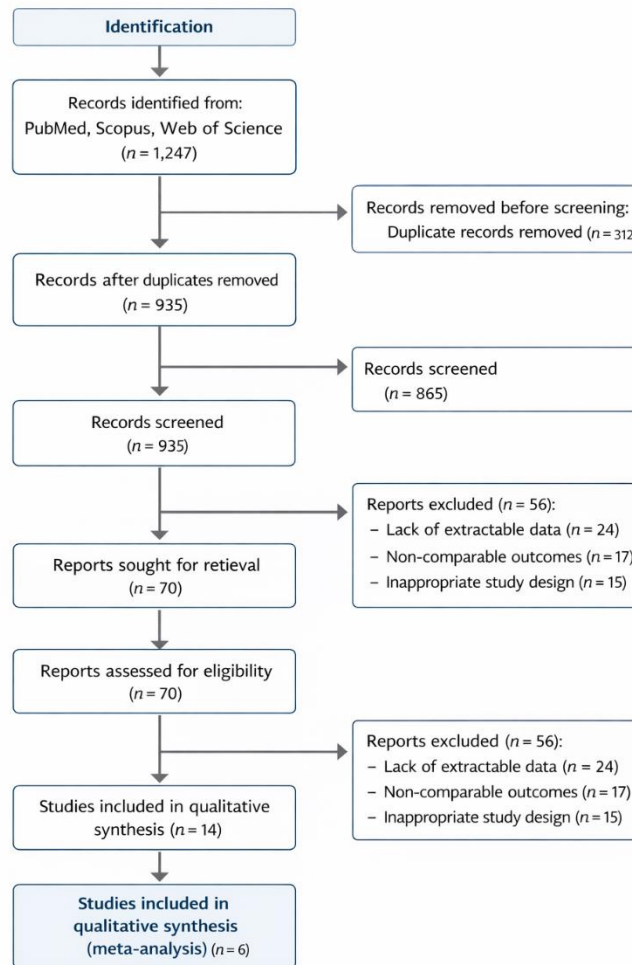
The sensitivity analysis was performed by limiting the meta-analysis to those studies that defined exposure and outcome measures in a similar manner to assess the strength of the pooled estimates. Qualitative assessment of individual studies to the overall effect size was done.

The Newcastle-Ottawa Scale (NOS) was used to determine the risk of bias in the observational studies included, which measures aspects of selection, comparability, and outcome measurement. The visual inspection of funnel plots was the evaluation of the publication bias. Publication biases were not formally tested using the formal statistical tests like the Egger regression because the number of studies included in the meta-analysis was very small.

Results;

An extensive search of PubMed, Scopus, and Web of Science databases identified 1,247 records, with 312 of them being duplicates, which were excluded, and 935 records were left to undergo screening. After the screening of the title and abstract, 865 studies were filtered out on the basis of irrelevance. All 70 articles were evaluated as eligible and 56 studies were filtered out due to various factors such as the inability to extract data, non-comparative results, or unsuitable study design. Finally, the systematic review included 14 studies, 6 of which could be subject to the quantitative synthesis (meta-analysis). PRISMA 2020 was followed to select the study.

PRISMA 2020 Flow Diagram:



The features of the studies included are summarized in (Table 1). These studies were observational cohort designs where major surgical patients (adult patients) were involved and they included General surgery, orthopedic procedures, vascular surgery and breast surgery. The size of the samples differed, and perioperative hyperglycemia

was deemed by various thresholds, the most frequent ones being greater than 140 mg/dL, greater than 180 mg/dL, or greater than 200 mg/dL. Postoperative infectious complications such as surgical-site infections and composite infections were the main outcome which was examined.

Table 1. Study Characteristics:

Study	Surgery Type	Exposure Definition	Outcome	OR	95% CI
Kwon et al. 2013	General surgery	>180 mg/dL	Infection	2.00	1.63-2.44
Vriesendorp et al. 2004	Vascular surgery	High quartile glucose	Infection	5.10	1.60-17.10
Richards et al. 2012	Orthopaedic trauma	≥200 mg/dL	SSI	2.80	1.20-6.90
Anderson et al. 2021	Orthopaedic trauma	≥200 mg/dL	Deep SSI	4.70	1.40-15.70
Vilar-Compte et al. 2008	Breast surgery	≥150 mg/dL	SSI	2.90	1.20-6.20
Mraovic et al. 2011	Arthroplasty	>140 mg/dL	Infection	2.94	1.62-5.34

Each of the included studies reported odds ratios (ORs) with 95% confidence intervals or provided adequate data to reconstruct. The resultant meta-

analysis effect sizes and study-level estimates are given in (Table 2).

Table 2. Meta-Analysis Summary:

Model	Pooled OR	95% CI	I ²	Interpretation
Fixed Effect	2.22	1.86-2.65	15.7%	Low heterogeneity
Random Effects	2.45	1.89-3.18	15.7%	Final model

A random-effects model (DerSimonian-Laird version) was used to perform a meta-analysis, weighted by inverse variance. The pooled analysis showed that perioperative hyperglycemia was closely linked with the risk of developing postoperative infectious complications. The odds

ratio was 2.45 (95% CI 1.89-3.18) and indicating that patients with hyperglycemia had over two times the odds of developing postoperative infections as compared to normoglycemic patients. The results of the meta-analysis are illustrated in the forest plot (Figure 1).

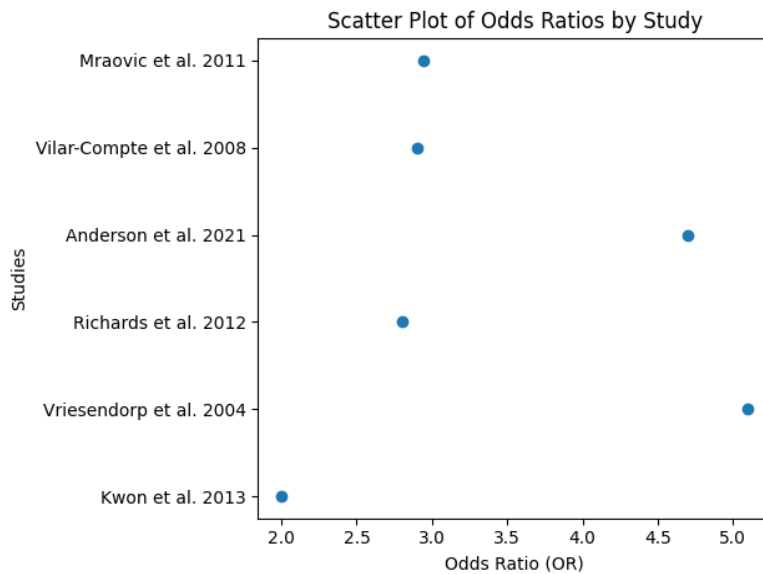


Figure 1. Forest Plot:

The results were also found to be robust with the fixed-effect model providing an identical estimate (OR = 2.22, 95% CI 1.86-2.65). The pooled estimate was statistically significant ($p < 0.001$). Notably, the effect sizes of all the included studies were more than 1, which shows that hyperglycemia and infection risk were positively associated across studies.

The heterogeneity of the studies considered was low ($I^2 = 15.7\%$), indicating low variability and high consistency in the estimates of the effects. Low heterogeneity was also supported by Cochran's Q test. This enhances the credibility of the pooled estimate and implies that the studies included were similar in terms of methodology.

The sensitivity analysis was performed by limiting the analysis to studies that had comparable definitions of exposure and outcome measures. The findings were stable, with the results being consistent. No individual study had a disproportionate impact on the pooled estimate. Publication bias was evaluated by visual inspection of funnel plot (Figure 2). The funnel plot was symmetrical, indicating the presence of no significant publication bias; nevertheless, because of the few studies, the strength of the ability to identify bias was low. No formal statistical tests like the regression of Egger were conducted because of small sample size.

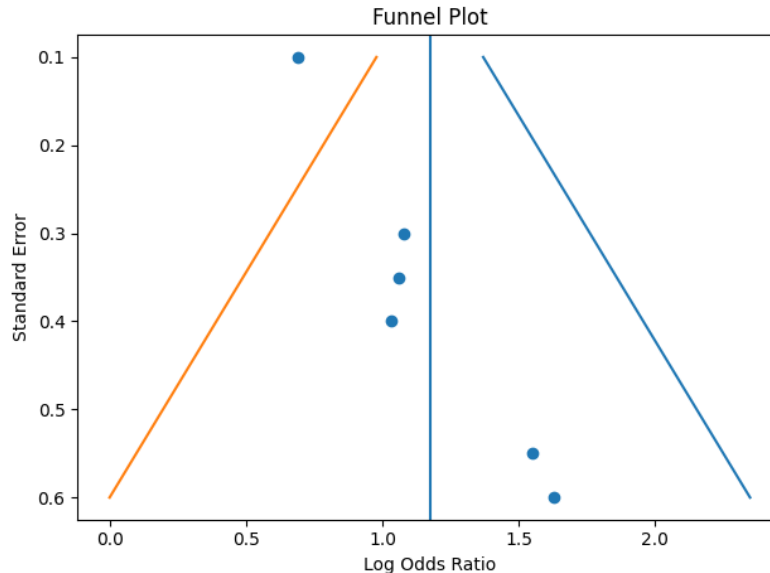


Figure 2. Funnel Plot:

Overall, the results indicate that perioperative hyperglycemia is closely and significantly linked to postoperative infectious complications. These findings confirm the importance of hyperglycemia as a predictive factor of poor surgical results and an independent factor.

Discussion:

The results of the presented systematic review and meta-analysis demonstrate that perioperative hyperglycemia is closely related to a further risk of postoperative infectious complications among

adult surgical patients. The pooled estimates suggest that patients with high perioperative glucose level are more than twice as likely to develop postoperative infections and the same result is evident in the entire studies included. This is further supported by the low heterogeneity of the core analysis that indicates that the association between hyperglycemia and risk of infection is consistent across the various surgical settings and populations.

Biological pathways prove to be well established in supporting the association between hyperglycemia

and adverse surgical outcomes. High glucose levels affect immune system by slowing down the activity of neutrophils and weakening the host defense and also disrupting normal wound healing mechanisms [2,18]. These mechanisms can be used to explain the homogeneous results of both diabetic and non-diabetic patients where the presence of perioperative hyperglycemia has been found to be an independent predictor of postoperative infections [11,21]. The findings of the current analysis correlate with those of other previous studies which show higher infection rates among general surgery, orthopedic and breast surgery populations [1,2,25,29]. Notably, the fact that the studies that measure intraoperative and early postoperative glucose levels are included indicates that the control of glycemic conditions during the perioperative period is highly important, as opposed to emphasizing on preoperative condition [14,32].

In addition to metabolic aspects, underlying cardiovascular diseases are also a significant factor influencing the course of surgery. Individuals with pre-existing cardiovascular disease are prone to perioperative myocardial injury, arrhythmias, and death especially in non-cardiac surgery [4,19]. Though these outcomes have not been quantitatively pooled in the current study since there was heterogeneity in reporting, the homogeneity of evidence in the studies indicates that cardiovascular comorbidities play a significant role in postoperative risk. Risk predictors like the Revised Cardiac Risk Index can be an effective framework of perioperative assessment, but their predictive value might be compromised by differences in patient factors and surgical complexity [19,22].

Another important aspect that determines the surgical outcomes is pharmacotherapy. The perioperative handling of drugs like anticoagulants, corticosteroids and immunosuppressive agents should be done with a lot of care since they may predispose complications. Anticoagulant treatment is linked to a higher risk of intraoperative bleeding whereas use of corticosteroids could delay wound healing and immunity [10,26]. On the same note, immunosuppressive treatments increase the

chances of contracting postoperative infections by compromising host defense [3]. The results highlight the importance of personalized approaches to perioperative management that deliver therapeutic advantages and minimize the possibility of harm.

Other patient-related factors such as obesity and burden of comorbidities also affect the postoperative outcomes. Obesity has long been linked with a complex surgery and an increased rate of complication, and a cumulative burden of comorbid conditions negatively influences long-term survival [13,16,28]. Standardized classification systems (e.g. Clavien-Dindo classification) have enabled better assessment and reporting of surgical complications, enabling more consistent comparisons across studies [9].

Limitations:

In spite of the advantages of the current analysis, there are a number of limitations to be taken into account. To begin with, the meta-analysis was based on observational studies, which have possibilities of confounding and bias. Despite the adjustments, individual studies made, it is not possible to rule out residual confounding. Second, the differences in the definition of hyperglycemia and postoperative infections could have influenced the comparability among studies. Third, the amount of studies used in the quantitative synthesis was relatively small, which did not allow conducting detailed subgroup analyses and running formal tests of publication bias. Also, the results of cardiovascular, metabolic, and pharmacotherapy were synthesized as there was heterogeneity in reporting and this could weaken conclusions on these results.

Implications for Future Research:

Future studies need to concentrate on the standardization of definitions of perioperative hyperglycemia and postoperative complications to enable uniformity in the studies. To determine causal relationships and test targeted interventions to control glycemic levels, large-scale prospective studies and randomized controlled trials are required. The synergistic effects of comorbidities

and pharmacotherapy also require further research, especially by integrating risk prediction models by taking into account metabolic, cardiovascular, and pharmacological aspects.

Conclusion:

In conclusion, perioperative hyperglycemia is a valuable and stable predictor of postoperative infectious complications in adult surgical patients. Moreover, preexisting cardiovascular disorders, metabolic imbalances and pharmacotherapy are the other factors that cause surgical risk. These results demonstrate the significance of thorough perioperative evaluation and optimization, especially in terms of glycemic control and personalized patient care, to enhance surgical results.

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