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Measuring the Cost of Liposomal Bupivacaine in Plastic and Reconstructive Surgery: A Scoping Review

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Abstract

Liposomal bupivacaine (LB) is a long-acting analgesic implemented within multimodal and enhanced recovery after surgery (ERAS) pathways in plastic and reconstructive surgery. While it has been popularized as an opioid-sparing alternative for postoperative pain management, LB costs far more to acquire than standard bupivacaine, and its contribution to downstream costs is difficult to isolate. This scoping review mapped the study designs, cost constructs, methods, and results of cost measures linked to LB in plastic and reconstructive surgery. Eligible studies gave LB to patients undergoing plastic and reconstructive surgery and reported at least one quantitative measure of cost or charge. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) and Joanna Briggs Institute (JBI) guidance, MEDLINE, the Cochrane Library, Web of Science, Embase, and ScienceDirect were searched for English-language studies published from January 2012 through August 2024. Data were charted using Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 as an extraction scaffold. As a declared extension of scoping methodology, the cost endpoint was appraised using American Society of Plastic Surgeons and the Oxford Centre for Evidence-Based Medicine (ASPS/OCEBM) levels of evidence, Cochrane risk of bias (RoB) 2 for randomized trials, and Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) for non-randomized studies. Three randomized trials and five non-randomized trials met the inclusion criteria. Cost constructs ranged from drug acquisition price and patient willingness-to-pay to charges derived from hospital length of stay (LOS), cost-to-charge-converted direct costs, data-warehouse costs, and claims costs compared with diagnosis-related group (DRG)-expected values. The only directly comparable element amongst the included studies was the LB acquisition price. This scoping review reveals that the cost evidence for LB in plastic and reconstructive surgery comprises widely heterogeneous endpoints that are not comparable with one another. Economic value-based positioning of LB in multimodal analgesia and ERAS pathways will require further prospective, adequately powered trials and full economic evaluations that declare their perspective, use contemporary comparators, standardize the price year, extend the time horizon beyond the index care event, and report uncertainty.

Categories: Plastic Surgery, Pain Management, Anesthesiology
Keywords: appraisal, cost assessment, enhanced recovery after surgery, hospital length of stay (los), liposomal bupivacaine, multimodal non-opioid analgesia, pain postoperative, plastic and reconstructive surgery, scoping review

Introduction And Background

Enhanced recovery after surgery (ERAS) protocols are multimodal, multidisciplinary perioperative pathways designed to attenuate the surgical stress response and accelerate functional recovery, in part through standardized, opioid-sparing analgesia [1]. Within plastic and reconstructive surgery, ERAS protocols have been associated with fewer complications, faster recovery, shorter hospital length of stay (LOS), and lower hospital costs [2-5]. Liposomal bupivacaine (hereafter referred to as 'LB'; Exparel®, Pacira BioSciences, Inc., San Diego, US) is a frequently cited opioid-sparing component of these pathways. It holds four FDA-approved indications for postsurgical analgesia: local infiltration in patients aged six years or older, and interscalene brachial plexus, popliteal sciatic, and adductor canal nerve blocks in adults. All other routes of administration are considered investigational or are not recommended by the FDA [6]. Structurally, LB consists of an admixture of approximately 10% standard (free) bupivacaine with the remainder of the local anesthetic contained within the aqueous chambers of multivesicular liposomal depots that have a honeycomb-like architecture. The free bupivacaine provides an early plasma peak akin to that of bupivacaine hydrochloride (HCL). Lipid erosion, diffusion of bupivacaine across the lipid bilayers, and gradual lipid membrane reorganization all contribute to the extended release of bupivacaine into plasma at the injection site over roughly the next twelve hours to seventy-two hours. Compared to bupivacaine HCL, LB has a bimodal plasma profile, a longer time to maximum plasma concentration, and longer apparent half-life. Because of the differences in pharmacokinetic properties, there is no validated, FDA-endorsed milligram-for-milligram conversion between LB and standard (unencapsulated) bupivacaine. This complicates acquisition-based cost comparisons and because LB may be part of a multimodal pain regimen or ERAS pathway, its independent contribution to downstream costs is difficult to isolate.

The clinical evidence which any economic argument for LB use rests upon is inherently heterogeneous. A systematic review of LB across plastic and reconstructive surgical procedures in 2016 noted that variability in dosing, comparators, and supplemental medications prevented firm conclusions on efficacy [7], and a systematic review of randomized trials found that studies with financial ties to the manufacturer were more likely to report reduced postoperative pain and opioid use [8]. Studies reporting cost as an outcome are scarcer still, and their methods have not been systematically characterized. This scoping review maps the study designs, cost constructs, methods, and results of measures of cost associated with LB in plastic and reconstructive surgery, regardless of the analgesic being incorporated into a formal ERAS protocol.

Review

Methods

This review was guided and is reported per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist [9]. No review protocol was officially registered on the Open Science Framework prior to screening. The PRISMA-ScR checklist is used here as the manuscript reporting standard and is applied in conjunction with Joanna Briggs Institute (JBI) methodology, consistent with the notion in published guidance that the two instruments serve complementary functions [10].

The objective of this review was to systematically map the measures of cost that have been applied to LB in plastic and reconstructive surgery, to characterize their heterogeneity, and to identify knowledge gaps to inform future economic research. The review questions were framed using the JBI 'population-concept-context' mnemonic as follows: (1) Population: patients, of any age, undergoing plastic and reconstructive surgical procedures, operationally defined by cross-reference to procedural competencies listed in an expert consensus panel regarding Canadian plastic surgery residency training [11]; (2) Concept: any reported measure of cost associated with LB, including but not limited to drug acquisition price, hospital or institutional cost, patient charges, modeled or benchmarked costs, and patient willingness-to-pay surveys, together with the economic perspective, costing method, time horizon, price year, and analytic approach used to generate each measure; and (3) Context: any care setting (inpatient, outpatient/ambulatory, ERAS pathways) and any country, with cost constructs mapped rather than converted to a common currency.

A scoping review approach was selected because the cost evidence was anticipated to be methodologically and economically heterogeneous, a situation for which mapping the extent, range, and nature of evidence, rather than pooling effect estimates, is the appropriate synthesis goal [9,12]. Eligibility criteria were specified a priori against the 'population-concept-context' framework above and applied with documented rationale. Sources were eligible if they (a) enrolled patients undergoing plastic and reconstructive surgery,

(b) administered LB as an analgesic intervention, and (c) reported at least one quantitative measure of cost or charge attributable to the index care episode. Both randomized and non-randomized comparative study designs were eligible. Conference abstracts, retracted studies, incomplete studies, and correspondence letters were excluded. The language of publication was restricted to English; this decision was based on the meta-epidemiological argument that exclusion of non-English publications from reviews had a minimal effect on overall conclusions for clinical interventions [13,14]. Narrative reviews, systematic reviews, and meta-analyses were accessed to support manuscript synthesis and to increase access to grey literature. Editorials without primary cost data and studies reporting only clinical (non-economic) endpoints were excluded.

A literature search was performed using MEDLINE (PubMed), the Cochrane Library, Web of Science, Embase, and ScienceDirect databases. Publication dates spanned from January 1, 2012, through August 31, 2024. January 1, 2012, was chosen as the terminus a quo to coincide with the release of Exparel® to commercial markets. August 31, 2024, was chosen as the terminus ad quem to coincide with the month immediately preceding this review's original data collection period beginning in September 2024. The review's conceptual design was subsequently narrowed in September 2026 without an update to the search timeframe. Filters specific to each database were applied. The full, reproducible electronic search strategy for all included databases are given in the appendix. The search strategy was developed by a member of the review team (NSB) and adapted for the syntax of each database without peer-review by a health sciences librarian.

A primary manual screening process was then applied to the initial list of results (n=719). Three members of the review team (NSB, LML, ANP) independently excluded articles deemed insufficiently related to plastic and reconstructive surgery and LB based on title, abstract, and original journal of publication. Duplicate records, retracted studies, and incomplete studies were removed before the search strategy progressed. Discordance in total counts of the independent lists was resolved by majority decision. Two members of the review team (NSB, LML) then independently performed a secondary manual screening process by reviewing full manuscript content for concrete evidence of each study's relevance to plastic and reconstructive surgery and LB. A measure of cost reported as a primary or secondary outcome was required for a record to meet final inclusion criteria. Discordance in total counts of the independent lists at this time was again resolved by majority decision, which was accomplished by including input from a third member of the review team (ANP). During this process, systematic reviews, narrative reviews, and meta-analyses were accessed for reference-list screening to increase capture of grey literature; they were then archived for later use during manuscript synthesis. The flow diagram of the screening process, including reasons for exclusion at each stage, is presented in Figure *1*.

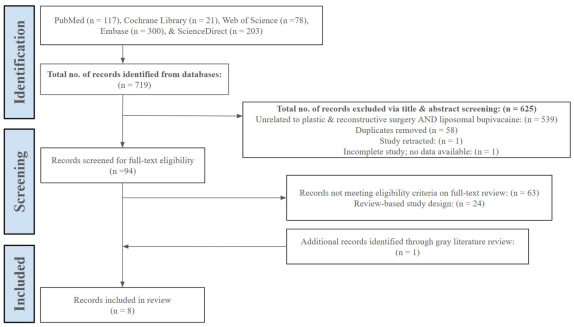


FIGURE 1: Flow diagram demonstrating search and screening process

Image credit: Created by the authors in Microsoft Word (Microsoft Corp., Redmond, WA, USA).

Data were charted using a standardized charting form developed a priori, piloted on two of the eight records included in the finalized search strategy, and refined iteratively by the review team. Charting was performed by one member of the review team (NSB) and independently verified by two additional members of the review team (LML, ANP); discrepancies were reconciled by consensus. Where cost constructs, perspective, or currency price-year descriptions were ambiguous, study authors were not contacted for clarification. Charted data were synthesized narratively and in tabular form. To render heterogeneous cost endpoints comparable, the charting form was structured via the 2022 Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [15], used here as a data-extraction scaffold. CHEERS is applied in this scoping review with two caveats. First, it was designed for full economic evaluations, so items such as incremental cost-effectiveness ratios, outcome valuation, and discounting are frequently not applicable to the partial cost analyses in the studies included in this review and are recorded as such. Second, because CHEERS assesses reporting completeness rather than methodological validity, it is paired with dedicated tools for critical appraisal.

Critical appraisal is an optional component of a scoping review. JBI and PRISMA-ScR guidance note that formal appraisal is generally not undertaken in scoping reviews and, when performed, must be accompanied by an explicit rationale and a description of how it informs the synthesis [9,10]. Its inclusion here is a deliberate, declared extension of standard scoping review conduct. The objective of this review is not merely to catalogue that costs were reported, but to characterize how they were measured and how dependable those measurements are. Because the included literature mixes randomized trials with retrospective, historical-control, and administrative-claims designs, and mixes true costs with charges, modeled benchmarks, and a willingness-to-pay survey, an undifferentiated map would imply a false equivalence amongst economically and methodologically different data. Appraisal is therefore integral to the stated aim, which is the precise condition under which critical appraisal is appropriate in scoping reviews. Per-study level of evidence was assessed using reviewer interpretations of the American Society of Plastic Surgeons (ASPS) and Oxford Centre for Evidence-Based Medicine (OCEBM) therapeutic hierarchy [16,17]. A design-matched risk of bias assessment, using the Cochrane risk of bias (RoB) 2 tool for randomized trials and the original iteration (2016) of the Risk Of Bias In Non-randomized Studies - of Interventions ROBINS-I tool for non-randomized comparisons was applied specifically to the cost endpoint [18,19]. Each tool's domains were rated by two independent reviewers (NSB, LML) with consensus adjudication, and the standard algorithms were followed.

Results

Eight studies met inclusion criteria and reported at least one measure of cost associated with LB in plastic and reconstructive surgery: three randomized trials and five non-randomized (observational) trials [20-27].

Figure *2* is a traffic-light diagram of the ROBINS-I assessment of the five non-randomized studies, pertaining specifically to their cost endpoint(s).

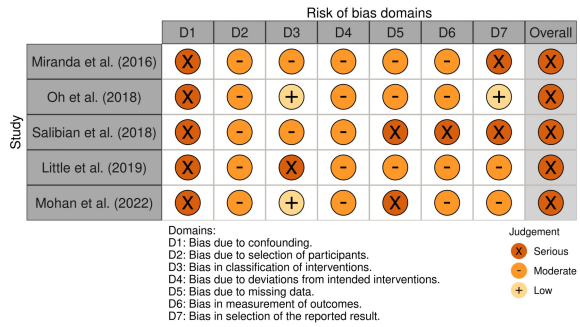


FIGURE 2: ROBINS-I traffic-light diagram for critical appraisal of cost endpoint(s) in the five non-randomized trials

ROBINS-I: Risk Of Bias In Non-randomized Studies - of Interventions [28].

[23-27]

The seven ROBINS-I domains are confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. Overall judgements range from 'low' to 'moderate' to 'serious' to 'critical'; under the standard algorithm, a 'serious' rating in any one domain renders the overall rating 'serious'. All five non-randomized studies [23-27] were rated 'serious' overall, driven in every case by confounding, a consequence of non-randomized allocation, temporal/historical comparison groups, and entanglement of LB with broader multimodal or ERAS co-interventions. Because no non-randomized study can rise above 'serious' when confounding is 'serious', the discriminating information lies in the downstream domains: Oh et al. (2018) [23] is the strongest (adjusted generalized linear modeling (GLM), fixed-year costing, and 'low' concern in classification and reporting), whereas Salibian et al. (2018) [24] is the weakest ('serious' in four domains, driven by abstract-level reporting and crude cost estimation).

Figure 3 is a traffic-light diagram of the RoB 2 assessment of the three randomized trials, pertaining specifically to their cost endpoint(s).

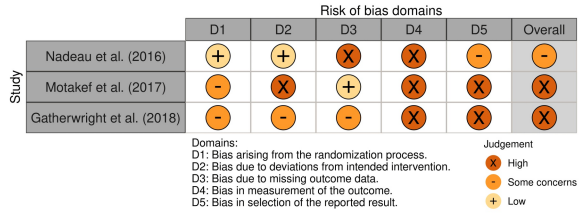


FIGURE 3: RoB 2 traffic-light diagram for critical appraisal of cost endpoint(s) in the three randomized trials

RoB: Risk of Bias [28].

[20-22]

RoB 2 grades five domains: randomization, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result; the overall judgement is driven by the worst domain. Two cross-cutting features depress every studies' overall rating. LB is a milky, viscous suspension that is visually distinct from standard bupivacaine, which makes blinding of the individual administering the drug essentially impossible without masking. Additionally, all three randomized trials are small in size and single-center in design. None reached 'low' overall risk of bias. Nadeau et al. (2016) [20] has the strongest randomization and blinding of the three (within-patient comparator study design; syringes were taped to mask LB's appearance), yet its cost endpoint is its weakest element from an overall critical appraisal standpoint: a subjective, single-item willingness-to-pay survey obtained in 23 of 34 patients, which was administered months postoperatively by the unblinded senior author (who performed the surgical procedure). Motakef et al. (2017) [21] and Gatherwright et al. (2018) [22] are rated 'high' principally on selection of the reported result. Motakef et al. (2017) was terminated early at a planned interim analysis when significance was reached for all major outcomes; early stopping of data collection for benefit systematically overestimates effect size [29]. Gatherwright et al. (2018) [22] reported cost descriptively with no inferential test, while underpowered (LOS difference was a trend only; p=0.08). Both are compounded by the lack of blinding during drug administration (single-blind in Motakef et al. (2017) [21]; an On-Q pump that cannot be blinded against a single-shot transversus abdominis plane block in Gatherwright et al. (2018) [22]).

Table *1* maps each study onto the CHEERS 2022 reporting domains.

#	CHEERS 2022 item	Nadeau et al., 2016 [20]	Motakef et al., 2017 [21]	Gatherwright et al., 2018 [22]	Oh et al., 2018 [23]	Salibian et al., 2018 [24]	Mohan et al., 2022 [25]	Miranda et al., 2016 [26]	Little et al., 2019 [27]
1	Title (identify as economic evaluation + interventions)	P	P	P	Y	P	P	Y	Y
2	Abstract (structured economic summary)	P	P	P	Y	P	P	P	Y
3	Background and objectives	Y	Y	P	Y	P	Y	P	Y
4	Health economic analysis plan	N	N	N	N	N	N	N	N
5	Study population	Y	Y	Y	Y	P	Y	Y	Y
6	Setting and location	Y	Y	Y	Y	Y	Y	Y	Y
7	Comparators (and rationale)	Y	Y	Y	Y	Y	Y	P	Y
8	Perspective (analytic viewpoint stated)	N	N	N	P	N	N	N	P
9	Time horizon	N	N	N	P	N	N	P	P
10	Discount rate	NA	NA	NA	NA	NA	NA	NA	NA
11	Selection of (health) outcomes	P	P	P	NA	P	P	NA	NA
12	Measurement of outcomes	P	P	P	NA	P	P	NA	NA
13	Valuation of outcomes (utilities/monetary)	NA	NA	NA	NA	NA	NA	NA	NA
14	Measurement and valuation of resources and costs	P	P	P	Y	P	P	P	Y
15	Currency, price date, and conversion	P	N	N	Y	N	P	N	P
16	Rationale and description of model	NA	NA	NA	NA	NA	NA	NA	NA
17	Analytics and assumptions	P	P	N	Y	P	P	P	P
18	Characterizing heterogeneity	N	N	N	P	P	N	N	N
19	Characterizing distributional (equity) effects	N	N	N	N	N	N	N	N
20	Characterizing uncertainty	N	P	N	P	P	P	P	P
21	Approach to patient/stakeholder engagement	N	N	N	N	N	N	N	N
22	Study parameters (model inputs)	NA	NA	NA	NA	NA	NA	NA	NA
23	Summary of main results	P	Y	P	Y	P	Y	Y	Y
24	Effect of uncertainty (sensitivity analysis)	N	N	N	P	N	N	N	N
25	Effect of patient/stakeholder engagement	N	N	N	N	N	N	N	N
26	Findings, limitations, generalizability	Y	Y	P	Y	N	Y	P	Y
27	Source of funding	Y	Y	Y	Y	N	Y	Y	Y
28	Conflicts of interest	Y	Y	Y	Y	N	Y	Y	Y
—	Items fully reported (Y), of 28	7	8	5	13	2	8	6	11
—	Items NA (legitimately excluded)	4	4	4	6	3	4	6	6

TABLE 1: CHEERS 2022 domain assessments of the eight included studies

Domains per study that were fully reported (Y) or not applicable (NA) are cumulatively displayed at the bottom of the table.
#: CHEERS 2022 domain item. Y: fully reported domain item. P: partially reported domain item. N: domain item not reported. NA: domain item not applicable or legitimately excluded on the basis of overall study design.

Because the checklist has no validated scoring system and its developers explicitly discourage its use as a scoring tool, no summary CHEERS score was generated [15]. Each applicable item was instead described as reported (Y), partially reported (P), not reported (N), or not applicable (NA).

Nadeau et al. (2016) was a prospective, within-patient (split-breast), double-blind, randomized controlled trial in 34 women undergoing primary cosmetic subpectoral breast augmentation, in which each patient received LB infiltration in one implant pocket versus standard bupivacaine infiltration in the contralateral pocket before closure [20]. On CHEERS reporting, the perspective was explicitly a patient perspective (willingness-to-pay for a $250 upcharge), and the comparator (standard, unencapsulated bupivacaine) was clearly reported as administered within the same patient. Resource valuation was reported only as list acquisition prices ($285 per 20 cc versus $1.15), with no broader resource use captured; time horizon, currency price-year standardization, uncertainty characterization (confidence intervals, sensitivity analysis), and analytic handling of cost data were not reported, and the industry-supplied study drug was disclosed under funding. On critical appraisal, the within-patient, double-blind design corresponds to Oxford/ASPS Level I-II, although the study is labeled as Level III within the original journal of publication. For the cost

endpoint, the RoB 2 overall rating is 'some concerns': randomization and blinding are 'low', but missing outcome data are 'high' (willingness-to-pay survey was obtained in 23 of 34 (68%) patients) and outcome measurement is 'high' (a subjective, single-item, post hoc query administered unblinded by the performing surgeon months postoperatively). On the economic-quality layer, willingness-to-pay is a weak, bias-prone cost proxy rather than a measured resource-use costing, and no price year standardization or uncertainty analysis is provided.

Motakef et al. (2017) was a single-blind parallel-group randomized controlled trial in patients undergoing immediate unilateral or bilateral tissue expander or direct-to-implant breast reconstruction following mastectomy. The authors compared field block LB (n=12) to field block using bupivacaine with epinephrine (n=12) [21]. On CHEERS reporting, the perspective was institutional (hospital charges), the comparator (bupivacaine with epinephrine) was reported, and the costing method was transparently described as a derivation: a flat $297 drug add-on, plus a fixed per-midnight charge of $9,721 multiplied by the hospital length of stay. However, this was a charge, not a true cost; price-year standardization, uncertainty characterization, and skew-appropriate analytics were not reported, and early stopping was reported without a prespecified cost-analysis plan. On critical appraisal, the study is Oxford/ASPS Level II, but the overall RoB 2 overall rating is 'high', driven by three domains. Deviations from intended interventions are 'high' (single-blind only; the milky appearance of liposomal bupivacaine versus the clear appearance of standard bupivacaine makes blinding of the administering surgeon relevant and therefore an unmitigated performance-bias threat). Outcome measurement is 'high' (charges computed from the LOS rather than from billed or costed resource use; this was assessed unblinded). Selection of the reported result is 'high' (the trial was stopped early "when significance was reached for all major outcome measures," which systematically overestimates effect sizes, with no registered cost-analysis plan). On the economic-quality layer, a LOS-derived charge with no inflation adjustment or sensitivity analysis is a low-rigor costing approach, so the favorable headline (charges lower with the liposomal bupivacaine, $10,828 versus $18,632) must be read against a 'high' risk of bias cost endpoint.

Gatherwright et al. (2018) was a prospective, three-arm, blinded randomized controlled trial in women undergoing unilateral delayed deep inferior epigastric perforator (DIEP) flap breast reconstruction. Authors compared a single-shot LB TAP block (n=8) versus a single-shot standard bupivacaine TAP block (n=8) versus a continuous standard bupivacaine TAP infusion (n=5) via an On-Q® Pain Relief System (Avanos Medical, Inc., Alpharetta, GA); an appended arm of the study was a retrospective cohort that received no regional intervention (n=6), which served as a historical control [22]. On CHEERS reporting, this study had the best resource-valuation reporting of the trials: the drug/device price was itemized per patient ($299.90 for liposomal bupivacaine TAP versus $68.05 for bupivacaine TAP and $368.14 for the On-Q), satisfying the micro-costing expectation for the numerator. The institutional perspective and the multiple comparators (plain bupivacaine TAP, On-Q catheter, historical control) were clearly reported. However, the bundled "medication + LOS" cost was reported descriptively with no inferential test, uncertainty was not characterized, and price-year standardization was not reported. No financial conflicts were declared by the authors of this study, which was a reporting strength. On critical appraisal, the randomized arms are Oxford/ASPS Level II and the appended historical-control arm is Level III, making this a hybrid design appraised with both tools utilized in this review. The RoB 2 rating for the trial arms is 'high': randomization detail, blinding against an un-blindable On-Q pump, and sparse/unevenly available outcome data (cells of 8/8/5, with the On-Q arm lacking enough data for several endpoints) raise 'some concerns' across D1-D4, and selection of the reported result is 'high' because the cost comparison is descriptive, underpowered (LOS difference only a trend, p=0.08), and not prespecified. The retrospective historical arm (n=6) adds ROBINS-I confounding. On the economic-quality layer, the itemized drug pricing is a genuine strength, but reporting cost as a secondary descriptive observation without inferential testing or adjustment means the finding of cost neutrality ($3,215 versus $3,154 versus $3,686 versus $3,256) is hypothesis-generating rather than confirmatory.

Oh et al. (2018) was a retrospective cohort on microvascular free-flap breast reconstruction that compared patients managed on an ERAS pathway that incorporated LB with a historical (LB-excluding) 'traditional recovery after surgery' (TRAS) pathway [23]. On CHEERS reporting, the institutional perspective was explicit; standardized direct costs were derived through cost-to-charge ratios; and it was the only study to standardize currency to a fixed price year (2014 USD) and the only one, with Mohan et al. (2022) [25], to report confidence intervals - directly satisfying CHEERS items on valuation, currency/price date, and uncertainty. The time horizon (index hospitalization) and skew-appropriate generalized linear model (GLM) are reported. The principal reporting gap was that liposomal bupivacaine is bundled within ERAS and not separately costed. On critical appraisal, the study is Oxford/ASPS Level III and rates 'serious' overall on ROBINS-I, driven entirely by the confounding domain: LB cannot be isolated from the full ERAS bundle, and the ERAS and TRAS groups span different calendar years with TRAS patients selectively admitted to the ICU. A GLM adjusted for BMI, laterality, and transfusion partially mitigates this, and the remaining domains are 'low' to 'moderate' (classification 'low' via a dated, EMR-embedded order set; reported result 'low' with a prespecified full breakdown of the utilized Berenson-Eggers Type of Service codes). On the economic-quality layer, Oh et al. (2018) [23] contained the most methodologically rigorous cost analysis (adjusted GLM plus fixed-year costing) out of the studies included in this review. Yet, it realized a ROBINS-I ceiling of 'serious' due to irreducible bundle-level and temporal confounding, so its favorable result (ERAS $4,576 lower; $38,688 versus $43,264) is robust in reporting but confounded in attribution.

Salibian et al. (2018) was a retrospective cohort focused on microsurgical DIEP reconstruction using TAP block with LB versus standard bupivacaine [24]. On CHEERS reporting, the abstract format precluded adequate reporting across most domains: the perspective was institutional and the comparator was reported, but resource valuation was a crude estimate (per-diem plus medications plus OR, with LB folded into "medication cost" and not itemized), and currency standardization, time horizon detail, uncertainty, analytics, and funding were not reported. On critical appraisal, the study is Oxford/ASPS Level III (reporting incomplete) and rates 'serious' overall on ROBINS-I. It contains 'serious' ratings in four domains: confounding (no multivariable cost adjustment; groups differed, e.g., mastectomy flap necrosis 17.5% versus 7.4%), missing data (abstract format precludes verification of completeness), outcome measurement (hospital expenses estimated from average per-diem figures, a crude cost proxy), and selection of the reported result (conference abstract with no protocol and high selective-reporting potential). On the economic-quality layer, the combination of a non-itemized drug cost, a per-diem-based estimate, and abstract-only reporting makes this the lowest-rigor costing analysis in this review, so the null finding (no significant difference, $21,531 versus $22,050) appears to carry minimal evidentiary weight.

Mohan et al. (2022) was a prospectively maintained database of implant-based breast reconstruction that compared LB versus paravertebral block versus no block in three separate and sequential time periods [25]. On CHEERS reporting, the perspective was institutional, the three comparators were clearly reported, and total and direct costs were drawn from a data warehouse - but the per-day cost was derived from an external $2,985/day estimate rather than measured, currency price-year is not standardized, and the time horizon is readmission-inclusive. Mohan et al. (2022) [25] reported confidence intervals, a reporting strength shared only with Oh et al. (2018) [23]. On critical appraisal, the study is Oxford/ASPS Level III and rates 'serious' overall on ROBINS-I: confounding is 'serious' because allocation is by treatment era (paravertebral block from August 2016, liposomal bupivacaine from September 2017), creating temporal confounding, with more axillary lymph node dissection in the paravertebral group; and missing data are 'serious' because their cost analysis used only 128 of 491 patients (26%) with complete cost data. Classification is 'low' (standardized protocol) and the reported result is 'moderate' (the cost analysis was a sequential add-on to an original quality-improvement aim). On the economic-quality layer, warehouse-derived costs are reasonable but the external per-day estimate and the 26% cost-data subset weaken the costing, so the finding that LB ($26,183) is statistically similar to paravertebral block ($27,148) but costlier than no block ($23,113) should be interpreted with era-confounding in consideration.

Miranda et al. (2016) was a retrospective study of two consecutive six-month cohorts undergoing tissue expander breast reconstruction that compared intercostal LB versus a traditional multimodal regimen consisting of intercostal standard bupivacaine, paravertebral ropivacaine, or patient-controlled analgesia [26]. On CHEERS reporting, Miranda et al. (2016) is the pivotal study for this review's central message because it is the one paper that reports both economic contexts (hospital cost and patient charges) side by side, making the incommensurability explicit. The same cohort yields a $2,416 hospital cost saving (statistically significant) and a $4,495 patient charge saving (not statistically significant). This dual reporting is a reporting strength, but the correspondence/letter format limits detail on costing-source mechanics, complication capture, time horizon, currency standardization, uncertainty, and analytics; liposomal

bupivacaine is not separately itemized. On critical appraisal, the study is Oxford/ASPS Level III and rates 'serious' overall on ROBINS-I: confounding is 'serious'. They report a sequential six-month pre/post study design with significant baseline imbalance in axillary procedures and intraoperative expander fills, both p=0.03; after adjustment the charge difference lost significance at p=0.11 while the cost difference persisted. This suggests a direct, documented demonstration of residual confounding. Selection of the reported result is 'serious' (correspondence format, no protocol). Classification is 'moderate' (a heterogeneous "traditional" comparator spanning intercostal bupivacaine, paravertebral ropivacaine, or PCA). On the economic-quality layer, the separate reporting of cost and charges is methodologically valuable even though neither is individually high-rigor in terms of data analysis undertaken; the attenuation of the charge difference after adjustment is within-study evidence of cost-versus-charge divergence, and the savings are explicitly attributed to tripling the outpatient (<24 h) discharge rate (78.7% versus 27.7%).

Little et al. (2019) conducted a retrospective analysis from a database set of 958 abdominal and breast reconstructive cases from 54 institutions. The authors compared observed versus diagnosis-related group (DRG)-expected costs between cases with LB use and without LB use [27]. On CHEERS reporting, Little et al. (2019) contributes the only system/payer-adjacent perspective to this scoping review and provides the largest dataset - from Vizient Clinical Data Base (Vizient, Inc., Irving, TX). It reports both direct and total costs benchmarked against DRG risk-expected values; the acquisition price is itemized ($315 per 366-mg vial versus $5.24). The costing source, perspective, and comparator are reported, but the observed-versus-DRG-expected construct is neither a contemporaneous head-to-head cost nor a charge and must be labeled as a distinct third register. Price-year standardization and sensitivity analyses are not reported, and the industry conflicts are disclosed under funding (three authors with financial ties to Pacira Pharmaceuticals, Inc.). On critical appraisal, the study is Oxford/ASPS Level III (due to it being observational in design) and rates 'serious' overall on ROBINS-I: confounding is 'serious' (confounding by indication - liposomal bupivacaine use likely marks adoption of broader multimodal/ERAS programs, author-acknowledged - with only DRG benchmarking rather than patient-level adjustment on aggregate data), and, uniquely amongst the studies included in this review, classification of interventions is 'serious' (reliance on ICD-10/administrative coding with coder-provider concordance assumptions, cited by the authors as the greatest limitation). The remaining domains are 'moderate', including the reporting-bias flag for ties to the manufacturer of LB. On the economic-quality layer, their self-applied "cost-minimization analysis" label is aspirational, because a true cost-minimization analysis presupposes equivalent outcomes that a claims comparison cannot establish. The result (total $28,021 versus $39,531, p=0.02; direct $17,561 versus $23,960; length of stay 5.8 versus 9.2 days) is the largest system-level signal in the review but is confounded by indication and limited to in-hospital events.

Discussion

Cost constructs in the included studies ranged from a raw drug acquisition price and a patient willingness-to-pay survey [20] to charges derived arithmetically from hospital LOS [21], standardized cost-to-charge-converted direct costs [23], warehouse costs [25], and observed-versus-DRG-expected claims costs [27]. The only element directly comparable across studies was the LB acquisition price, which converged at roughly $285-$315 per vial. Downstream cost offsets tracked hospital LOS: savings appeared where an inpatient stay could be compressed [26,27] and disappeared where it could not [20,22]. Reporting of perspective, price year, time horizon, and uncertainty was frequently incomplete under CHEERS 2022, and no study reached 'low' overall risk of bias for the cost endpoint(s) under RoB 2 utilization or under the 2016 version of the ROBINS-I tool. Taken together, these findings indicate that the economic question surrounding LB use in plastic and reconstructive surgery has yet to be settled, and that rigorous economic assessment is warranted.

The case for such assessment begins with a mismatch between price and marginal benefit. The acquisition price of LB has risen since its 2011 FDA approval, from an initial estimate of $285 to more than $350 for a single 266-mg vial in one report [30]. Relative to standard bupivacaine, this premium has been described as eight to 12 times the acquisition cost [31] and, in other analyses, as more than 100 times the cost [32]; the magnitude depends on the formulation and volume compared, but in every framing, the drug is the dominant incremental input. Within plastic and reconstructive surgery, the clinical benefit of LB is modest and inconsistent. In a 117-patient randomized trial of DIEP flap reconstruction within an ERAS pathway, LB lowered pain scores after the first 24 hours postoperatively but did not reduce opioid consumption (66.9 vs 60.2 morphine milligram equivalents; p=0.47) or hospital LOS (2.1 vs 2.2 days) [33], and a systematic review of autologous breast reconstruction found heterogenous opioid effects and inconsistent recovery outcomes that depended on the underlying analgesic protocol and comparator [34]. Whether a benefit of this size and inconsistency is worth the price in each setting is an explicitly economic question.

The answer is also setting-specific. In the included studies, LB offsets its acquisition cost, if at all, by shortening an inpatient stay, consistent with the conclusion that the cost-effectiveness of LB is highly context-dependent and supports selective rather than universal use [30]. As plastic and reconstructive procedures move toward outpatient or short-stay care, the inpatient days available for LB to offset shrink, and its acquisition cost becomes a larger share of incremental cost. The DIEP trial by Park et al. (2024), conducted with a hospital LOS near two days, illustrates this ceiling effect [33], as does the outpatient cosmetic setting of Nadeau et al. (2016) [20], in which there was no postoperative hospital stay to shorten. Cost findings generated in cohorts with longer stays, such as the 9.2-day versus 5.8-day comparison reported by Little et al. (2019) [27], may therefore not transfer to contemporary pathways, and only setting-specific economic assessment can determine where, if anywhere, the offset persists.

The time horizons of existing studies are similarly limited. The principal clinical argument for LB is opioid sparing, and prolonged opioid use is a recognized problem after reconstruction: among 4,113 opioid-naive women undergoing immediate breast reconstruction, 90% filled perioperative opioid prescriptions and 10% continued to fill prescriptions beyond three months [35]. If LB meaningfully reduced persistent opioid use, the resulting economic benefit would accrue largely after discharge, beyond the index-hospitalization horizons used by most included studies; if its opioid-sparing effect is confined to the first 24-72 hours [30], long-term savings may be negligible. Neither proposition can be tested with index-stay cost comparisons, and longer-horizon designs would still face the bundle-entanglement problem identified in Oh et al. (2018) [23] and Little et al. (2019) [27].

Economic conclusion also inherit the biases of the clinical evidence on which they rest. A systematic review of 63 randomized trials found that LB did not demonstrate significant pain relief in 74.58% of trials or opioid reduction in 85.71% of trials evaluating narcotic use; trials with a manufacturer-related financial conflict of interest were significantly more likely to report pain relief (OR: 14.31; 95% CI: 2.8 - 73.10) and decreased opioid consumption (OR: 12.35; 95% CI: 1.40 - 109.07), and 47.54% of 265 registered but unpublished trials were withdrawn, terminated, suspended, or completed without available results [8]. The Cochrane review of surgical-site LB infiltration found that none of its five parallel-arm trials performed or reported a health economic assessment [36]. In the present review, the largest and most favorable cost analysis was authored by investigators with declared manufacturer financial ties [27], and one randomized trial used industry-supplied study drug [20]. This does not invalidate those findings, but it reinforces the need for independent, transparently reported economic evaluations with prespecified analysis plans, full funding disclosure, and sensitivity analyses that test the robustness of cost conclusions.

The methodological gaps observed here mirror documented deficits in the plastic and reconstructive surgery economic literature as a whole. A systematic review of economic evaluations in plastic surgery found that 82% were partial cost analyses and only 18% were full economic evaluations [37]. A CHEERS-based appraisal of 92 plastic surgery economic evaluations reported an average compliance of 63%, with time horizon (15%), discount rate (18%), and assessment of heterogeneity (15%) the least reported items and 32% of studies methodologically mistitled [38]. Cost-utility studies in the specialty averaged three of nine points on a guideline-based scoring tool, with only 11% including indirect costs and 14% applying discounting [39]. The LB literature mapped here reproduces these shortcomings in health economic methodology: only one study standardized to a fixed price year, few reported cost confidence intervals or sensitivity analyses, and the single self-labeled cost-minimization analysis could not establish the outcome equivalence that the method presupposes. Because health-related quality of life is central to plastic and reconstructive surgery, the field is well-suited to cost-utility analysis using consistent perspectives, costs, outcomes, and utilities [40], and LB, as a well-defined, high-volume, single-agent intervention, offers a suitable case on which to apply such methods.

Economic findings for LB depend on whose costs are counted. Under bundled inpatient payment, the

hospital absorbs the acquisition price and captures any LOS savings, whereas in elective cosmetic surgery the patient may bear the cost directly; in that setting, 70% of patients in Nadeau et al. (2016) [20] stated they would have declined to pay the upcharge. Reimbursement policy also shifts the calculus. Cost concerns were reported to have eased when LB was approved for reimbursement in Medicare-associated ambulatory surgical centers in the United States in 2019 [41], and Little et al. (2019) [27] framed their findings in terms of value-based payment and whole-process measurement. However, studies that do not declare their perspective cannot inform the decisionmaker who actually pays. With the implementation of the Non-Opioids Prevent Addition in the Nation (NOPAIN) Act in January 2025, LB became reimbursable by Medicare separately up to pre-specified CMS limits; this represented a distinct change from the drug's previous positioning within bundled procedure payment models, which discouraged its use from an economic standpoint beyond ambulatory surgical centers [42,43]. While this expanded access may encourage wider use, no studies in this review have assessed the impact of NOPAIN Act on the cost efficacy of LB.

Limitations

Limitations apply to this review. The evidence base comprises eight studies, most of which are small and single-center, which limits the depth of appraisal possible. All included studies were conducted in the United States, so findings may not generalize to health systems with different price structures. The electronic search strategy was limited to records published through August 31, 2024, which reflected the project's initiation in September 2024. However, subsequent conceptual narrowing of the review's design to economic cost assessments occurred in September 2026, which was associated with the creation of a novel electronic search strategy. Because this end-date restriction was not updated in conjunction with the redirection of the scoping review's conceptual narrowing, it introduces the risk of study-identification (selection) bias and may incorporate time-lag bias. Any records with eligible cost analyses published between September 2024 and September 2026 were as a result not screened for. These findings should be interpreted as 'current' insofar as their extent to August 2024. Additionally, critical appraisal is an optional extension in scoping reviews, and domain judgements reflect this review team's interpretation of incompletely reported economic endpoints. Finally, consistent with scoping review intent, no quantitative synthesis of cost outcomes was attempted, and the findings describe the evidence landscape (up to August 2024) rather than estimate the cost-effectiveness of LB.

Conclusions

The cost evidence for LB in plastic and reconstructive surgery in this scoping review is inconclusive. Beyond a relatively stable acquisition price of LB, no other outcomes can be compared directly. Prospective, adequately powered trials and full economic evaluations that declare their perspective, specify contemporary comparators, standardize price year, extend the time horizon beyond the index admission, and report uncertainty are needed before LB can be positioned on a value-based footing in plastic and reconstructive surgery.

Appendices

Formal database search parameters

MEDLINE (PubMed)

Search: [(plastic surgery OR plastic and reconstructive surgery) AND (Exparel OR liposomal bupivacaine OR Liposomal bupivacaine)] Filters: English, Humans, from 2012/1/1 - 2024/8/31 Sort by: Publication Date

(("surgery, plastic"[MeSH Terms] OR ("surgery"[All Fields] AND "plastic"[All Fields]) OR "plastic surgery"[All Fields] OR ("plastic"[All Fields] AND "surgery"[All Fields]) OR ("plast reconstr surg"[Journal] OR "plast reconstr surg glob open"[Journal] OR "plast reconstr surg 1946"[Journal] OR "keisei geka"[Journal] OR ("plastic"[All Fields] AND "and"[All Fields] AND "reconstructive"[All Fields] AND "surgery"[All Fields]) OR "plastic and reconstructive surgery"[All Fields])) AND ("bupivacaine liposome"[All Fields] OR "bupivacaine"[Supplementary Concept] OR "bupivacaine"[All Fields] OR "bupivacain"[All Fields] OR "bupivacaine"[MeSH Terms] OR "bupivacaine s"[All Fields] OR "exparel"[All Fields] OR (("liposomalization"[All Fields] OR "liposomalized"[All Fields] OR "liposomally"[All Fields] OR "liposome s"[All Fields] OR "liposomes"[Pharmacological Action] OR "liposomes"[Supplementary Concept] OR "liposomes"[All Fields] OR "liposomal"[All Fields] OR "liposomes"[MeSH Terms] OR "liposome"[All Fields] OR "liposomic"[All Fields] OR "liposomized"[All Fields]) AND ("bupivacaine"[Supplementary Concept] OR "bupivacaine"[All Fields] OR "bupivacain"[All Fields] OR "bupivacaine"[MeSH Terms] OR "bupivacaine s"[All Fields])) OR (("liposomalization"[All Fields] OR "liposomalized"[All Fields] OR "liposomally"[All Fields] OR "liposome s"[All Fields] OR "liposomes"[Pharmacological Action] OR "liposomes"[Supplementary Concept] OR "liposomes"[All Fields] OR "liposomal"[All Fields] OR "liposomes"[MeSH Terms] OR "liposome"[All Fields] OR "liposomic"[All Fields] OR "liposomized"[All Fields]) AND ("bupivacaine"[Supplementary Concept] OR "bupivacaine"[All Fields] OR "bupivacain"[All Fields] OR "bupivacaine"[MeSH Terms] OR "bupivacaine s"[All Fields])))) AND ((humans[Filter]) AND (2012/1/1:2024/8/31[pdat]) AND (english[Filter]))

Translations

plastic surgery: "surgery, plastic"[MeSH Terms] OR ("surgery"[All Fields] AND "plastic"[All Fields]) OR "plastic surgery"[All Fields] OR ("plastic"[All Fields] AND "surgery"[All Fields])

plastic and reconstructive surgery: "Plast Reconstr Surg"[Journal:__jid1306050] OR "Plast Reconstr Surg Glob Open"[Journal:__jid101622231] OR "Plast Reconstr Surg (1946)"[Journal:__jid101243648] OR "Keisei Geka"[Journal:__jid0413676] OR ("plastic"[All Fields] AND "and"[All Fields] AND "reconstructive"[All Fields] AND "surgery"[All Fields]) OR "plastic and reconstructive surgery"[All Fields]

Exparel: "bupivacaine liposome"[All Fields] OR "bupivacaine"[Supplementary Concept] OR "bupivacaine"[All Fields] OR "bupivacain"[All Fields] OR "bupivacaine"[MeSH Terms] OR "bupivacaine's"[All Fields] OR "exparel"[All Fields]

liposomal: "liposomalization"[All Fields] OR "liposomalized"[All Fields] OR "liposomally"[All Fields] OR "liposome's"[All Fields] OR "liposomes"[Pharmacological Action] OR "liposomes"[Supplementary Concept] OR "liposomes"[All Fields] OR "liposomal"[All Fields] OR "liposomes"[MeSH Terms] OR "liposome"[All Fields] OR "liposomic"[All Fields] OR "liposomized"[All Fields]

bupivacaine: "bupivacaine"[Supplementary Concept] OR "bupivacaine"[All Fields] OR "bupivacain"[All Fields] OR "bupivacaine"[MeSH Terms] OR "bupivacaine's"[All Fields]

Liposomal: "liposomalization"[All Fields] OR "liposomalized"[All Fields] OR "liposomally"[All Fields] OR "liposome's"[All Fields] OR "liposomes"[Pharmacological Action] OR "liposomes"[Supplementary Concept] OR "liposomes"[All Fields] OR "liposomal"[All Fields] OR "liposomes"[MeSH Terms] OR "liposome"[All Fields] OR "liposomic"[All Fields] OR "liposomized"[All Fields]

bupivacaine: "bupivacaine"[Supplementary Concept] OR "bupivacaine"[All Fields] OR "bupivacain"[All Fields] OR "bupivacaine"[MeSH Terms] OR "bupivacaine's"[All Fields]

Cochrane Library

#1 ((plastic surgery OR plastic and reconstructive surgery) AND (Exparel OR liposomal bupivacaine OR Liposomal bupivacaine)) with Cochrane Library publication date: Between Jan 2012 and Aug 2024, in Trials (Word variations have been searched)

Web of Science

Database: All Databases

1: TS=([(plastic surgery OR plastic and reconstructive surgery OR plastic & reconstructive surgery) AND (Exparel OR liposomal bupivacaine OR Liposomal bupivacaine OR LB OR bupivacaine liposomal

suspension)]) Editions:
WOS.IC,WOS.CCR,WOS.SCI,WOS.AHCI,WOS.BHCI,WOS.BSCI,WOS.ESCI,WOS.ISTP,WOS.SSCI,WOS.ISSHP,BCI.BCI,CCC.CCCA,CCC.CCCB,CCC.CCCC,CCC.CCCP,CCC.CCCS
Timespan: 2012-01-01 to 2024-08-31.

Embase

('plastic surgery'/exp OR 'plastic surgery' OR (('plastic'/exp OR plastic) AND ('surgery'/exp OR surgery)) OR 'plastic'/exp OR plastic) AND ('reconstructive surgery'/exp OR 'reconstructive surgery' OR (reconstructive AND ('surgery'/exp OR surgery))) AND ('exparel'/exp OR exparel OR 'liposomal bupivacaine'/exp OR 'liposomal bupivacaine' OR (liposomal AND ('bupivacaine'/exp OR bupivacaine))) AND (2012-2024)/py AND 'humans'/exp AND [humans]/lim AND (2012-2024)/py AND english:la AND ('article'/it OR 'review'/it)

ScienceDirect

[(plastic surgery OR plastic and reconstructive surgery) AND (Exparel OR liposomal bupivacaine OR Liposomal bupivacaine)]

Years: Range: 2012 - 2024

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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