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The Effect of Anesthesia on TGF-β Levels in Lung Tumor Patients Undergoing Bronchoscopy: A Literature Review

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Abstract

Lung cancer remains the leading cause of cancer-related mortality worldwide. Bronchoscopy is a cornerstone diagnostic procedure that frequently requires anesthesia to ensure patient comfort and procedural success. Emerging evidence suggests that perioperative anesthetic exposure may modulate immune responses and cytokine profiles, potentially influencing tumor biology. Transforming Growth Factor-Beta (TGF-β) is a pleiotropic cytokine that exhibits dual roles in carcinogenesis, acting as a tumor suppressor in early stages and a promoter of metastasis and immune evasion in advanced disease. This narrative review evaluates current evidence on the effects of anesthetic agents and techniques on TGF-β levels and their implications for tumor progression in patients with lung tumors undergoing bronchoscopy. A systematic literature search was conducted across PubMed, Scopus, and Google Scholar. Six studies met the inclusion criteria and were synthesized qualitatively. Findings indicate that inhalational anesthetics may upregulate pro-tumorigenic pathways, including TGF-β-mediated epithelial–mesenchymal transition (EMT) and immunosuppression. In contrast, propofol-based total intravenous anesthesia (TIVA) may attenuate inflammatory stress and partially modulate TGF-β signaling. However, direct evidence linking anesthesia to TGF-β dynamics specifically during bronchoscopy remains limited. Standardized prospective studies with serial biomarker monitoring are warranted to clarify perioperative immunomodulation and guide anesthetic selection in oncologic bronchoscopy.

Keywords

Lung Cancer, Bronchoscopy, Anesthesia, TGF-β, Tumor Micro-environment, Immunomodulation

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1. BACKGROUND

Lung cancer remains the leading cause of cancer-related mortality worldwide. According to data from the Global Cancer Observatory (GLOBOCAN) 2020, approximately 1.8 million deaths were attributed to lung cancer (Huang et al., 2022; Sung et al., 2021). In the United States, an estimated 121,680 cases in men and 112,350 cases in women were reported

in 2018. Mortality rates reached approximately 83,550 in men and 70,500 in women. Lung cancer is the second most common malignancy after prostate cancer in men and breast cancer in women (de Groot et al., 2018). The incidence of lung cancer in Europe is comparable to that in the United States. The EUROCARE-5 study reported a 5-year survival rate of approximately 13% in Europe (Barta & Powell, 2019), while in the United States it is around 12% 3, In countries such as Brazil, Bulgaria, and India, survival rates are reported to be less than 10%, whereas Japan has a higher survival rate of 32.9% (Sharma, 2022). Uganda has one of the lowest reported 5-year survival rates at 1.7% (Bogere et al., 2022).

Early detection and prompt management are crucial in improving survival outcomes in lung cancer. Bronchoscopy has become an important diagnostic modality and has demonstrated considerable success. Biswas et al. (2019) reported that a virtual bronchoscopic navigation system achieved a diagnostic success rate of 67.3% and a sensitivity of 72.5%. Similarly, Kano et al. reported a diagnostic success rate of 83.7% using bronchoscopic biopsy.8 In addition to its high success rate and sensitivity, bronchoscopy is also considered a safe procedure. (Biswas et al., 2019; Folch et al., 2020; Kano et al., 2021).

Bronchoscopic procedures often involve the use of anesthesia to facilitate the intervention. Anesthesia plays a critical role not only in diagnostic procedures but also in the overall management of cancer, including lung cancer. Approximately 80% of cancer patients require anesthesia for diagnostic, therapeutic, or palliative procedures. Emerging evidence suggests that anesthesia administered during the perioperative period may influence cancer progression and metastasis (Dubowitz & Sloan, 2017). Anesthesia and surgical stress activate the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system. Activation of the HPA axis suppresses immune function by releasing catecholamines, prostaglandin E2, cytokines, and cortisol, leading to decreased activity of natural killer (NK) cells and cytotoxic T lymphocytes. This process reduces levels of interleukin-2 (IL-2), tumor necrosis factor-alpha (TNF-α), and interferon-gamma, thereby shifting the Th1/Th2 balance toward Th2 dominance. As a result, cell-mediated immunity is suppressed. Catecholamines also stimulate pro-inflammatory cytokines such as IL-6 and IL-8. Meanwhile, anti-inflammatory cytokines, including IL-10, IL-4, and TGF-

β, are also upregulated in response to this imbalance (Kim, 2018).

Lung cancer cells can secrete various growth factors that contribute to tumor progression. One of the key factors is Transforming Growth Factor-Beta (TGF-β), a member of the growth factor family that regulates cell proliferation. TGF-β plays a crucial role in regulating the extracellular matrix composition of alveolar epithelium and induces epithelial–mesenchymal transition (EMT), which enhances tumor invasiveness and cellular migration. The extracellular matrix formed under TGF-β's influence provides a supportive environment for tumor growth. Fibroblasts and mononuclear cells surrounding tumor cells further contribute to the tumor microenvironment and simultaneously produce TGF-β (Khan et al., 2017). Several studies have shown that cancer cells can evade immune surveillance by increasing TGF-β expression. This condition is associated with an increased risk of tumor recurrence and metastasis. High levels of TGF-β expression are also associated with poor prognosis in patients with non-small cell lung cancer (Li et al., 2019).

The immune response following anesthesia is frequently associated with alterations in pro-inflammatory and anti-inflammatory cytokines. These changes may affect the balance of cytokines such as TGF-β, which plays a significant role in lung cancer progression. Suppression of the perioperative immune response may create a favorable environment for tumor survival and metastasis, and modulate the tumor microenvironment through alterations in TGF-β levels.

Understanding the effects of different anesthetic techniques on TGF-β levels is essential to advancing oncologic anesthesia. Insights into how anesthesia influences TGF-β modulation during the perioperative period may help minimize immunosuppression that contributes to tumor progression during surgical or diagnostic interventions such as bronchoscopy. Furthermore, understanding the role of TGF-β may serve as a bridge linking anesthesia, inflammation, and lung cancer progression, ultimately contributing to improved perioperative management and long-term outcomes in patients with lung cancer.

2. METHODS

This study employed a narrative literature review design to evaluate the relationship between anesthesia, immune modulation, and TGF-β levels in lung cancer patients. A systematic search was

conducted in PubMed, Scopus, and Google Scholar using the following Boolean string: ("anesthesia" OR "anesthetic agents" OR "propofol" OR "sevoflurane" OR "TIVA") AND ("TGF-β" OR "transforming growth factor beta") AND ("lung cancer" OR "pulmonary neoplasm" OR "bronchoscopy")

Inclusion criteria: (1) peer-reviewed original articles or comprehensive reviews published in English; (2) studies investigating the effect of anesthetic agents or techniques on TGF-β levels, signaling, or related immune pathways; (3) relevance to lung cancer or perioperative oncology; (4) full-text availability.

Exclusion criteria: (1) animal-only or in vitro studies without clinical/ perioperative relevance; (2) studies focusing exclusively on non-TGF-β biomarkers; (3) conference abstracts, editorials, or duplicate publications.

Articles were independently screened by two reviewers based on titles/abstracts, followed by full-text assessment. Data extraction included the author, year, study design, anesthetic modality, TGF-β- related outcomes, and key findings. Quality appraisal followed standard narrative review principles, emphasizing methodological transparency, biological plausibility, and clinical relevance. The selection process adhered to PRISMA guidelines.

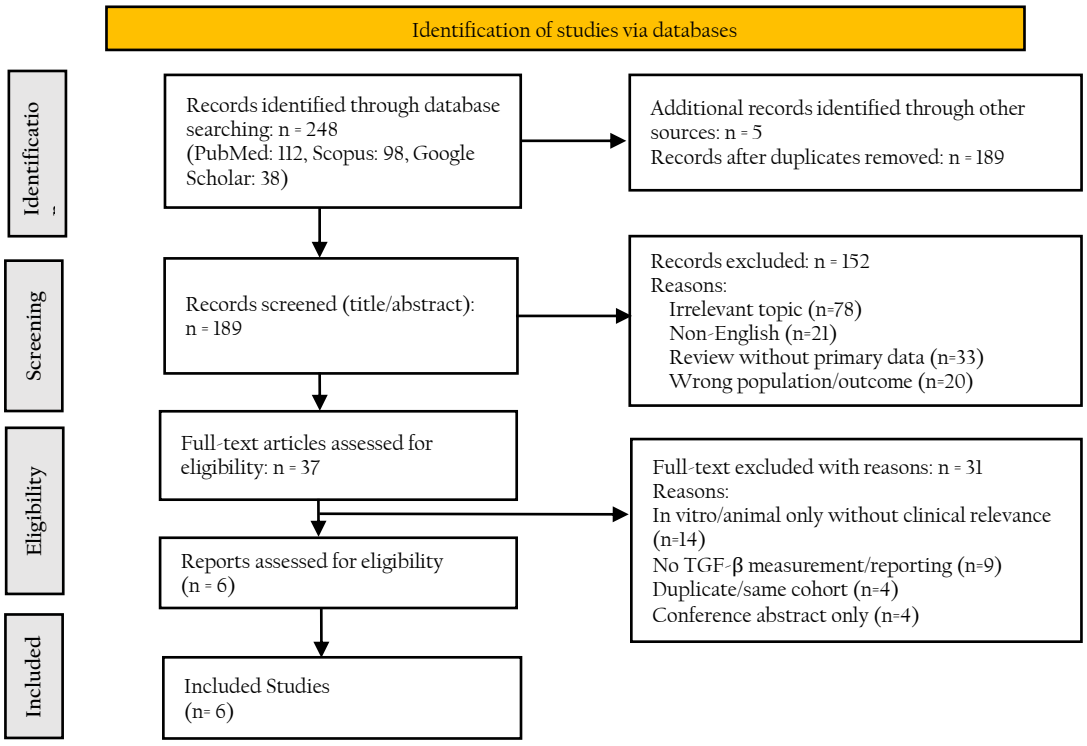

Figure 1. PRISMA Flow diagram Study selection for Review TGF-β in Lung Cancer

3. RESULTS

Table 1. Summary of Included Studies

No	Author(s) (Year)	Title	Methods	Key Findings Related to TGF-β & Anesthesia
1	Aftabi et al. (2025)	Therapeutic targeting of TGF-β in lung cancer	Narrative review	TGF-β transitions from tumor suppressor to metastatic driver; targeting its pathway may overcome chemoresistance and immunosuppression.
2	Baba et al. (2022)	TGF-β Signaling in Cancer-A Betrayal Within	Systematic synthesis	Context-dependent TGF-β signaling; advanced tumors exploit TGF-β for immune evasion and ECM remodeling.
3	Furler (2018)	TGF-β Sustains Tumor Progression through Biochemical and Mechanical Signal Transduction	Mechanistic review	TGF-β integrates mechanical/ECM cues with biochemical signaling; suppresses pro-inflammatory immunity while promoting tumor survival.
4	Ma et al. (2024)	TGF-β in the formation of exhausted CD8+ T cells	Pathway review	TGF-β drives terminal exhaustion of CD8+ T cells; blockade restores anti-tumor immunity, suggesting perioperative relevance.
5	Sheikh et al. (2024)	Exploring TGF-β Signaling in Cancer Progression	Signaling architecture review	Canonical/non-canonical TGF-β pathways crosstalk with PI3K/Akt and Wnt; targeted ligand traps show clinical promise.
6	Xue et al. (2020)	TGF-β: A Multifunctional Regulator of Cancer Immunity	Immunomodulatory review	TGF-β acts as an immune checkpoint; cell-type-specific interactions dictate tumor-promoting vs. suppressive outcomes.

Role of TGF-β as a Tumor Suppressor And Promoter

Transforming Growth Factor-Beta (TGF-β) is a multifunctional polypeptide cytokine involved in various physiological processes, including cell proliferation, differentiation, migration, and apoptosis. Multiple immune cell types produce it and play a crucial role in regulating T-cell differentiation, suppressing T-cell activation, enhancing tolerance in antigen-presenting cells (APCs), and modulating B-cell activity. Dysregulation of TGF-β production or signaling pathways has been implicated in the pathogenesis of various diseases, including cancer, fibrosis, and autoimmune disorders (Aftabi et al., 2025; Ma et al., 2024). Elevated levels of TGF-β expression in both serum and tumor tissues have been associated with increasing tumor grade, suggesting a strong relationship between TGF-β levels and malignant transformation (Aftabi et al., 2025; Xue et al., 2020).

TGF-β exhibits a dual role in cancer biology, functioning as both a tumor suppressor and a tumor promoter. As a tumor suppressor, TGF-β inhibits the

proliferation of normal epithelial and pre-malignant cells and induces apoptosis, thereby preventing carcinogenesis (Furler, 2018). Canonical TGF-β signaling inhibits cell cycle progression at the G1 phase by activating cyclin-dependent kinase inhibitors (CDKIs), including p21 and p15, thereby blocking the transition from G1 to S phase. Additionally, TGF-β suppresses the expression of key proto-oncogenes such as c-Myc, reinforcing its anti-proliferative effects (Baba et al., 2022; Sheikh et al., 2024).

TGF-β-induced apoptosis occurs through regulation of B-cell lymphoma-2 (Bcl-2), activation of death receptors such as Fas, and modulation of genes involved in DNA damage and repair, including GADD45-β, death-associated protein kinase (DAPK), and caspases. Furthermore, TGF-β enhances anti-tumor immune responses by modulating immune cells involved in tumor recognition and elimination. During early carcinogenesis, TGF-β exerts protective effects by arresting the cell cycle, repairing or eliminating damaged cells, and inducing programmed cell death (Baba et al., 2022).

In advanced stages, tumor cells often develop resistance to TGF-β's suppressive effects and instead exploit it as a tumor promoter. Dysregulated TGF-β expression has been reported in multiple malignancies, including lung cancer, hepatocellular carcinoma, colorectal cancer, prostate cancer, and breast cancer. TGF-β promotes epithelial–mesenchymal transition (EMT), enhances tumor invasiveness, stimulates angiogenesis, facilitates immune evasion, and supports metastasis (Sheikh et al., 2024).

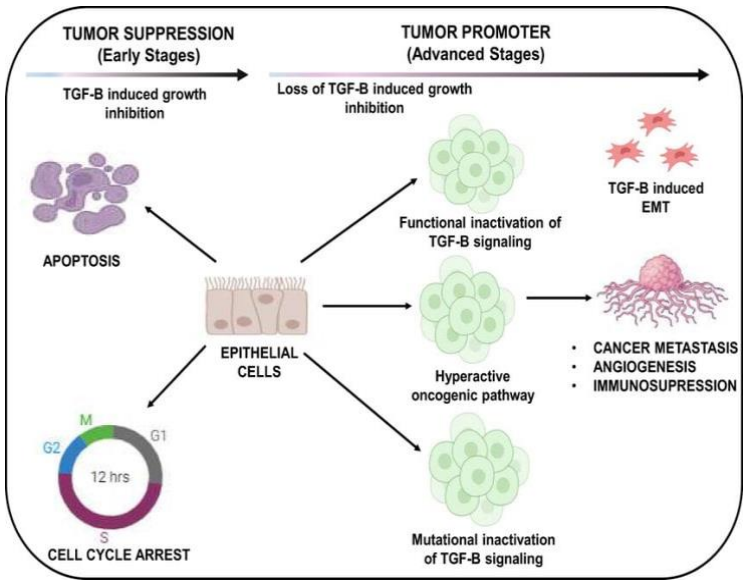

Figure 1. Role of TGF-β as a Tumor Suppressor and Tumor Promoter.

As a key regulator of the tumor microenvironment (TME), TGF-β is secreted by tumor cells, stromal cells (including cancer-associated fibroblasts), endothelial cells, and immune cells such as macrophages, dendritic cells, and T lymphocytes. It promotes extracellular matrix (ECM) deposition, including collagen and fibronectin, contributing to fibrosis and desmoplastic reactions surrounding tumors. These changes increase tissue stiffness, which supports tumor growth and impairs immune cell infiltration (Furler RL, 2018).

GF-β also creates an immune-suppressive environment within the TME by directly inhibiting the function of key anti-tumor immune cells, including cytotoxic T cells, natural killer (NK) cells, and dendritic cells. This enables tumor cells to evade immune surveillance and destruction. Given its central role in immunosuppression and therapeutic resistance, including resistance to immunotherapy, TGF-β represents a promising target for combination treatment strategies. Evaluation of TGF-β levels in cancer patients may help identify subgroups that could benefit from therapies targeting the TGF-β signaling pathway (Baba et al., 2022; Furler, 2018).

4. DISCUSSION

Bronchoscopy in Lung Tumors

Bronchoscopy was first introduced in the 18th century as a rigid illuminated tube used to visualize bronchial branches. The development of fiberoptic bronchoscopy by Ikeda revolutionized pulmonary medicine. In lung cancer, advancements in real-time imaging and catheter-based techniques have expanded the role of bronchoscopy beyond diagnosis to include airway intervention. Bronchoscopy is particularly useful for the early detection of central lung tumors and for peripheral lesions that are difficult to reach with conventional fiberoptic bronchoscopy. Techniques such as computed tomography (CT)-guided procedures, navigation systems, and endobronchial ultrasonography (EBUS) enable accurate targeting. The ability of bronchoscopy to access lung tissue also enables the study of carcinogenesis, the identification of diagnostic and prognostic biomarkers, and the assessment of treatment response (Lee, 2010).

Airway manipulation during bronchoscopy may cause mechanical injury, triggering both local and systemic inflammatory responses. Systemic inflammation following bronchoscopy may manifest as fever, neutrophilia, and increased cytokine levels such as IL-6, IL-

1β, and TNF-α within 12–24 hours after the procedure (Bauer et al., 2001).

Bronchoscopy is generally considered a safe procedure. However, potential complications include bleeding, pneumothorax, fever, infection, and cardiac arrhythmias. Hypoxia is one of the most common complications, particularly in patients undergoing bronchoscopy with sedation, despite oxygen supplementation. This hypoxia is usually transient and resolves spontaneously (Choi et al., 2020). Hypoxic conditions during bronchoscopy may activate Hypoxia-Inducible Factor-1 alpha (HIF-1α) in tumor cells. Under normoxic conditions, HIF-1α is degraded; under hypoxic conditions, it accumulates and translocates into the nucleus, activating genes involved in tumor survival. This activation promotes angiogenesis, glycolysis, tumor invasion, and metastasis (Aerts et al., 2007).

HIF-1α also activates the TGF-β/Smad signaling pathway, enhances extracellular matrix (ECM) synthesis, and promotes fibroblast proliferation. It increases collagen production and fibroblast activity by upregulating connective tissue growth factor (CTGF) and TGF-β. Conversely, TGF-β1 has also been shown to increase HIF-1α expression under both normoxic and hypoxic conditions, indicating a reciprocal regulatory relationship in response to environmental stress (Tai et al., 2023).

Anesthesia and Immune System Modulation

Anesthesia plays a critical role in cancer management. Approximately 80% of cancer patients require anesthesia for diagnostic, therapeutic, or palliative procedures. Similar to surgical stress, anesthesia may influence cancer progression and metastasis (Dubowitz & Sloan, 2017). Anesthesia and surgery activate the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system. This activation suppresses immune function by releasing catecholamines, prostaglandin E2, cytokines, and cortisol. Consequently, the activity of natural killer (NK) cells and cytotoxic T lymphocytes is reduced. This leads to decreased levels of interleukin-2 (IL-2), tumor necrosis factor-alpha (TNF-α), and interferon-gamma, shifting the Th1/Th2 balance toward Th2 dominance and suppressing cell-mediated immunity. Catecholamines also stimulate pro-inflammatory cytokines such as IL-6 and IL-8, while anti-inflammatory cytokines, including IL-10, IL-4, and TGF-β, are upregulated in response to immune imbalance (Kim, 2018). Activation of the

HPA axis also induces the release of neuroendocrine factors such as vascular endothelial growth factor (VEGF) and matrix metalloproteinases, which contribute to tumor growth and angiogenesis. This immune modulation may activate dormant cancer cells (micrometastases) and contribute to treatment resistance (Longhini et al., 2020). Anesthesia during bronchoscopy may involve inhalational agents, such as sevoflurane, for volatile induction and maintenance anesthesia (VIMA), or intravenous agents, such as propofol, for total intravenous anesthesia (TIVA).

Numerous studies have investigated the effects of anesthetic agents and techniques on immune function and cancer progression. Pi et al. (2019) evaluated the effects of combined epidural and general anesthesia on inflammatory responses and postoperative outcomes in patients with lung cancer. Seokha et al. (2019) compared total intravenous anesthesia with inhalational anesthesia in relation to breast cancer recurrence. Other studies have also demonstrated the influence of anesthesia on tumor growth and recurrence (Jing et al., 2022; Lai et al., 2020; Sen & Xiyang, 2019; Seokha et al., 2019). However, current findings remain inconsistent, and the relationship between anesthesia, surgery, and cancer progression is not yet fully understood. Experimental studies suggest that anesthetic exposure may influence tumor growth through immuno-suppression (Dubowitz & Sloan, 2017).

Inhalational Anesthesia and Tumor Cells

Inhalational anesthetics, particularly sevoflurane, are widely used in the management of cancer patients. These agents facilitate both diagnostic and surgical procedures, including bronchoscopy. Emerging evidence suggests that perioperative use of inhalational anesthesia may influence tumor progression through modulation of the immune system. Several studies have demonstrated that sevoflurane may induce proliferation in various cancer cell types. An in vitro study by Zhang et al. reported that sevoflurane promotes tumor cell proliferation and may enhance metastasis in cervical cancer by upregulating histone deacetylase 6 (HDAC6), which activates the phosphatidylinositol 3-kinase (PI3K)/AKT and ERK1/2 signaling pathways (Huang et al., 2019; Jin et al., 2019; Kim et al., 2017). Similarly, Ecimovic et al. demonstrated that sevoflurane increases proliferation, migration, and invasion in estrogen receptor-positive breast cancer cells, and enhances proliferation and migration (but not invasion) in estrogen receptor-negative

breast cancer cells (Ecimovic et al., 2013; Zhang et al., 2020).

In contrast, Wang et al. reported that exposure of lung cancer cells to 3% sevoflurane increased apoptosis and reduced tumor cell dissemination after surgery. This effect was associated with alterations in microRNA expression involved in apoptotic pathways.

Intravenous Anesthesia and Tumor Cells

Propofol is widely used in anesthesia practice, both for induction and maintenance (total intravenous anesthesia, TIVA). Propofol has been shown to modulate immune responses and influence tumor biology. It suppresses pro-inflammatory cytokines, including IL-6, IL-1β, and TNF-α, in various cell types. Propofol exerts its hypnotic effects by activating gamma-aminobutyric acid type A (GABA_A) receptors, which reduce central nervous system excitability. Importantly, several immune cells including monocytes, macrophages, and T cells also express GABA receptors. Activation of these receptors in T cells leads to suppression of cytokine secretion and modulation of cellular proliferation. Propofol also inhibits chemotaxis and phagocytosis of monocytes via GABA_A receptor pathways (Kochiyama et al., 2019).

In breast cancer cells, propofol has been shown to induce apoptosis by inhibiting the miR-24/p27 signaling pathway (Yu et al., 2018). Additionally, propofol reversibly inhibits HIF-1 activity and suppresses HIF-1-mediated gene expression by blocking the synthesis of HIF-1 subunits under hypoxic conditions (Takabuchi et al., 2004). Li et al. reported that propofol effectively inhibits the proliferation of hepatocellular carcinoma cells. It increases TGF-β1 activity and expression by approximately 12% and 20%, respectively, suppresses tumor cell proliferation via the Smad2 signaling pathway, and significantly enhances apoptosis. These findings suggest that propofol has a notable inhibitory effect on the cancer cell cycle.

Effect of Anesthesia on TGF-β

Anesthetic techniques and surgical procedures may influence TGF-β levels, thereby affecting immune responses and postoperative cancer progression. Anesthetic agents may exhibit either pro-tumor or anti-tumor properties, making anesthetic selection an important consideration during the perioperative period, including bronchoscopy. Several studies have investigated the effects of anesthesia and surgery on cancer growth. Evidence suggests that perioperative

anesthesia may influence serum levels of TGF-β and vascular endothelial growth factor (VEGF), both of which play critical roles in tumor growth and progression, particularly in non-small cell lung cancer (Sen & Xiyang, 2019)

Yan et al. compared propofol–remifentanil-based total intravenous anesthesia (TIVA) with inhalational sevoflurane anesthesia in breast cancer surgery. Their findings showed that TIVA significantly reduced surgery-induced VEGF-C release; however, no significant difference in TGF-β levels was observed between the two groups (Yan et al., 2018).

A meta-analysis by Li et al. demonstrated that propofol-based TIVA is associated with lower postoperative IL-6 levels than inhalational anesthesia. However, no significant differences in TGF-β levels were observed between the two techniques (Li et al., 2023). Similarly, a prospective randomized study by Fang et al. in breast cancer patients found no significant differences in TGF-β levels before and after surgery between propofol and sevoflurane groups, suggesting that anesthetic technique may not directly influence TGF-β activity (Fang et al., 2022). Oliveira et al. reported that both sevoflurane and propofol did not affect TGF-β and IL-10 mRNA expression in alveolar macrophages, indicating minimal influence of these anesthetics on TGF-β at the cellular immune level (Oliveira et al., 2023).

In contrast, Sen et al. demonstrated that propofol-based intravenous anesthesia, combined with a thoracic paraspinal block, significantly reduced VEGF and TGF-β levels compared with inhalational sevoflurane anesthesia in lung cancer patients. This effect may be attributed to regional anesthesia's ability to preserve natural killer (NK) cell activity by attenuating the neuroendocrine stress response, enhancing anti-tumor cytokines such as IL-2 and IL-10, and reducing regulatory T cells, Th2 cells, and C-reactive protein levels (Sen & Xiyang, 2019).

A meta-analysis by Tang et al. evaluating long-term outcomes in cancer patients reported that propofol may influence molecular pathways associated with immunomodulation and the tumor microenvironment, including the TGF-β signaling pathway. Propofol appears to preserve anti-tumor immunity by maintaining NK cell activity and inhibiting tumor proliferation and invasion. In contrast, sevoflurane and other inhalational anesthetics may promote the production of factors such as VEGF and hypoxia-related mediators, potentially facilitating tumor progression, including

TGF-β-mediated pathways. Differences between propofol and sevoflurane may be significant in certain cancer types and are likely related to their differential effects on TGF-β expression and activity during the perioperative period (Tang et al., 2024).

5. CONCLUSION

TGF-β plays a critical role in lung cancer biology and immune regulation. Anesthesia has the potential to modulate immune responses and cytokine profiles; however, current evidence regarding its direct impact on TGF-β levels in lung tumor patients undergoing bronchoscopy remains limited. A deeper understanding of the underlying mechanisms and clinical implications requires well-designed prospective studies to clarify the relationship between anesthetic techniques, TGF-β modulation, and immunological processes relevant to tumor progression.

AUTHOR CONTRIBUTIONS

Substantial contributions to conceptualization, data curation, analysis: JJ, EE, MB, and ED. Supervision Writing - review & editing: JJ, MB. Manuscript revisions: EE, and ED

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest in this research.

DATA AVAILABILITY STATEMENT

The data are available from the corresponding author upon reasonable request.

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