Am J Cancer Res 2025;15(8):3728-3739
www.ajcr.us /ISSN:2156-6976/ajcr0165729

Original Article

Effects of liposomal bupivacaine for erector spinae plane block on perioperative immune function and analgesia in thoracoscopic lung cancer surgery

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Received April 29, 2025; Accepted August 18, 2025; Epub August 25, 2025; Published August 30, 2025

Abstract: Objective: To assess the immunomodulatory and analgesic effects of liposomal bupivacaine compared to ropivacaine on erector spinae plane block (ESPB) for patients undergoing thoracoscopic lung cancer surgery. Methods: This retrospective study included 260 patients undergoing thoracoscopic lung cancer surgery. Patients were divided into two groups based on anesthesia methods: the liposomal bupivacaine group (n = 134) and the ropivacaine group (n = 126). Both groups received general anesthesia followed by ESPB. Perioperative inflammatory markers (IL-6, TNF-α, CRP), immunoglobulins (IgA, IgG, IgM), and analgesic outcomes (Numerical Rating Scale (NRS) scores) were measured at various postoperative time points. Cellular inflammatory markers, including white blood cell (WBC) counts and neutrophil percentages, were also assessed. Tumor markers (galectin-3 (Gal-3), carbohydrate antigen 125 (CA125), cytokeratin 21-1 fragment (CY-FRA21-1), soluble programmed death ligand-1 (sPD-L1)) were analyzed at 3-month follow-up. Results: The liposomal bupivacaine group exhibited significantly reduced inflammatory responses with lower levels of IL-6 (P = 0.005), TNF-α (P = 0.007), and CRP (P = 0.01) at 12-72 hours postoperatively. Immunoglobulin levels were better preserved in this group (IgA P = 0.007, IgG P = 0.016, IgM P = 0.033). Analgesia outcomes were superior, with lower NRS scores at 36 h (P = 0.002) and 72 h (P = 0.006). Cellular inflammatory markers, including WBC counts and neutrophil percentages, were also significantly reduced (P < 0.05). At the 3-month follow-up, the liposomal bupivacaine group showed significantly lower levels of tumor markers, particularly sPD-L1 (all P < 0.001). Conclusions: Liposomal bupivacaine for ESPB enhances both immunoprotective effects and postoperative analgesia in thoracoscopic lung cancer surgery.

Keywords: Erector spinae plane block, liposomal bupivacaine, immune function, thoracoscopic surgery, lung cancer, perioperative analgesia

Introduction

Lung cancer remains one of the most prevalent and lethal cancers globally, with thoracoscopic surgery being a common intervention for resectable non-small cell lung cancer (NSCLC) [1]. Despite the minimally invasive nature of thoracoscopic approaches, patients undergoing such procedures experience significant stress and inflammatory responses, leading to perioperative immune suppression [2]. This immune dysfunction increases the risk of postoperative complications, slows recovery, and may facilitate tumor recurrence and metastasis [3]. Consequently, refining perioperative management to alleviate immune suppression has become a key focus in clinical practice [4].

Regional anesthesia techniques, particularly the erector spinae plane block (ESPB), have gained attention for their ability to reduce surgical stress responses while enhancing pain management [5]. First described in 2016, the ESPB delivers local anesthetic to the plane deep to the erector spinae muscle [6]. It offers several advantages, including ease of applica-

https://doi.org/10.62347/SQHE7607

tion, effective multi-dermatomal analgesia for both somatic and visceral pain, and a low risk of major complications [7]. Studies have shown that the ESPB reduces opioid consumption and improves pulmonary function, especially in thoracic procedures [8].

Bupivacaine, a commonly used local anesthetic, is often employed in ESPB [9]. However, its short duration of action limits its clinical application, necessitating repeated doses or indwelling catheters to maintain its effects [10]. Recent advances in pharmaceutical technology have introduced liposomal encapsulation techniques for bupivacaine [11]. This formulation provides controlled release, extending analgesic duration and reducing the frequency of drug administration [12, 13]. The use of liposomal bupivacaine in ESPB for thoracoscopic lung cancer surgeries has emerged as a promising strategy to enhance analgesic efficacy while minimizing systemic exposure and side effects [14].

While considerable research has focused on the pain relief effects of liposomal bupivacaine, its impact on immune function during surgery remains underexplored [15]. The perioperative period plays a crucial role in modulating immune responses [15]. Surgery activates both the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, leading to the release of catecholamines and glucocorticoids. These substances can suppress immune cell function, reduce natural killer (NK) cell activity, and alter cytokine production [16, 17]. These immune changes may not only influence immediate postoperative outcomes but could also contribute to long-term effects, such as tumor progression or metastasis in cancer patients [18].

Several studies suggest that regional anesthesia techniques like ESPB can help preserve immune function by reducing surgical stress and opioid use [19, 20]. Opioids, while effective for pain management, are known to suppress immune function. Liposomal bupivacaine, by reducing opioid requirements, may contribute to maintaining perioperative immune competence [20]. However, the direct effects of liposomal bupivacaine on immune parameters, such as leukocyte subsets, cytokine profiles, and NK cell function in thoracic surgery, have not been thoroughly investigated [21].

The rationale for comparing liposomal bupivacaine with ropivacaine stems from ropivacaine's widespread use as a standard local anesthetic for regional blocks, including ESPB, due to its favorable safety profile and intermediate duration of action [22]. Liposomal bupivacaine's sustained-release properties may reduce surgical stress by decreasing pro-inflammatory cytokines and preserving immunoglobulins. This immune-protective effect, combined with prolonged analgesia, could mitigate the immunosuppression linked to cancer progression [23]. Thus, comparing these agents in ESPB for lung cancer surgery is valuable to evaluate their differential impacts on immune function and recovery.

In addition to opioid-sparing effects, local anesthetics like bupivacaine can modulate immune responses [10]. Bupivacaine has been shown to affect various immune cells, including T cells and macrophages, influencing their activation and function in vitro [19]. However, the clinical significance of these findings, particularly with sustained-release formulations used for ESPB, remains unclear. Understanding the interaction between analgesia, immune modulation, and oncological outcomes is critical for optimizing perioperative management in lung cancer patients. Additionally, studies have demonstrated that both ropivacaine and bupivacaine can impair neutrophil functions, such as reactive oxygen species production, with varying degrees of immunosuppressive effects. However, evidence comparing ropivacaine and liposomal bupivacaine in clinical settings is limited, warranting further research [24]. This study aims to fill the knowledge gap by evaluating the effects of liposomal bupivacaine used in ESPB on perioperative immune function in patients undergoing thoracoscopic lung cancer surgery.

Materials and methods

General information

This study retrospectively analyzed patients who underwent thoracoscopic lung cancer surgery at Yantaishan Hospital from January 2021 to June 2024.

The inclusion criteria were as follows: (1) patients meeting the diagnostic criteria for lung cancer; (2) those meeting surgical indications and having undergone thoracoscopic sur-

gery for lung cancer; (3) classified as ASA I-II [25]; (4) aged 18 years or older; (5) a body mass index between 18 and 32 kg/m^2 [26]; and (6) normal liver and kidney function [27].

Exclusion criteria included: (1) pregnant or lactating individuals; (2) patients with cognitive impairment or mental disorders; (3) individuals with suicidal or violent tendencies; (4) allergies to general anesthetics or study drugs; (5) individuals unable to cooperate due to poor compliance or communication difficulties; (6) excessive alcohol consumption or severe dependence on narcotic drugs; (7) long-term oral administration of opioids or beta-blockers [28]; and (8) presence of other types of malignant tumors.

Patients were categorized into two groups based on their surgical anesthesia methods: the liposomal bupivacaine group (n = 134) and the ropivacaine group (n = 126). Data were collected from the medical record system, including demographic characteristics, surgery and anesthesia duration, and perioperative immune function indicators.

Ethical statement

In accordance with the Declaration of Helsinki (World Medical Association, 2013) [29], medical research involving human participants must prioritize their safety and well-being. This study was approved by Yantaishan Hospital's ethics committee. As the study was retrospective and posed no risk or impact on patients, informed consent was waived.

Anesthesia method

Both groups underwent general anesthesia with mechanical ventilation via a double-lumen bronchial tube. Patients were connected to monitoring devices before induction, and radial artery puncture was performed post-induction for invasive arterial blood pressure monitoring.

Anesthesia procedure

Anesthesia induction for both groups was achieved with propofol (2.5 mg/kg; Jiangsu Enhua Pharmaceutical Co., Ltd., National Medical Products Approval H20123138), sufentanil (0.3 μg/kg; Yichang Renfu Pharmaceutical Co., Ltd., National Medical Products Approval H20054172), and cisatracurium (0.2 mg/kg; Jiangsu Shangyao Dongying Pharmaceutical Co., Ltd., National Medical Products Approval H20133373). For maintenance, sevoflurane (0.7-1.3 MAC) was administered in a fresh air-oxygen mixture (oxygen concentration: 50%-80%; flow rate: 2 L/min) combined with remifentanil (Yichang Renfu Pharmaceutical Co., Ltd., National Medical Products Approval H20030197) infused at 0.05-0.20 μg/(kg·min).

Following general anesthesia induction, ultrasound-guided ESPB was performed on the affected side in both groups. The liposomal bupivacaine group received 266 mg liposomal bupivacaine (Aihengping, 266 mg/20 mL; National Medical Products Approval H2022-3899) diluted in 30 mL physiological saline. The ropivacaine group received 100 mg ropivacaine (Ropivacaine, 10 mg/mL; National Medical Products Approval H20133178) diluted in 30 mL physiological saline.

Intraoperatively, mean arterial pressure was maintained within 20% of baseline, and the bispectral index (BIS) was kept between 40 and 60. Sufentanil dosage was adjusted based on blood pressure and heart rate. After surgery, patients were extubated and transferred to the post-anesthesia care unit (PACU) for observation, and returned to the ward once meeting discharge criteria.

Upon extubation, all patients received a patient-controlled intravenous analgesia (PCIA) pump (Jiangsu Aipeng Medical Technology Co., Ltd., National Medical Device Approval No. 2023-3140406) containing sufentanil (2 μg/kg) in a total volume of 100 mL. The PCIA settings were: no background infusion, a bolus dose of 4 mL, and a lockout interval of 20 minutes. No other analgesics were administered.

Recorded data included surgical duration, intraoperative fluid replacement volume, tracheal intubation time, PACU stay time, and intraoperative occurrences of hypotension or bradycardia.

Perioperative immune function indicators

Venous blood samples were collected at five time points: 24 hours before surgery (T0), 5 minutes after surgery (T1), 12 hours after surgery (T2), 36 hours after surgery (T3), and 72 hours after surgery (T4). White blood cell (WBC) count and neutrophil percentage were analyzed using a fully automated blood cell analyzer

(Mindray BC6800, Shenzhen Mindray Biomedical Electronics Co., Ltd., China). Each sample was processed by centrifugation at 3000 rpm for 10 minutes using a refrigerated high-speed centrifuge (TLD 12A, Hunan Xiangxi Scientific Instrument Factory, China). The separated plasma was stored at -80°C. Interleukin 6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-α) levels were measured using an enzyme-linked immunosorbent assay (ELISA) method (Roche Diagnostics, Elecsys 2010, Switzerland). C-reactive protein (CRP), Immunoglobulin A (IgA), Immunoglobulin G (IgG), and Immunoglobulin M (IgM) levels were determined through immunoturbidimetric analysis using the Mindray SA 5800 automatic specific protein analyzer (Mindray Medical, China).

Pain assessment

At T2/T3/T4, the Numerical Rating Scale (NRS) was used to assess patients' pain intensity. The scale ranges from 0 (no pain) to 10 (the most severe pain imaginable), and patients selected a number based on their subjective pain perception.

Serum tumor markers

At 3 months postoperatively, venous blood (5 mL) was collected in the morning. The blood samples were centrifuged at 3000 rpm (radius: 10 cm) for 5 minutes, and the supernatant was collected. The levels of human galectin-3 (Gal-3), carbohydrate antigen 125 (CA125), and human cytokeratin 21-1 fragment (CYFRA21-1) were measured using enzyme-linked immunosorbent assay (ELISA) kits (Shanghai Enzyme-linked Biotechnology Co., Ltd.). Plasma sPD-L1 levels were measured using a commercial ELISA kit (Human PD-L1 ELISA Kit, Proteintech, KE00074).

Statistical analysis

Statistical analyses were performed using SPSS software version 26.0. Categorical data were expressed as frequencies and percentages, analyzed using the chi-square test. For continuous variables, normality and homogeneity of variance were assessed using the Shapiro-Wilk test. Data following a normal distribution were presented as mean ± standard deviation ($\bar{x} \pm s$), and comparisons between two groups were conducted using independent samples t-tests. Non-normally distributed data were represented by the median and interquartile range (median, IQR) and analyzed using the Mann-Whitney U test. Repeated measures analysis of variance (ANOVA) was used for repeated measurement data, and post-hoc tests with Bonferroni correction were applied when significant differences were detected. For non-normally distributed data, non-parametric methods were employed, such as the Mann-Whitney U test for comparisons between two groups and the Kruskal-Wallis H test for comparisons among multiple groups. A *p*-value of less than 0.05 was considered statistically significant.

Results

Comparison of demographic characteristics

The demographic characteristics were similar between the two groups. The mean age did not differ significantly between the ropivacaine group and the liposomal bupivacaine group (P = 0.358). Gender, body mass index, smoking and drinking histories, as well as the prevalence of common diseases such as hypertension, diabetes, coronary heart disease, and cerebrovascular disease, did not show significant differences (all P > 0.05). Chronic pain was present in a similar percentage of patients in both groups (P = 0.723). Educational levels, marital status, ethnic distribution, pulse rates, and blood pressures were comparable, with no statistical significance found (all P > 0.05). The ASA grade distribution was nearly identical (P = 0.996), ensuring comparable baseline characteristics between the groups. See **Table 1**.

Comparison of surgical indicators

Surgical indicators, including surgery time, intraoperative fluid replacement volume, incidence of hypotension and bradycardia, tracheal intubation times, and PACU stay times, showed no significant differences between the two groups (all P > 0.05). See **Table 2**.

Comparison of postoperative pain score

Repeated-measures ANOVA of NRS scores revealed significant main effects for both Group (P = 0.012) and Time (P < 0.001), along with a significant interaction effect (P = 0.012), indi-

Table 1. Comparison of demographic characteristics between two groups

	Ropivacaine group (n = 126)	Liposomal Bupivacaine group (n = 134)	t/χ^2	P
Age (years)	56.37 ± 7.98	57.32 ± 8.65	0.92	0.358
Female/Male	44 (34.92%)/82 (65.08%)	47 (35.07%)/87 (64.93%)	0.001	0.979
Body Mass Index (kg/m^2)	23.18 ± 1.34	23.21 ± 1.41	0.158	0.875
Smoking history (Yes/No)	38 (30.16%)/88 (69.84%)	35 (26.12%)/99 (73.88%)	0.525	0.469
Drinking history (Yes/No)	35 (27.78%)/91 (72.22%)	33 (24.63%)/101 (75.37%)	0.334	0.563
Basic diseases	36 (28.57%)/90 (71.43%)	33 (24.63%)/101 (75.37%)	0.518	0.472
Hypertension (Yes/No)	18 (14.29%)/108 (85.71%)	19 (14.18%)/115 (85.82%)	0.001	0.98
Diabetes (Yes/No)	3 (2.38%)/123 (97.62%)	5 (3.73%)/129 (96.27%)	0.073	0.787
Coronary heart disease (Yes/No)	6 (4.76%)/120 (95.24%)	4 (2.99%)/130 (97.01%)	0.178	0.673
Cerebrovascular disease (Yes/No)	3 (2.38%)/123 (97.62%)	2 (1.49%)/132 (98.51%)	0.005	0.945
Chronic pain (Yes/No)	77 (61.11%)/49 (38.89%)	79 (58.96%)/55 (41.04%)	0.126	0.723
Educational level (Junior college graduate/College graduate or higher)	106 (84.13%)/20 (15.87%)	112 (83.58%)/22 (16.42%)	0.014	0.905
Marital Status (Married/Unmarried)	118 (93.65%)/8 (6.35%)	124 (92.54%)/10 (7.46%)	0.125	0.724
Ethnicity (Han/Other)	73.98 ± 7.85	74.32 ± 8.65	0.336	0.737
Pulse rate (times/min)	128.65 ± 22.69	127.54 ± 23.54	0.384	0.701
Systolic blood pressure	82.32 ± 17.65	83.15 ± 18.65	0.369	0.713
Diastolic blood pressure	56.37 ± 7.98	57.32 ± 8.65	0.92	0.358
ASA grade			0	0.996
ASA II	94 (74.6%)	100 (74.63%)		
ASA III	32 (25.4%)	34 (25.37%)		

Table 2. Comparison of surgical indicators between two groups

	Ropivacaine group (n = 126)	Liposomal Bupivacaine group (n = 134)	t/χ^2	P
Surgery time (min)	80.65 ± 24.67	81.65 ± 23.93	0.331	0.741
Intraoperative fluid replacement volume (ml)	410.65 ± 91.54	407.65 ± 89.68	0.266	0.790
Intraoperative hypotension	10 (7.94%)/116 (92.06%)	11 (8.21%)/123 (91.79%)	0.006	0.936
Intraoperative bradycardia	8 (6.35%)/118 (93.65%)	8 (5.97%)/126 (94.03%)	0.016	0.899
tracheal intubation time (min)	18.65 ± 3.94	18.95 ± 4.32	0.592	0.554
PACU stay time (min)	37.96 ± 5.98	38.65 ± 5.65	0.949	0.344

PACU: Post-Anesthesia Care Unit.

cating differential trajectories of pain scores between treatment groups (Table S1). At T3 and T4, NRS scores in the ropivacaine group were significantly higher than those in the liposomal bupivacaine group (T3: P = 0.002; T4: P = 0.006; **Figure 1**). At T4, NRS scores were below 3, indicating no or mild pain; however, intergroup differences remained statistically significant. These differences may be clinically meaningful, as even minor reductions in pain can enhance patient comfort and potentially improve recovery outcomes. This suggests that liposomal bupivacaine may exert more sustained analgesic effects.

Comparison of postoperative WBC and neutrophil levels

Repeated-measures ANOVA of WBC counts revealed significant main effects for Group (P = 0.001) and Time (P < 0.001), along with a significant interaction effect (P = 0.015), reflecting distinct white blood cell response patterns between the liposomal bupivacaine and ropivacaine groups (Table S1). At T0 and T1, WBC counts and neutrophil percentages were comparable between the two groups (all P > 0.05; **Table 3**). At T2, the liposomal bupivacaine group exhibited significantly lower WBC levels

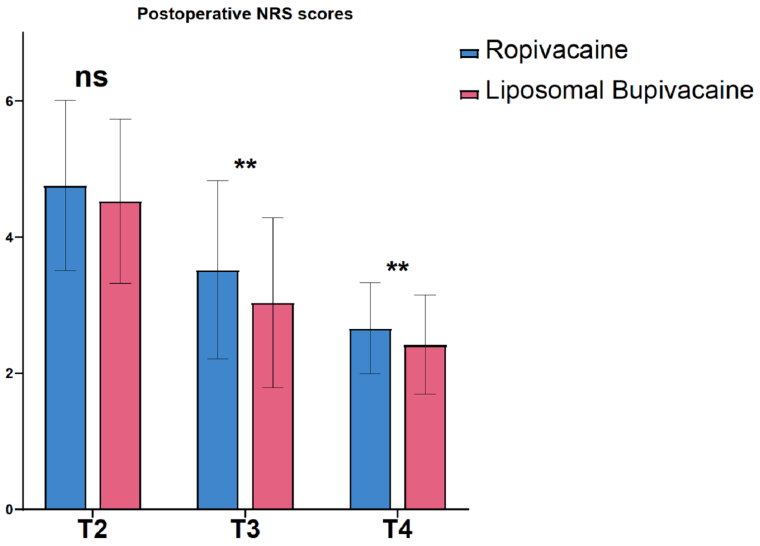

Figure 1. Comparison of postoperative NRS scores between two groups. NRS: Numerical Rating Scale. ns: no statistically significant difference; *: P < 0.05; **: P < 0.01.

Table 3. Comparison of white blood cell and neutrophil levels between two groups

		Ropivacaine group (n = 126)	Liposomal Bupivacaine group (n = 134)	t	P
T0	WBC (109/L)	7.46 ± 1.65	7.53 ± 1.34	0.403	0.687
	Neutrophils (%)	67.85 ± 3.49	67.54 ± 4.01	0.658	0.511
T1	WBC (109/L)	8.05 ± 1.83	8.12 ± 1.28	0.377	0.707
	Neutrophils (%)	69.65 ± 3.68	70.12 ± 4.27	0.937	0.349
T2	WBC (109/L)	12.96 ± 2.25	12.23 ± 2.21	2.609	0.010
	Neutrophils (%)	83.31 ± 4.51	82.16 ± 3.96	2.183	0.030
T3	WBC (109/L)	11.28 ± 1.37	10.82 ± 1.4	2.712	0.007
	Neutrophils (%)	78.17 ± 4.26	77.25 ± 3.07	1.982	0.049
T4	WBC (109/L)	10.35 ± 1.08	9.94 ± 1.35	2.707	0.007
	Neutrophils (%)	73.31 ± 3.24	72.36 ± 2.98	2.459	0.015

WBC: white blood cell.

than the ropivacaine group (P = 0.010). For neutrophil percentages, significant main effects were observed for Group (P = 0.006) and Time (P < 0.001), though the interaction effect did not reach statistical significance (P = 0.096), suggesting parallel but non-converging temporal patterns between groups (Table S1). Similarly, neutrophil percentages were lower in the liposomal bupivacaine group than in the ropivacaine group (P = 0.030). This trend continued at T3, where the liposomal bupivacaine group had lower WBC counts (P = 0.007) and neutrophil percentages (P = 0.049). At T4, WBC levels (P = 0.007) and neutrophil percentages (P = 0.015) remained significantly lower in the liposomal bupivacaine group.

Comparison of inflammatory marker levels

Repeated-measures ANOVAs for IL-6, TNF-α, and CRP consistently revealed significant main effects for Group and Time, along with significant interaction effects (IL-6: all P < 0.001; TNF-α: Group and Time P < 0.001, interaction P = 0.004; CRP: Group and Time P < 0.001, interaction P = 0.003), indicating differential inflammatory responses between the liposomal bupivacaine and ropivacaine groups (Table S1).

At T0, IL-6, TNF-α, and CRP levels were comparable between the two groups, with no significant differences (IL-6: P = 0.299; TNF-α: P = 0.812; CRP: P = 0.822; **Table 4**).

At T1, the absence of significant intergroup differences persisted across all three cytokines (IL-6: P = 0.688; TNF-α: P = 0.785; CRP: P = 0.897; **Table 4**), confirming similar baseline profiles in the early post-surgical phase.

At T2, the liposomal bupivacaine group exhibited significantly lower levels of all cytokines compared to the ropivacaine group: IL-6 (P = 0.007), TNF-α (P = 0.007), and CRP (P = 0.010; **Table 4**).

This trend continued at T3, with the liposomal bupivacaine group maintaining significantly lower levels of IL-6 (P = 0.007), TNF-α (P = 0.045), and CRP (P = 0.040; **Table 4**).

At T4, significant reductions in the liposomal bupivacaine group remained consistent across

Table 4. Comparison of in inflammatory marker levels perioperative period between two groups

	Ropivacaine group (n = 126)	Liposomal Bupivacaine group (n = 134)	t	P
IL-6				
T0	1.97 ± 0.22	1.94 ± 0.23	1.041	0.299
T1	1.57 ± 0.18	1.58 ± 0.17	0.402	0.688
T2	1.47 ± 0.21	1.54 ± 0.22	2.732	0.007
T3	2.69 ± 0.22	2.76 ± 0.23	2.742	0.007
T4	1.72 ± 0.28	1.82 ± 0.26	2.789	0.006
TNF-α				
T0	8.72 ± 1.65	8.77 ± 1.85	0.238	0.812
T1	10.14 ± 2.31	10.21 ± 2.27	0.273	0.785
T2	29.91 ± 6.54	27.84 ± 5.64	2.741	0.007
T3	21.36 ± 4.59	20.18 ± 4.84	2.013	0.045
T4	13.58 ± 3.61	12.34 ± 3.75	2.710	0.007
CRP				
T0	6.45 ± 2.15	6.5 ± 1.98	0.226	0.822
T1	6.78 ± 2.05	6.81 ± 2.04	0.129	0.897
T2	113.83 ± 29.65	104.36 ± 28.94	2.606	0.010
T3	58.61 ± 19.65	53.65 ± 18.97	2.068	0.040
T4	29.41 ± 9.58	26.54 ± 8.73	2.524	0.012

IL-6: Interleukin-6; TNF-α: tumor necrosis factor-alpha; CRP: C-reactive protein.

Table 5. Comparison of immunoglobulin levels in perioperative period between two groups

	Ropivacaine group (n = 126)	Liposomal Bupivacaine group (n = 134)	t	P
IgA				
T0	1.97 ± 0.22	1.94 ± 0.23	1.041	0.299
T1	1.57 ± 0.18	1.58 ± 0.17	0.402	0.688
T2	1.47 ± 0.21	1.54 ± 0.22	2.732	0.007
T3	2.69 ± 0.22	2.76 ± 0.23	2.742	0.007
T4	1.72 ± 0.28	1.82 ± 0.26	2.789	0.006
IgG				
T0	9.06 ± 2.31	9.08 ± 2.24	0.068	0.946
T1	7.94 ± 2.17	7.93 ± 2.14	0.043	0.966
T2	7.02 ± 1.31	7.41 ± 1.25	2.427	0.016
T3	11.04 ± 3.54	11.95 ± 3.62	2.066	0.040
T4	7.68 ± 2.14	8.51 ± 2.17	3.128	0.002
IgM				
T0	1.95 ± 0.43	1.96 ± 0.44	0.213	0.831
T1	1.53 ± 0.41	1.56 ± 0.38	0.532	0.595
T2	1.24 ± 0.34	1.34 ± 0.42	2.148	0.033
T3	1.32 ± 0.32	1.41 ± 0.31	2.384	0.018
T4	1.61 ± 0.45	1.74 ± 0.42	2.348	0.020

IgA: Immunoglobulin A; IgG: Immunoglobulin G; IgM: Immunoglobulin M.

all three cytokines: IL-6 (P = 0.006), TNF-α (P = 0.007), and CRP (P = 0.012; **Table 4**).

Comparison of immunoglobulin levels

Repeated-measures ANOVAs for IgA, IgG, and IgM revealed consistent patterns of significant main effects for Group and Time, with varying interaction effects: IgA showed a significant interaction (P = 0.006), IgG approached but did not reach significance (P = 0.070), and IgM had no significant interaction (P = 0.365). Group and Time effects were significant for all three immunoglobulins (IgA: both P < 0.001; IgG: Group P = 0.001, Time P < 0.001; IgM: both P = 0.001 and P < 0.001, respectively), indicating distinct immunological response profiles between treatments (Table S1).

At T1, IgA, IgG, and IgM levels were comparable between the liposomal bupivacaine and ropivacaine groups, with no statistically significant differences (IgA: P = 0.688; IgG: P = 0.966; IgM: P = 0.595; **Table 5**).

At T2, the liposomal bupivacaine group exhibited significantly higher levels across all three immunoglobulins relative to the ropivacaine group: IgA (P = 0.007), IgG (P = 0.016), and IgM (P = 0.033; **Table 5**).

This trend continued at T3, with the liposomal bupivacaine group maintaining significantly elevated levels of IgA (P = 0.007), IgG (P = 0.040), and IgM (P = 0.018; **Table 5**).

At T4, significant differences persisted, with the liposomal bupivacaine group showing hi-

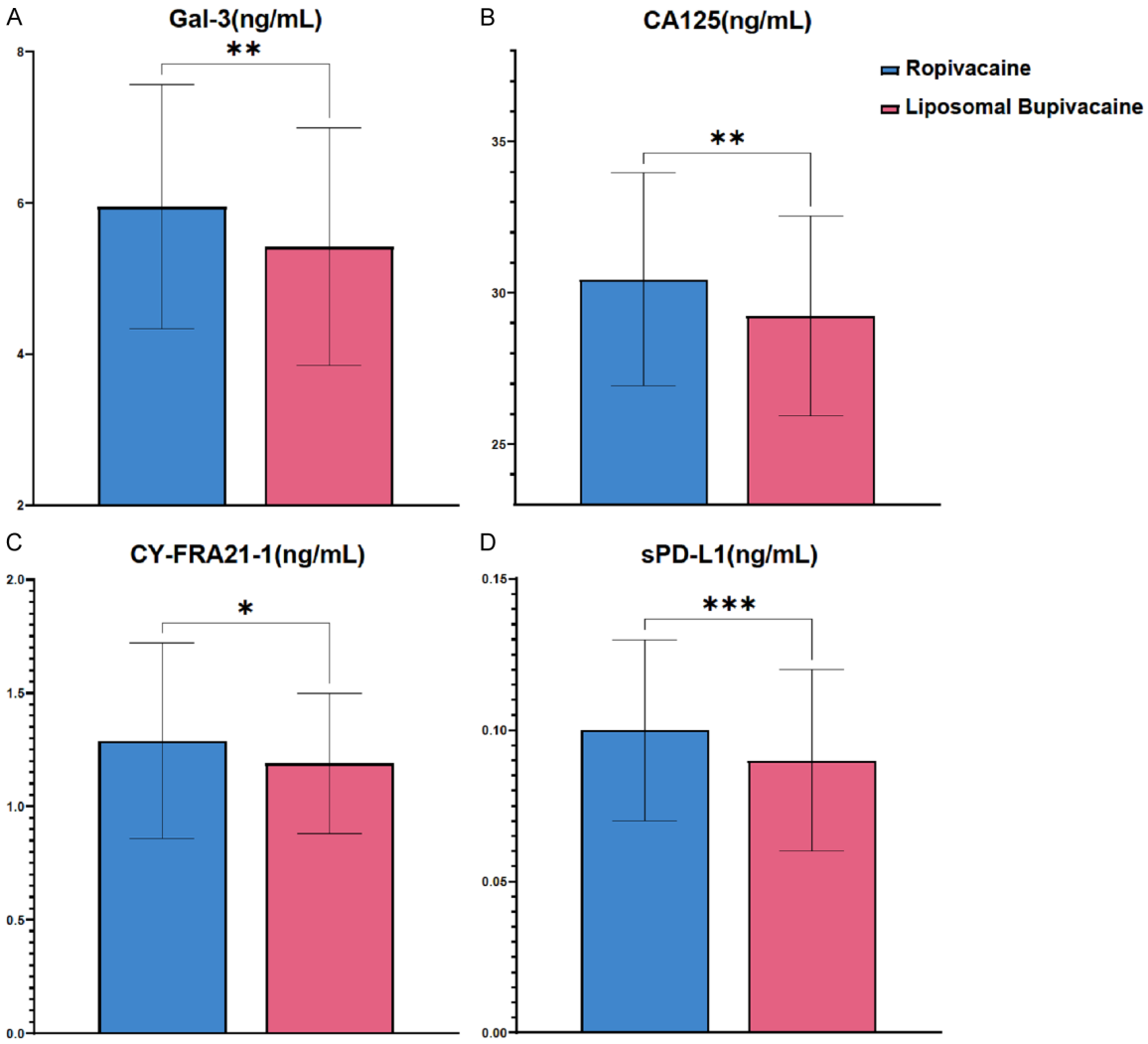

Figure 2. Comparison of serum tumor markers between two groups. A: Gal-3 (ng/mL); B: CA125 (ng/mL); C: CY-FRA21-1 (ng/mL); D: sPD-L1 (ng/mL). Gal-3: Galectin-3, CA125: Carbohydrate Antigen 125, CY-FRA21-1: Cytokeratin Fragment 21-1, sPD-L1: Soluble Programmed Death-Ligand 1. *: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.001$.

gher levels of IgA ($P = 0.006$), IgG ($P = 0.002$), and IgM ($P = 0.020$; **Table 5**).

Comparison of serum tumor marers

Significant differences were observed in serum tumor marker levels between the ropivacaine and liposomal bupivacaine groups (**Figure 2**). Gal-3, CA125, CY-FRA21-1, and soluble PD-L1 levels were significantly lower in the liposomal bupivacaine group (all $P < 0.05$ for all). Notably, the difference in sPD-L1 levels was the most pronounced ($P < 0.001$).

Discussion

This study evaluated the impact of liposomal bupivacaine on perioperative immune function in patients undergoing thoracoscopic lung cancer surgery. Our findings demonstrate that the administration of liposomal bupivacaine significantly influenced perioperative immune function and provided more sustained analgesia, as evidenced by changes in key inflammatory and immune markers, including IL-6, TNF-α, CRP, immunoglobulins, and serum tumor markers. These differences suggest a potential mechanistic pathway through which liposomal bupivacaine might offer advantages over traditional ropivacaine in thoracoscopic lung cancer surgery.

The significantly lower WBC counts and neutrophil percentages in the liposomal bupivacaine group at 12-72 hours post-surgery provide com-

pelling evidence of attenuated surgical stress responses. Neutrophilia typically reflects the severity of surgical trauma, and the reduction in neutrophil percentages observed with liposomal bupivacaine suggests meaningful biological effects.

The inflammatory response to surgery is well-recognized and can affect patient recovery and morbidity. IL-6 and TNF-α are key players in the body's inflammatory response. Elevated levels of these cytokines often indicate a stronger inflammatory reaction, which is associated with prolonged recovery and increased postoperative complications. In this study, patients who received liposomal bupivacaine showed much lower levels of IL-6 and TNF-α at 12, 36, and 72 hours post-surgery compared to those who received ropivacaine. This suggests that liposomal bupivacaine may be more effective in reducing the surgical inflammatory response than ropivacaine.

A possible explanation for this could be the sustained release properties of liposomal bupivacaine [30]. Unlike conventional bupivacaine or ropivacaine, which only provide transient nerve blockade, liposomal bupivacaine is designed to maintain drug concentrations over an extended period. This sustained release may reduce the need for additional analgesics that could intensify systemic inflammation [31, 32]. This prolonged action not only provides effective pain relief but may also help reduce the inflammatory cascade by limiting nociceptive input and stress responses related to pain [33].

Moreover, CRP, an acute-phase reactant synthesized by the liver in response to inflammation, was significantly lower in the liposomal bupivacaine group at multiple postoperative time points. This finding aligns with the cytokine data and supports the idea of reduced systemic inflammation [34]. The lower levels of CRP and cytokines in the liposomal bupivacaine group may contribute to a reduced incidence of postoperative complications, such as infections or prolonged hospitalization, which are often driven by systemic inflammation.

Furthermore, the study revealed that immunoglobulin levels (IgA, IgG, and IgM) were better preserved in the liposomal bupivacaine group. Immunoglobulins play a crucial role in humoral immunity, protecting against infections, which is particularly important during the perioperative period [35]. The ability of liposomal bupivacaine to preserve higher levels of these immunoglobulins suggests a protective mechanism that may enhance immune vigilance and responsiveness postoperatively [36].

The preservation of immunoglobulin levels may be linked to the same underlying mechanisms that govern the cytokine responses: reduced systemic inflammation enables better maintenance of normal immune function [37]. Surgical stress and inflammation typically cause a temporary decline in immune function, increasing the risk of infections [38]. By alleviating inflammation, liposomal bupivacaine may mitigate this weakened immune state, helping maintain the production and function of immunoglobulins [38].

Another potential mechanism for the observed effects relates to the analgesic efficacy of liposomal bupivacaine [39]. Effective pain management plays a significant role in modulating immune function [39]. Uncontrolled pain can activate the hypothalamic-pituitary-adrenal (HPA) axis, leading to immunosuppressive effects [40]. Liposomal bupivacaine's prolonged pain relief may reduce HPA axis activity and the resulting immune suppression, thus helping maintain a strong immune response.

These findings suggest that liposomal bupivacaine may improve surgical outcomes by modulating immune function during the perioperative period. The reduction in inflammation, coupled with preserved immune activity, could lead to fewer postoperative infections, shorter hospital stays, and faster recovery times. This effect aligns well with the goals of enhanced recovery after surgery protocols, which aim to reduce surgical stress responses, optimize pain control, and accelerate recovery. The immunomodulatory properties of liposomal bupivacaine appear to complement these objectives.

While this study provides valuable insights into how liposomal bupivacaine affects immune function during surgery, it has some limitations. The relatively small sample size may limit the generalizability of the findings. Additionally, the study was conducted at a single hospital, where local treatment protocols or patient character-

istics could have influenced the results. Moreover, the study only tracked patients shortly after surgery, leaving the long-term effects on immunity and recovery unclear. Although meaningful changes in immune markers were observed, practical outcomes such as infection rates or surgical complications were not examined - factors that could better illustrate how immune changes relate to patient health. Future studies should involve larger patient populations across multiple hospitals with extended follow-up periods to confirm these results and evaluate their real-world significance.

In conclusion, this study demonstrates that the use of liposomal bupivacaine for ESPB in thoracoscopic lung cancer surgery offers significant benefits. It reduces systemic inflammation while preserving immune function, leading to better recovery outcomes. Future research should explore its long-term effects, patient-reported outcomes, and cost-effectiveness. These findings could contribute to improving pain management guidelines, especially for cancer surgeries and other major operations. Ultimately, this highlights the importance of managing pain in a way that supports overall recovery, rather than just providing short-term relief.

Disclosure of conflict of interest

None.

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Table S1. Repeated measures ANOVA

Effect	F	P
NRS scores		
Group	6.338	0.012
Time	544.380	< 0.001
Group × time	4.439	0.012
WBC scores		
Group	10.521	0.001
Time	437.664	< 0.001
Group × time	3.076	0.015
Neutrophils (%) scores		
Group	7.480	0.006
Time	671.079	< 0.001
Group × time	1.970	0.096
IL-6 scores		
Group	11.630	< 0.001
Time	2312.777	< 0.001
Group × time	5.995	< 0.001
TNF-α scores		
Group	14.037	< 0.001
Time	1157.819	< 0.001
Group × time	3.490	0.007
CRP scores		
Group	14.522	< 0.001
Time	1816.148	< 0.001
Group × time	3.883	0.003
IgA scores		
Group	12.359	< 0.001
Time	1252.044	< 0.001
Group × time	3.551	0.006
IgG scores		
Group	10.129	0.001
Time	125.428	< 0.001
Group × time	2.172	0.070
IgM scores		
Group	9.787	0.001
Time	121.090	< 0.001
Group × time	1.079	0.365