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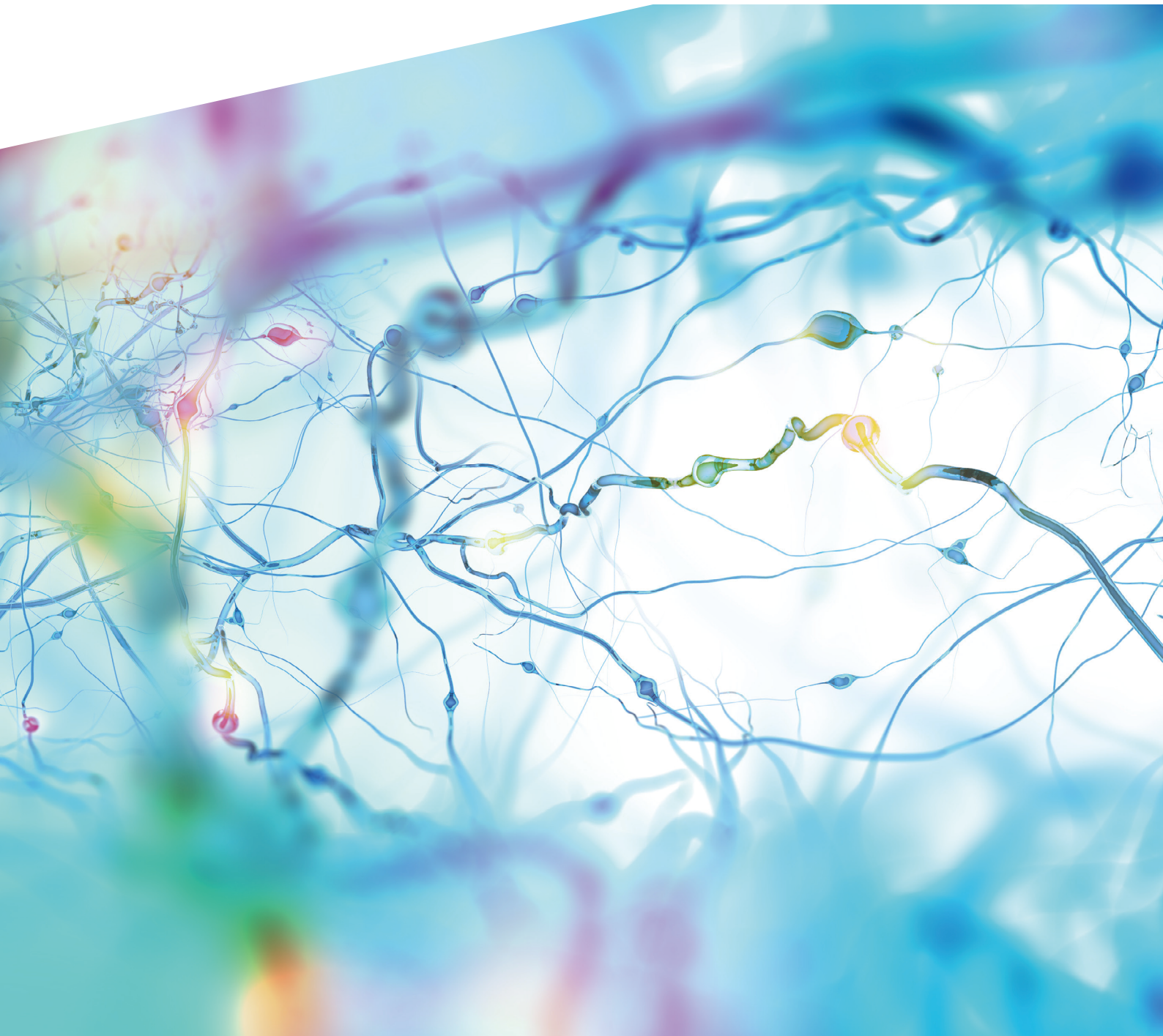

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Aims & scope

Aims

Ewha Medical Journal aims to provide medical professionals with essential healthcare information and fundamental medical knowledge. The journal will contribute to improving and serving human society based on the Christian values of education, truth, goodness, and beauty. Additionally, the journal strives to nurture young editors, enabling them to demonstrate exceptional women's editorial leadership and provide innovative learning methods.

Scope

Its scope includes:

- Up-to-date medical knowledge and skills essential for patient care
- Preparing for the future of medicine
- Effective interprofessional communication
- Ensuring gender equity and diversity
- Medical education materials
- Sharing data and protocols

Regional scope

The journal primarily focuses on Korea but welcomes submissions from researchers worldwide.

Copyright & Open access policy

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Editorial board

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The Ewha Medical Journal

Building on a strong foundation: a new chapter for the *Ewha Medical Journal*

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Advancing the *Ewha Medical Journal*: continuity, quality, and future indexing goals

It is an honor to assume the role of Editor-in-Chief of the *Ewha Medical Journal*. I am deeply grateful to Professor Sun Huh, the previous Editor-in-Chief, for his dedicated leadership over the past 2 years. Under his guidance, the journal achieved substantial growth in publication volume, strengthened its editorial infrastructure, and was indexed in PubMed Central (PMC) [1]. His commitment to scientific rigor and educational mentorship, particularly for undergraduate and early-career authors, has established a strong and durable foundation for the journal's continued development.

The *Ewha Medical Journal* holds a distinctive position as a college-based general medical journal that balances academic excellence with an educational mission. The previous editorship strengthened this dual identity through systematic editorial policies, standardized reporting guidelines, and transparent publication workflows. Together, these efforts improved overall manuscript quality and positioned the journal for broader international visibility.

As we enter this new phase, my primary goal is continuity combined with thoughtful evolution. We will maintain strict adherence to ethical standards and scientific integrity while strengthening thematic coherence, encouraging methodologically sound research, and further refining our editorial focus. Our inclusive and educational ethos will remain central to this mission.

We will pursue strategic inclusion in major indexing databases, including the Korea Citation Index and Scopus. Building on our success with PMC indexing, we aim to enhance article quality, consistency, and visibility, recognizing that indexing is the outcome of sustained editorial discipline and collective scholarly commitment.

The increase in submissions following PMC indexing presents both opportunity and responsibility. A broader submission pool allows for more selective editorial decision-making while simultaneously demanding greater efficiency in the peer-review process. Digital tools, including generative artificial intelligence, may support editorial workflows such as formatting checks and guideline compliance, provided that confidentiality and editorial independence are fully respected [2].

The *Ewha Medical Journal* represents a collective effort. Its progress depends on the dedication of authors, reviewers, editorial board members, and the continued support of the leadership of Ewha Womans University College of Medicine. I look forward to fostering a journal that is methodologically robust, clinically relevant, and educationally meaningful.

Editorial overview of this issue

This issue presents 6 articles spanning infection control, cardiovascular biology, clinical interventions, and professional perspectives.

An opinion article examines norovirus infection control in Korea, critiquing current regulatory practices related to oyster cooking and proposing evidence-based policy improvements. A review article explores the T-cadherin–adiponectin axis in cardiovascular disease, highlighting its therapeutic potential through exosome-mediated myocardial repair.

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The original articles published in this issue address important clinical questions. The first evaluates endoscopic vacuum therapy for gastrointestinal transmural defects, demonstrating high technical success while identifying factors associated with complications. The second investigates the expression of Ki67, estrogen receptor, and HER2 in p16-positive cervical squamous lesions, providing foundational biomarker evidence relevant to cervical neoplasia.

A case report describes glycopyrrolate-induced tachycardia occurring in the left lateral decubitus position, illustrating how ventilatory mechanics may modulate autonomic responses during anesthesia. Finally, a Correspondence article continues our interview series, featuring a dialogue between an alumnus and a junior colleague that highlights professional experiences and intergenerational academic connections.

This issue reflects the collaborative spirit and scholarly excellence that sustain the *Ewha Medical Journal*. Through the collective efforts of our authors, reviewers, and editorial team, we continue to advance clinically meaningful research. I look forward to our shared journey toward greater impact and broader recognition.

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Authors' contribution

All work was completed by Ji Yeon Byun.

Conflict of interest

Ji Yeon Byun has served as the editor of the *Ewha Medical Journal* since January 2026. However, she was not involved in the peer review process or decision-making for this article. No other potential conflicts of interest relevant to this article were reported.

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References

1. Huh S. Leaving behind fond memories, I am stepping away from my role as editor of the Ewha Medical Journal after finalizing this issue's theme. Ewha Med J 2025;48:e51. https://doi.org/10.12771/emj.2025.00962
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Opinion

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The Ewha Medical Journal

Norovirus infection control in Korea: points to consider

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Introduction

Norovirus infection is the most frequent cause of foodborne outbreaks in Korea, with most cases occurring between November and April. Although no studies have quantified the disease burden of norovirus infection in Korea, estimates from the United States Centers for Disease Control and Prevention indicate that norovirus causes 19 to 21 million illnesses, approximately 2.27 million outpatient clinic visits, 109,000 hospitalizations, and 900 deaths annually in the United States [1]. Norovirus is highly contagious, even at very low infectious doses. Transmission typically occurs via the fecal–oral route; however, the virus can also be transmitted through aerosols generated from the vomitus or diarrhea of infected individuals [2]. Because vaccines and antiviral treatments for norovirus infection are not currently available, excluding symptomatic individuals or those exposed to norovirus from food handling or caregiving activities is considered an important strategy to minimize public health impacts.

Humans are the only reservoir for human-infecting noroviruses; therefore, viral particles present in the stool or vomitus of infected individuals constitute the primary sources of transmission [2]. Bivalve molluscan shellfish, such as oysters, are of particular concern in norovirus transmission because they typically inhabit or are harvested from coastal areas that are vulnerable to wastewater contamination and can accumulate the virus through filter-feeding [1]. Consequently, oysters are a well-established vector in foodborne norovirus infections. A UK study reported that oysters accounted for 16% of foodborne norovirus infections between 1992 and 2000 [3]. A high prevalence of norovirus gastroenteritis in the community represents an important risk factor for shellfish-associated norovirus transmission. Therefore, efforts to reduce community-level norovirus incidence should accompany measures aimed at controlling shellfish-related norovirus transmission.

The incidence of norovirus infection in Korea declined in 2020, likely as a result of countermeasures implemented during the COVID-19 (coronavirus disease 2019) pandemic; however, it has increased since 2021. According to the Korean sentinel surveillance system, 3,219 cases of norovirus infection were reported in 2020, a number that doubled to 6,766 in 2024. As of the 46th week of 2025, the cumulative case count for the year had reached 8,172, indicating a continuing upward trend (Fig. 1). This report presents key points to consider for the control of norovirus infections in Korea.

Sources of norovirus: oysters for cooking

In Korea, when oysters test positive for norovirus at the market or are harvested from production areas that test positive for norovirus, they are supplied to the market as "oysters for cooking (OfC)." Although there is no formal definition of OfC, the Korean Food Code defines "oysters for eating raw (OfR)" as packaged whole-shell, half-shell, or shelled oysters that can be eaten raw by consumers and that are harvested from areas meeting water-quality standards. Accordingly, OfC can be understood as oysters that do not meet the criteria for OfR. OfC contaminated with norovirus may increase the risk of norovirus infection at the community level for 3 reasons.

First, OfC can cause cross-contamination of other ready-to-eat (RTE) foods through hands, utensils, or kitchen facilities. Norovirus present in OfC can be inactivated when oysters are adequately heated during cooking. However, viral particles transferred to oth-

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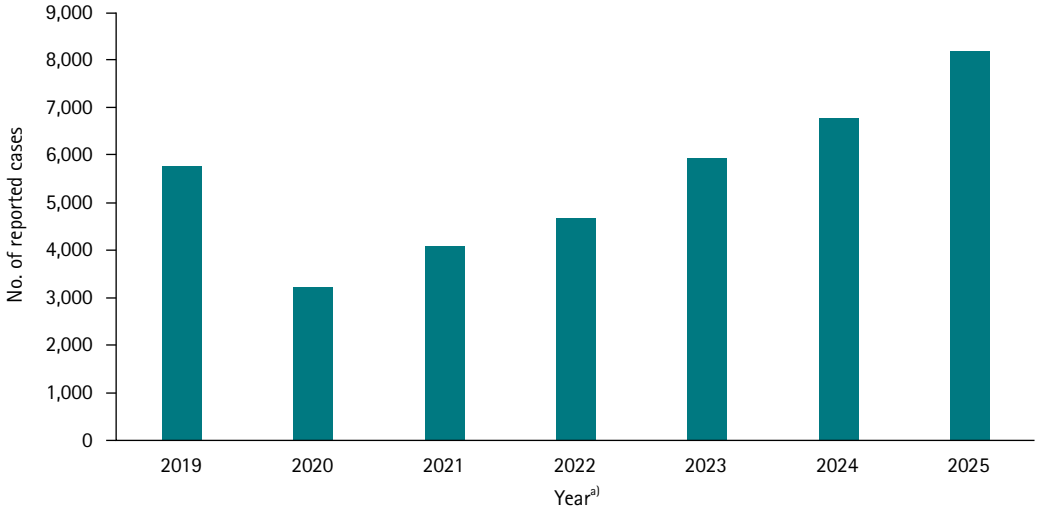

Fig. 1. Annual number of reported norovirus infections in Korea, 2019–2025. Data from the Korea Disease Control and Prevention Agency's sentinel surveillance system (https://dportal.kdca.go.kr/pot/index.do). [a)]Data up to the 46th week were used for 2025.

er objects during food preparation are likely to survive and infect susceptible individuals. Second, OfC can increase the risk of norovirus infection among workers or food handlers during production, distribution, and preparation. If primary infections occur among exposed individuals, secondary transmission is highly likely, particularly to other workers or back to oysters via handling. Such transmission can occur even when infected workers are asymptomatic. Third, OfC are often consumed raw despite being designated for cooking, thereby bypassing the heating step. Medicinal products, which are subject to stricter regulation than food, are frequently involved in medication errors that can significantly compromise safety. Given the comparatively lower level of regulatory oversight for food, it is reasonable to expect that OfC may frequently lead to norovirus infection when consumed raw.

Statistics on the volume of OfC distributed to the market and consumed raw in Korea are not publicly available. In addition, no prior research has examined the risks associated with OfC in relation to norovirus infections in Korea. Consequently, it is difficult to assess the contribution of OfC to the observed increase in norovirus infections. However, Article 4, paragraph 3 of the Food Sanitation Act in Korea prohibits the sale of products that are potentially or genuinely contaminated with pathogens [4]. In the United States, the sale and distribution of potentially contaminated oysters are prohibited by the government [5]. In the United Kingdom and Japan, contaminated oysters must be recalled and cannot be sold [6,7]. Although economic and supply-chain considerations may have influenced current regulatory practices, protection of public health should remain the primary guiding principle when managing potentially contaminated shellfish. Accordingly, Korean regulatory decisions that permit the distribution and sale of oysters that are potentially or genuinely contaminated with pathogens such as norovirus are inconsistent with sound public health policy. Proper regulatory management of OfC should therefore be grounded in valid scientific evidence.

Norovirus transmission in catering, nursing, and childcare settings

Restaurants and childcare facilities are well recognized as settings in which foodborne outbreaks, including norovirus infections, occur frequently. In restaurants, if factors contributing to foodborne diseases are not adequately controlled, causative pathogens can be readily transmitted to a large number of visitors within a short period. In childcare facilities, norovirus infection may lead to serious health complications in children, whose immune systems are still developing. Therefore, minimizing the risk of secondary transmission in these settings is particularly important.

First, the exclusion of food handlers who are infected with or exposed to norovirus should be recommended and actively supported. According to a modeling study of norovirus transmission in restaurants, if infected food workers continue to participate in food preparation, preventive measures such as handwashing, glove use, or toilet cleaning are largely ineffective [8]. Exclusion of ill employees in these settings can be facilitated through ill employee management policies and the provision of paid sick leave. A 2024 Korean study reported that only 10.3% of restaurants in Seoul had ill employee management policies and that 37.5% provided paid sick leave, underscoring the need to implement policies that support this practice [9].

Table 1. Comparison of the definitions of ready-to-eat food

Country	Definition
United States	"Ready-to-eat food" is in a form that is edible without additional preparation to achieve food safety
United Kingdom	A ready-to-eat food is one which is intended to be consumed without any further treatment or processing that would eliminate or reduce pathogens or their toxins to an acceptable level. Examples of ready-to-eat foods include cooked or sliced meats; cheese; washed salads; sandwiches; coleslaw and dips.
Korea	Ready-to-eat food refers to foods manufactured/processed by adding food or food additives to ingredients of animal/plant origin and intended for direct consumption without further heating or cooking processes; and includes lunch boxes, *gimbap* (Korean dried seaweed rolls), hamburgers and sunsik (dry grain food), etc.

U.S. Food and Drug Administration's "Food Code"; Food Standards Agency's "less than thoroughly cooked beef burgers : guidance for food businesses"; Ministry of Food and Drug Safety's "Food Code".

Second, proper handling of RTE food should be recommended and supported. RTE food refers to food that is edible without additional preparation to ensure food safety. This concept is critical for preventing foodborne diseases, because contaminated RTE food—resulting from bare-hand contact or the use of soiled gloves—is consumed without a pathogen-destroying step. To promote appropriate handling of RTE food, the correct definition of RTE food should be formally adopted in the Korean Food Code (Table 1), and policies supporting the use of clean utensils or gloves and preventing bare-hand contact should be developed [9].

Lastly, in childcare and nursing facilities, symptomatic employees and teachers should be immediately excluded from work. Similarly, symptomatic children should not attend school or nursery. Norovirus infection can only be confirmed through laboratory testing, which requires time to yield results. Therefore, exclusion measures to prevent further transmission must be implemented based on clinical symptoms, such as vomiting or diarrhea, rather than being delayed until laboratory confirmation is obtained. Policies supporting home care for symptomatic children, such as childcare services and family care leave, require review and improvement as appropriate. Staff must also be trained in proper methods for cleaning vomitus from norovirus-infected individuals, and adequate cleaning equipment should be readily available.

Norovirus infection statistics: a path toward epidemic control

Appropriate norovirus statistics are essential for tracking epidemic trends and estimating the magnitude of outbreaks. However, data from the Ministry of Food and Drug Safety (MFDS) on foodborne outbreaks do not appear to fully reflect the true trend of norovirus infections. For example, the MFDS reported that the number of norovirus foodborne outbreaks in 2024 decreased by 40% compared with 2023. Given the consistently increasing trend observed since 2021, this reported decrease may not accurately represent the underlying epidemiological pattern of norovirus infections [10]. Accordingly, diverse and detailed data, including modes of transmission and associated risk factors, need to be collected consistently using standardized methods.

Conclusions

The incidence of norovirus infections has increased rapidly in Korea since 2021, highlighting the urgent need for effective countermeasures to control transmission. OfC that are potentially or genuinely contaminated with norovirus may serve as an unrecognized source of infection in the population. Policies related to OfC should therefore be reviewed and amended to ensure safe consumption. In addition, preventive measures that have demonstrated effectiveness, such as exclusion of ill food employees and proper handling of RTE food, should be actively promoted through the implementation of appropriate supporting policies.

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Authors' contribution

Conceptualization: JWL. Methodology/formal analysis/validation: JWL. Project administration: JWL. Writing–original draft: JWL. Writing–review & editing: JWL.

Conflict of interest

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Review article

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The Ewha Medical Journal

Revisiting the multiple roles of T-cadherin and adiponectin in cardiovascular disease: from receptor function to exosome-mediated therapeutic potential

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Cardiovascular disease, particularly ischemic heart disease, remains a leading cause of death worldwide. Although advances in pharmacological and device-based therapies have improved clinical outcomes, effective strategies for myocardial repair and regeneration remain limited. T-cadherin, a glycosylphosphatidylinositol-anchored atypical cadherin, has recently been identified as a functional receptor for both low-density lipoprotein cholesterol and adiponectin, a cardioprotective adipokine. Notably, the interaction between T-cadherin and adiponectin has emerged as a key regulator of exosome biogenesis and paracrine signaling within cardiovascular tissues. Exosomes are nanosized extracellular vesicles that carry protective molecular cargo, including microRNAs and proteins, and contribute to anti-inflammatory, antifibrotic, and angiogenic effects in the ischemic myocardium. However, their clinical translation is challenged by factors such as variability in yield, heterogeneity of exosome populations, and inefficient tissue targeting. Enhancing endogenous exosome production through the T-cadherin–adiponectin pathway may therefore offer a novel cell-free therapeutic strategy. This review explores the biological roles of T-cadherin and adiponectin in cardiovascular diseases, their regulatory influence on exosome formation, and the future potential of leveraging this axis for myocardial repair and regeneration.

Keywords: Adiponectin; Cardiovascular diseases; Extracellular vesicles; Regenerative medicine; T-cadherin

Introduction

Cardiovascular disease, particularly ischemic heart disease, remains the leading cause of morbidity and mortality worldwide, accounting for approximately 17.9 million deaths annually and 32% of all deaths [1]. Despite major advances in pharmacological and interventional therapies, myocardial infarction continues to result in irreversible cardiomyocyte loss and fibrotic remodeling, reflecting the heart's limited capacity for endogenous regeneration. This persistent limitation underscores the pressing need for novel strategies to restore myocardial structure and function.

Among emerging regenerative mechanisms, exosomes, which are small extracellular vesicles that mediate intercellular communication, have attracted increasing attention for their ability to deliver bioactive molecules, including microRNAs, lipids, and proteins. These vesicles are now widely recognized as key effectors of paracrine signaling that contribute to tissue repair and cardiovascular homeostasis.

T-cadherin, an atypical member of the cadherin superfamily, has emerged as an upstream regulator of exosome production and is uniquely anchored to the plasma membrane via a glycosylphosphatidylinositol (GPI) linkage. Unlike classical cadherins, T-cadherin lacks a transmembrane domain and functions primarily as a receptor rather than as a cell adhesion molecule.

T-cadherin binds selectively to high-molecular-weight (HMW) adiponectin, a cardioprotective adipokine, as well as to low-density lipoprotein (LDL), mediating distinct biological responses depending on the ligand involved. Upon adiponectin binding, T-cadherin facilitates its internalization into multivesicular bodies (MVBs), a process that stimulates the biogenesis and release of exosomes enriched with regenerative cargo [2,3]. These adiponectin-induced exosomes have been reported to exert anti-in-

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flammatory, antifibrotic, and angiogenic effects in experimental models of ischemic injury [4,5].

Notably, T-cadherin deficiency abrogates the protective effects of adiponectin in cardiac tissues, underscoring the functional interdependence of this signaling axis [5]. Furthermore, recent evidence suggests that both T-cadherin expression and circulating adiponectin levels are influenced by sex, genotype, and hormonal status, factors that may critically modulate the efficacy of exosome-based therapeutic approaches [6,7].

This review examines the structure and function of T-cadherin and adiponectin, their interactions within cardiovascular contexts, and the emerging concept of leveraging this axis to enhance endogenous exosome-mediated repair. By integrating recent molecular and translational evidence, the T-cadherin–adiponectin–exosome triad is proposed as a promising foundation for next-generation cell-free strategies aimed at myocardial regeneration.

Structural and functional integration of T-cadherin and adiponectin

Structure and ligand-binding properties of T-cadherin

T-cadherin (CDH13) is a structurally distinct member of the cadherin superfamily that lacks the canonical transmembrane and cytoplasmic domains present in classical cadherins. Instead, it is anchored to the outer leaflet of the plasma membrane through a GPI moiety, which allows it to function primarily in ligand binding and signal organization rather than in cell–cell adhesion [8]. The extracellular domain of T-cadherin consists of 5 tandemly arranged cadherin repeats (EC1–EC5) that mediate homophilic dimerization as well as selective ligand binding. Structural modeling studies indicate that EC1 and EC2 are pivotal for ligand engagement and receptor conformational stability [9,10]. This unique architecture positions T-cadherin as a modulator of extracellular signaling, particularly in vascular and metabolic tissues.

Notably, T-cadherin selectively binds the HMW forms of adiponectin and exhibits markedly lower binding affinity for globular or low-molecular-weight isoforms, suggesting a preferential and functionally significant role in the retention and intracellular trafficking of the HMW isoform [4].

In addition to adiponectin, T-cadherin also binds LDL. However, in contrast to the protective effects mediated by adiponectin, LDL–T-cadherin binding appears to promote pro-atherogenic oxidative stress and vascular dysfunction, particularly under atherosclerotic conditions [11]. Furthermore, the interaction between LDL and T-cadherin is functionally distinct. Specific binding of LDL to T-cadherin can be competitively reduced by anti-apolipoprotein B antibodies, indicating that apolipoprotein B serves as a recognition site [10]. Notably, LDL modifications, such as acetylation or carbamylation, do not significantly affect this interaction, in contrast to classical apolipoprotein B/E receptors. Moreover, the T-cadherin–LDL interaction is biologically active, promoting cell migration along LDL gradients and initiating mitogenic signaling in endothelial and epithelial cells through calcium mobilization, ERK1/2 phosphorylation, and nuclear translocation of NF-κB [10]. This ligand-dependent functional dichotomy underscores the context-specific role of T-cadherin as a receptor for distinct ligands and as a signaling scaffold that modulates cellular outcomes in response to extracellular cues.

In addition to its dual role as a receptor for both HMW adiponectin and LDL, T-cadherin contributes to intracellular regulatory events, particularly those related to vesicle biology. Despite lacking a cytoplasmic tail, T-cadherin indirectly influences intracellular signaling by partitioning into lipid rafts, where it facilitates receptor clustering and signalosome assembly in coordination with proteins such as caveolin-1, a lipid raft–associated scaffolding protein [12]. Through these interactions, T-cadherin may modulate key cellular processes, including endocytosis, ceramide efflux, and exosome biogenesis. Indeed, T-cadherin has been shown to spatially regulate MVB organization, a critical step in exosome release, particularly in response to adiponectin stimulation [2,3].

Clinically, T-cadherin is expressed in cardiovascular tissues, including endothelial cells, smooth muscle cells, and cardiomyocytes, and its expression is reduced in pathological conditions such as heart failure and atherosclerosis [13,14].

Adiponectin physiology and its receptors

Adiponectin is an adipocyte-derived hormone that circulates at high concentrations and exerts broad protective effects on the cardiovascular system. It exists in several multimeric forms, including low-molecular-weight trimers, middle-molecular-weight hexamers, and HMW multimers. Among these isoforms, the HMW form is considered the most biologically active in cardiovascular tissues, particularly in anti-inflammatory, insulin-sensitizing, and anti-atherogenic contexts [15-17].

During puberty, a notable decrease in circulating adiponectin levels is observed in males. In addition, adiponectin levels are known to increase with advancing age. A circadian variation of approximately 20% in adiponectin concentration occurs over a 24-hour period, with levels declining overnight and reaching their nadir in the early morning. This diurnal fluctuation is more pronounced in females than in males, but it does not appear to differ according to obesity status [18].

Adiponectin exerts its effects through 3 main receptors: AdipoR1, AdipoR2, and T-cadherin [14]. AdipoR1 is predominantly

expressed in skeletal muscle and exhibits high affinity for globular adiponectin, whereas AdipoR2 is primarily expressed in the liver and mediates peroxisome proliferator-activated receptor-α (PPARα)–dependent signaling pathways [19]. In contrast, T-cadherin binds specifically to the HMW form of adiponectin and is highly expressed in cardiovascular tissues, including endothelial cells lining blood vessels, cardiomyocytes, smooth muscle cells, and the microvascular endothelium of skeletal muscle and the aorta [5,20]. This tissue distribution supports a central role for T-cadherin in vascular homeostasis and cardiac remodeling [20]. Unlike circulating adiponectin levels, adiponectin receptor expression in adipose tissue does not differ between sexes. However, in contrast to adipose tissue, adiponectin receptors are more highly expressed in the skeletal muscle of males. Interestingly, circulating adiponectin levels are lower in males than in females, a pattern that may be partially explained by increased receptor expression in male skeletal muscle [18].

Sex-specific modulation and competitive ligand dynamics of the T-cadherin-adiponectin axis

The 2 ligands for T-cadherin, adiponectin and LDL, are both large molecular complexes of comparable size. LDL particles are roughly spherical, with diameters of approximately 18–25 nm, whereas HMW adiponectin forms fan-shaped or compact, bunch-like structures, with globular domains extending up to 25–32 nm [14]. This structural similarity suggests the possibility of direct competition between LDL and HMW adiponectin for binding to T-cadherin [10].

This competition has important clinical implications because ligand concentrations fluctuate under physiological and pathological conditions. Under normal physiological conditions, the circulating concentration of LDL (approximately 0.6 mg/mL, protein basis) and adiponectin (approximately 1–30 μg/mL, representing levels 103–106-fold higher than those of typical hormones and cytokines) are relatively balanced [21]. However, in pathological states such as metabolic syndrome, LDL levels can rise above 2 mg/mL, while adiponectin concentrations may fall below 1 μg/mL.

This imbalance shifts the ligand ratio by more than tenfold in favor of LDL, potentially leading to the competitive displacement of cardioprotective adiponectin by atherogenic LDL at the level of T-cadherin binding [10]. Affinity data support this dynamic, as the dissociation constant of LDL for T-cadherin is approximately 40 μg/mL, whereas HMW adiponectin achieves half-maximal binding at a substantially lower concentration of approximately 2.2 μg/mL.

Hypoadiponectinemia, commonly defined as plasma adiponectin levels below 4 μg/mL, has been associated with impaired glucose and lipid metabolism and an increased risk of coronary artery disease, particularly in men without a prior history of cardiovascular disease [14,17]. Adiponectin exhibits clear sexual dimorphism, with women consistently displaying higher circulating levels than men [22]. Notably, menopause does not appear to affect adiponectin levels, and neither oophorectomy nor estrogen replacement therapy alters plasma adiponectin concentrations in women [22]. Similarly, oophorectomy in female mice does not result in significant changes in adiponectin levels [23]. In contrast, castration of male mice leads to a marked increase in adiponectin levels [24]. Likewise, in cell culture models, testosterone treatment reduces both circulating adiponectin levels and adiponectin secretion while simultaneously inducing insulin resistance. Collectively, these findings suggest that adiponectin deficiency may contribute to the elevated cardiovascular risk observed in men and that sex-based biological differences modulate the T-cadherin–adiponectin signaling axis [20].

In addition to sex-related hormonal and receptor differences, previous studies have demonstrated that plasma adiponectin levels are inversely correlated with body mass index and positively associated with age, indicating that metabolic and demographic variables jointly shape adiponectin signaling [25,26]. Therefore, a comprehensive framework incorporating sex, body mass index, and age is essential for elucidating the pathophysiological role of the T-cadherin–adiponectin axis and for developing more precise strategies for cardiovascular disease prevention and treatment.

Exosome biogenesis triggered by T-cadherin–adiponectin interaction

Upon binding to T-cadherin on the surface of cardiovascular cells, particularly endothelial cells and cardiomyocytes, HMW adiponectin initiates a noncanonical yet highly effective cardioprotective pathway. Unlike AdipoR1 and AdipoR2, which signal through intracellular phosphorylation cascades such as AMPK and PPARα, the T-cadherin–adiponectin axis does not involve direct enzymatic signaling within the cytoplasm. Instead, it depends on the biophysical clustering of GPI-anchored T-cadherin within lipid rafts, leading to recruitment of endocytic machinery and subsequent formation of MVBs [2].

These MVBs subsequently mature and release exosomes and nanovesicles containing diverse bioactive cargo, including angiogenic proteins, lipids, and microRNAs such as miR-126 and miR-21. Once secreted, these exosomes are taken up by neighboring or distant cardiovascular cells, thereby mediating paracrine effects that promote endothelial repair, stimulate capillary growth, attenuate proinflammatory signaling, and suppress myocardial fibrosis

[27,28]. This exosome-driven paracrine communication plays a critical role in maintaining vascular homeostasis, limiting infarct size during ischemic events, and facilitating cardioprotection [3,5,28].

The importance of this pathway is further underscored by experimental findings showing that deletion of the T-cadherin gene abolishes the tissue-binding and cardioprotective functions of adiponectin, despite adequate systemic levels of the hormone [2,4]. Thus, T-cadherin functions as a molecular gatekeeper for adiponectin-induced exosomal signaling in the heart.

The role of adiponectin beyond competitive binding dynamics

In addition to promoting exosome biogenesis through its interaction with T-cadherin, adiponectin exerts a distinct cardioprotective effect by directly inhibiting atherogenic LDL. Adiponectin interacts with modified LDL species, including oxidized LDL (oxLDL) and L5, forming molecular complexes that effectively neutralize their pathogenic activity. This neutralization occurs at physiological adiponectin concentrations and is independent of classical adiponectin receptor–mediated signaling pathways. Notably, adiponectin-bound oxLDL fails to trigger downstream inflammatory responses, including NF-κB activation and oxidative stress. Together, these findings identify an additional anti-atherogenic mechanism of adiponectin that involves direct ligand neutralization, as demonstrated in both in vitro and in vivo models [29].

Adiponectin also stabilizes T-cadherin protein on the plasma membrane by inhibiting its cleavage by GPI-specific phospholipases and is likely to prevent T-cadherin propeptide cleavage [10,21] (Fig. 1A). In T-cadherin-deficient mice, adiponectin fails to associate with tissues and instead accumulates in the circula-

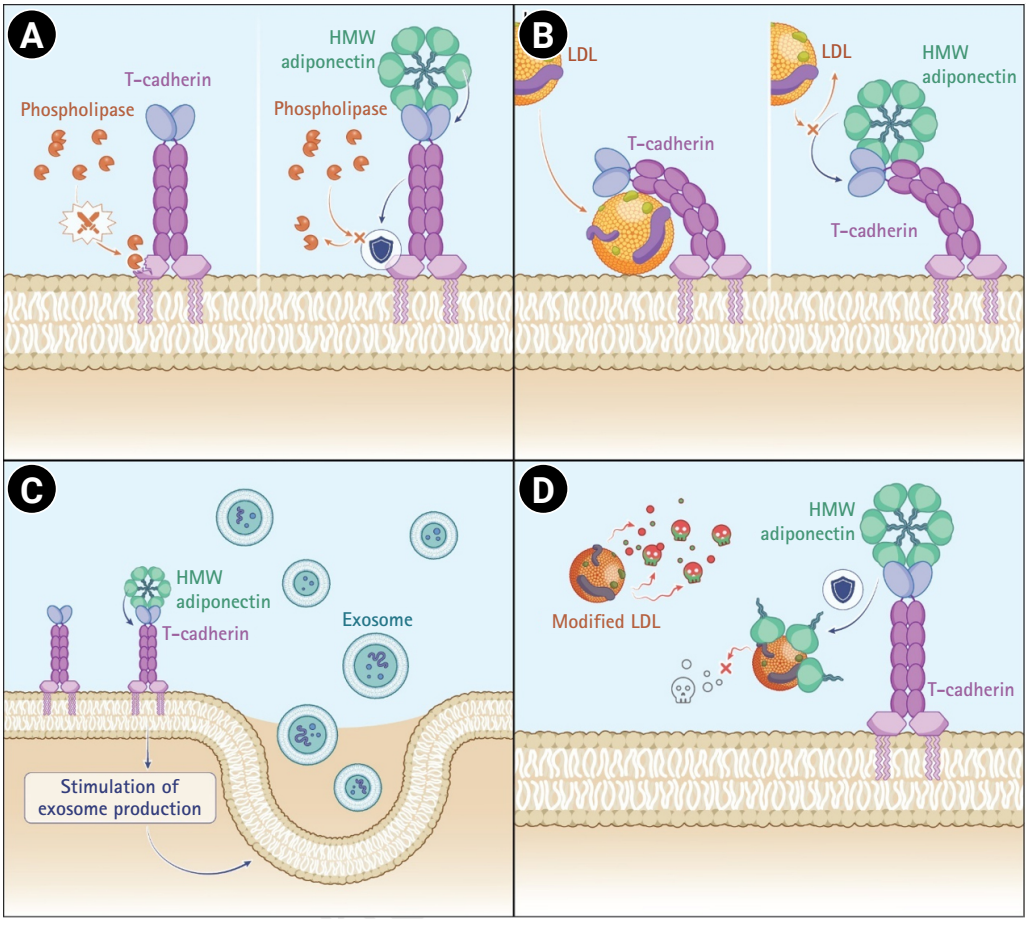

Fig. 1. High-molecular-weight (HMW) adiponectin–T-cadherin mechanism: 4 core cardioprotective effects. HMW adiponectin exerts 4 major actions: (A) stabilizing membrane-anchored T-cadherin by inhibiting phospholipase-mediated glycosylphosphatidylinositol (GPI)-anchor cleavage; (B) acting as a competitive ligand against atherogenic low-density lipoprotein (LDL) for T-cadherin binding; (C) promoting cardioprotective exosome production through engagement with T-cadherin; and (D) directly neutralizing the harmful effects of modified LDL through molecular complex formation.

tion, thereby mimicking the cardiovascular phenotype observed in adiponectin knockout models. Enzymatic cleavage of T-cadherin using phosphatidylinositol-specific phospholipase C increases plasma adiponectin levels while reducing tissue-bound adiponectin. In vivo animal studies further demonstrate that both circulating and tissue-bound adiponectin levels depend on T-cadherin expression. Thus, T-cadherin acts as a critical modulator of adiponectin distribution between the bloodstream and peripheral tissues. Moreover, adiponectin positively regulates T-cadherin protein expression, likely by suppressing enzymatic cleavage of T-cadherin, thereby establishing a positive feedback loop that reinforces adiponectin binding to T-cadherin at the plasma membrane [21].

Thus, adiponectin confers cardiovascular protection through 4 complementary mechanisms (Fig. 1): (1) stabilization of membrane-anchored T-cadherin through inhibition of GPI-anchor cleavage by phospholipases and regulation of propeptide processing to promote surface retention of the pro-form; (2) competitive binding against atherogenic LDL for T-cadherin engagement; (3) stimulation of cardioprotective exosome production via interaction with T-cadherin; and (4) direct neutralization of modified LDL species through molecular complex formation. Collectively, these pleiotropic actions position adiponectin as a central regulator of vascular homeostasis and a promising therapeutic target in atherosclerotic cardiovascular disease.

Cardiovascular clinical implications of the T-cadherin–adiponectin axis

Atherosclerosis

T-cadherin modulates endothelial responses to LDL, while adiponectin directly binds oxLDL [29,30]. Together, T-cadherin and adiponectin inhibit foam cell formation, reduce vascular inflammation, and modulate lipid uptake within the arterial wall [31,32]. Elevated plasma LDL levels combined with reduced adiponectin concentrations are characteristic features of atherosclerosis, dyslipidemia, and metabolic syndrome [14]. Genetic models deficient in T-cadherin exhibit enhanced atherogenesis, even in the presence of normal circulating adiponectin levels [5].

Genetic investigations and experimental studies in preclinical models have provided robust evidence supporting the cardioprotective role of the T-cadherin–adiponectin axis in atherosclerosis. Mouse models lacking T-cadherin develop larger and more advanced atherosclerotic plaques with increased inflammatory cell infiltration, even when circulating adiponectin levels are preserved [5]. Similarly, adiponectin-knockout mice exhibit exaggerated lipid accumulation and heightened vascular inflammation [4].

Genome-wide association studies (GWAS) further support these observations. Polymorphisms in *CDH13* (e.g., rs3865188) and *ADIPOQ* (e.g., rs266729) are associated with interindividual variation in adiponectin levels and susceptibility to coronary artery disease [33,34]. A pilot study demonstrated that carotid intima-media thickness is inversely correlated with HMW adiponectin levels in males, and that the G allele of the rs12444338 single-nucleotide polymorphism in the *CDH13* gene is associated with lower circulating T-cadherin levels and reduced intima-media thickness, a profile that may be considered atheroprotective [35].

Collectively, these findings highlight the dual role of T-cadherin as a receptor for both adiponectin and atherogenic LDL and underscore the importance of adiponectin bioavailability, mediated by its binding to T-cadherin and its capacity to suppress oxidized LDL, in regulating atherogenic processes. Together, these insights support the T-cadherin–adiponectin axis as a promising target for preventive and therapeutic strategies in cardiovascular disease.

Myocardial injury and fibrosis

Animal models of myocardial infarction have demonstrated that T-cadherin is essential for local adiponectin-mediated cardioprotection. In the absence of T-cadherin, infarct size increases, neovascularization is suppressed, and ventricular function deteriorates as a result of impaired AMPK activation and increased myocardial apoptosis [5]. T-cadherin and adiponectin also regulate fibroblast activation and extracellular matrix remodeling. When this axis is downregulated, myocardial fibrosis and left ventricular hypertrophy are exacerbated, thereby contributing to the development and progression of heart failure [13]. Furthermore, T-cadherin is required for adiponectin-induced vascular regeneration, as demonstrated in hindlimb ischemia models, in which T-cadherin deficiency abolishes revascularization despite preserved adiponectin levels [36]. These findings indicate that T-cadherin mediates the acute cardioprotective effects of adiponectin and plays a central role in long-term structural remodeling following myocardial injury.

Therapeutic modulation of adiponectin and T-cadherin pathway

Lifestyle interventions: exercise and metabolic modulation

Regular endurance exercise and caloric modulation have been implicated in regulating the adiponectin–T-cadherin axis. Circulating adiponectin levels are responsive to lifestyle interventions. A comprehensive meta-analysis demonstrated that aerobic exer-

cise significantly increases circulating adiponectin levels in prediabetic and diabetic adults, independent of weight loss [37]. T-cadherin expression is likewise sensitive to metabolic cues and lifestyle factors. In murine models, caloric overload followed by caloric restriction has been shown to upregulate both adiponectin and T-cadherin expression in cardiac tissues. This nutritional modulation is accompanied by improvements in mitochondrial function, enhanced AMPK and endothelial nitric oxide synthase activity, and attenuation of oxidative stress markers, highlighting a potentially synergistic mechanism through which energy balance influences the adiponectin–T-cadherin axis [38].

Pharmacological modulation

Among pharmacological agents, thiazolidinediones such as pioglitazone are known to significantly increase adiponectin levels, particularly the HMW isoform, thereby improving insulin sensitivity and endothelial function [31]. In addition, sodium–glucose cotransporter 2 inhibitors, including empagliflozin, have been associated with elevated adiponectin concentrations, which may partially explain the cardiovascular benefits observed in patients with heart failure and diabetes [39]. In contrast, statins exert variable effects on adiponectin levels. Pravastatin does not alter adiponectin levels in healthy individuals but has been shown to increase plasma adiponectin concentrations in patients with impaired glucose tolerance or coronary artery disease [40]. Conversely, rosuvastatin significantly reduces both total and HMW adiponectin levels [41], whereas fluvastatin, atorvastatin, and simvastatin exhibit minimal or inconsistent effects [19].

Given the anti-inflammatory and insulin-sensitizing properties of adiponectin, such variability may partially explain the differential effects of statins on metabolic syndrome and cardiovascular outcomes. Alterations in adiponectin levels may influence atheroprotection and metabolic control, with important implications for precision medicine. Taken together, pharmacological strategies that increase adiponectin levels may enhance T-cadherin-mediated cardioprotective pathways, particularly in patients with hypoadiponectinemia or metabolic syndrome.

Although no approved therapy directly targets CDH13, several pharmacological agents may indirectly modulate its expression. Recent studies have shown that pharmacological activators of hypoxia-inducible factor-1 (HIF-1), including roxadustat and daprodustat, significantly upregulate T-cadherin expression in vitro. These agents enhance CDH13 transcription in murine endothelial cells under hypoxic conditions, suggesting that HIF-1 activation may represent a viable therapeutic strategy for increasing T-cadherin expression in ischemic cardiovascular settings [42].

Gene therapy and exosome-mediated regenerative approaches

In addition to endogenous modulation, preclinical studies have highlighted the therapeutic potential of directly augmenting T-cadherin expression through gene delivery approaches. Notably, T-cadherin appears to be essential for adiponectin-induced exosome biogenesis, providing a mechanistic link between receptor function and downstream regenerative signaling cascades [2]. These exosomes carry microRNAs and proteins that mediate angiogenesis, exert antifibrotic effects, and promote cardiomyocyte survival, thereby representing a promising therapeutic avenue for myocardial repair [2,3]. Upregulation of T-cadherin in cardiovascular tissues has been associated with increased extracellular vesicle release, suggesting a potential role for this pathway in myocardial repair following ischemic injury [2,5,42].

However, the direct causal relationship between cardiac-specific overexpression of T-cadherin and enhanced myocardial recovery—particularly through extracellular vesicle–mediated mechanisms—has not yet been fully elucidated. Further *in vivo* studies employing targeted gene delivery systems, such as adeno-associated viral vectors, are warranted to validate this mechanism and to explore its therapeutic potential in ischemic heart disease. Collectively, these findings support a multifaceted strategy for enhancing T-cadherin activity, encompassing both systemic metabolic modulation and targeted gene-based interventions. Further research is required to define tissue-specific effects, long-term safety, and the translational feasibility of these approaches in humans.

Future perspectives

Targeted modulation of the adiponectin–T-cadherin–exosome axis holds substantial promise in regenerative cardiology. Future investigations should explore pharmacological, gene therapy, and biomimetic strategies to harness this pathway within personalized medicine frameworks (Fig. 2). Given the influence of sex and hormonal status on adiponectin levels and T-cadherin signaling, therapeutic strategies may require stratification according to sex and age. Women, who typically exhibit higher baseline adiponectin levels in association with estrogen, may derive greater benefit from interventions that enhance T-cadherin signaling, whereas men, who generally have lower adiponectin levels, may require approaches that augment adiponectin availability or improve receptor sensitivity. Engineering biomimetic exosomes or T-cadherin–overexpressing stem cells represents another potential strategy to enhance myocardial repair. Furthermore, leveraging genetic polymorphism data related to T-cadherin may facilitate precision medicine approaches for cardiovascular regeneration.

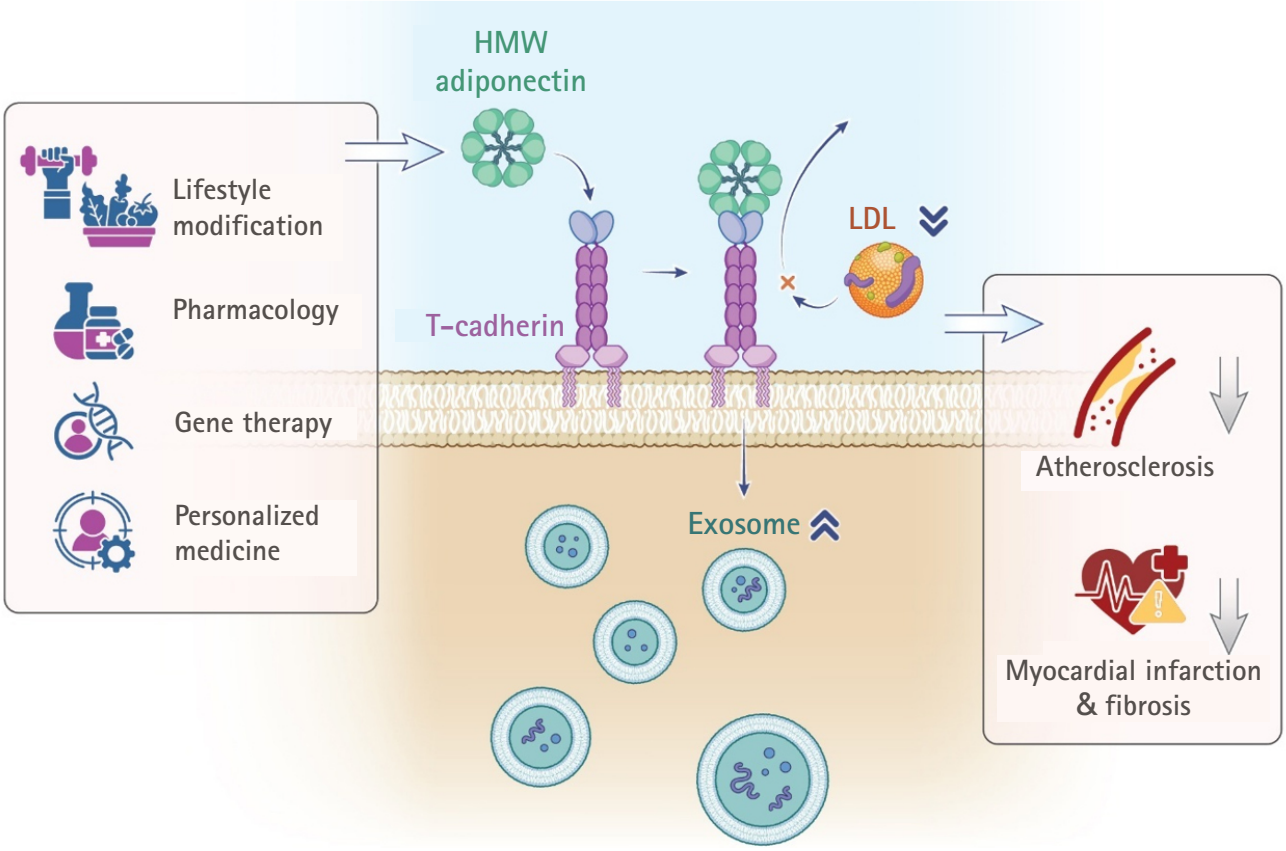

Fig. 2. Integrated overview of high-molecular-weight (HMW) adiponectin–T-cadherin–mediated cardiometabolic protection. This figure summarizes the overall conceptual framework of the study. Centrally, HMW adiponectin binding to T-cadherin promotes cardioprotective exosome biogenesis and attenuates low-density lipoprotein cholesterol (LDL-C)–driven atherogenic signaling. On the left, lifestyle modification, pharmacological interventions, gene-based strategies, and personalized medicine approaches are depicted as upstream modulators that increase circulating HMW adiponectin levels, strengthen T-cadherin interactions, and amplify exosome production. On the right, the downstream consequences of this enhanced signaling include suppression of LDL-C accumulation, attenuation of atherosclerotic plaque progression, reduction of myocardial infarction–related injury, and mitigation of post-ischemic fibrosis.

Conclusion

In conclusion, the T-cadherin–adiponectin axis represents a novel and physiologically relevant mechanism of cardiovascular protection, particularly through its role in promoting exosome biogenesis and paracrine regenerative signaling. Although adiponectin is a well-established cardioprotective adipokine, the identification of T-cadherin as its nonclassical receptor and regulator of vesicular trafficking has opened new avenues for cell-free therapeutic strategies. Harnessing or mimicking this axis through pharmacological agents, genetic modulation, or biomimetic exosome delivery offers a promising approach to myocardial regeneration following infarction or in chronic heart failure.

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Authors' contribution

All the work was done by In Sook Kang.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

Not applicable.

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Supplementary materials

None.

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Endoscopic vacuum therapy for gastrointestinal transmural defects: clinical outcomes and treatment implications: a retrospective study from Korea

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Purpose: Endoscopic vacuum therapy (EVT) has emerged as a highly effective approach for managing gastrointestinal transmural defects and may offer advantages over traditional methods, such as stenting. This study evaluated the clinical outcomes of EVT for gastrointestinal transmural defects resulting from leakages, perforations, and fistulas.

Methods: We retrospectively reviewed patients who underwent EVT for gastrointestinal transmural defects at Ewha Womans University Medical Center between February 2018 and September 2025 and analyzed clinical outcomes, adverse events, and risk factors associated with adverse events.

Results: Fourteen patients were included (mean age, 63.9 years; 85.7% male). Stomach surgery was the most common etiology (50.0%), and malignancy accounted for 71.4% of cases. The median number of EVT sessions was 2.5, and the mean interval from the index event to the first EVT session was 10.5 days. EVT achieved a 100% technical success rate, with no 30-day mortality; there was 1 in-hospital death (7.1%), 2 cases of stricture (14.3%), and 1 major bleeding event (7.1%). Adverse events were observed more frequently in patients who underwent ≥3 EVT sessions (57.1%) compared with those who underwent <3 sessions, in whom no adverse events occurred.

Conclusion: This study suggests that EVT is a safe and effective treatment for gastrointestinal transmural defects, with high technical success rates. The number of EVT sessions and the timing of treatment initiation appeared to be associated with complications and overall clinical outcomes.

Keywords: Endoscopy; Gastrointestinal tract; Anastomotic leak; Therapeutics; Vacuum; Republic of Korea

Introduction

Endoscopic treatment of wall defects of the upper gastrointestinal (GI) tract, whether postoperative or iatrogenic, remains challenging for endoscopists [1]. Several therapeutic approaches have been described, including endoscopic vacuum therapy (EVT), stenting, surgery, and conservative management [2]. Among these options, EVT has been recognized as a highly effective method for managing leakage or perforation throughout the GI tract and represents one of the most important innovative techniques in the treatment of GI transmural defects [3,4].

EVT is an endoscopic approach that applies continuous negative pressure to the affected area, facilitating recovery by removing infectious secretions and promoting tissue regeneration [5]. Compared with traditional stent placement therapy, EVT offers several advantages, including a reduced risk of infection and accelerated healing, while also minimizing stent-related complications such as migration and persistent leakage [6]. In a recent network meta-analysis, EVT demonstrated significantly lower complication rates (odds ratio [OR], 0.23; 95% confidence interval [CI], 0.09–0.58) and mortality rates (OR, 0.43; 95% CI, 0.21–0.87) compared with stenting, whereas surgery was more frequently required for larger leaks than stenting (mean difference, 14.66; 95% CI, 4.61–24.70) [2]. Other studies have reported favorable clinical outcomes, including a treatment success rate of 94.2% in a large-scale prospective study of 52 patients who underwent EVT for esophageal perforation or anastomotic leakage following esophagectomy or gastric cancer surgery [7]. More recently, in

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Korea, the efficacy of EVT for anastomotic leaks following upper GI surgery has also been reported. In a cohort of 20 patients with anastomotic leakage after esophageal surgery, EVT achieved a treatment success rate of 95%, with a median fistula closure duration of 14.5 days. Preoperative chemotherapy was identified as a significant factor associated with a treatment duration exceeding 3 weeks [8].

EVT has emerged as an effective treatment option for transmural gastrointestinal defects of various etiologies. However, data regarding risk factors for adverse events, such as stricture, bleeding, and infection, remain limited, and evidence supporting optimal treatment protocols is still lacking. Therefore, the primary objective of this study was to evaluate the success rate, clinical course, and adverse events associated with EVT. The secondary objectives were to identify risk factors associated with adverse events and to propose a safe and effective EVT protocol aimed at minimizing procedure-related risks.

Methods

Patient selection

This retrospective observational study was conducted at Ewha Womans University Medical Center. All patients who underwent EVT for leakage after GI surgery or foreign body impaction between February 2018 and September 2025 were included in this study. Exclusion criteria included cases in which EVT was performed for an aortoesophageal fistula after abdominal aortic aneurysm surgery, as well as cases in which initial vacuum therapy was performed intraoperatively for esophageal perforation.

The presence of leakage was determined based on computed tomography (CT) scanning and/or contrast swallowing examination and/or endoscopic identification of a defect. Medical records of eligible patients were reviewed, and clinical, radiological, and endoscopic data were collected. EVT was not applied to malignant tissue itself, and in patients with underlying malignancy, all procedures were restricted to leakage sites that were not directly associated with tumor involvement.

The study adhered to the principles outlined in the Declaration of Helsinki. The requirement for informed consent was waived following approval by the Institutional Review Board (IRB) of Ewha University Seoul Hospital (IRB approval no., 2024-10-062).

Definitions and outcome measures

The diagnosis of gastrointestinal transmural defects was based on clinical presentation and endoscopic and radiological findings, including esophagography, abdominal and pelvic CT, and chest CT. Clinical presentation was defined as physical findings such as abdominal pain, an increasing amount of drainage, fever, leukocytosis, and elevated C-reactive protein levels, or as changes in the content of the Hemovac drain. Endoscopic findings indicative of leakage consisted of direct visualization of a defect. Radiologic findings were defined as extraluminal contrast extravasation on esophagography, infiltration around the anastomotic site, and/or fistula tract formation on abdominal, pelvic, or chest CT.

Successful closure was defined as the absence of evidence of transmural defects on radiologic or endoscopic imaging after device removal, accompanied by the absence of clinical signs of persistent defects. Therapeutic outcomes of EVT were evaluated based on technical success, number of procedures, interval from defect diagnosis to EVT initiation, total indwelling duration, and indwelling period per exchange. Total indwelling duration was defined as the number of days from the first device insertion to final removal, whereas the indwelling period per exchange was defined as the number of days each EVT device remained in place before replacement. The interval between EVT procedures was defined as the number of days between consecutive EVT sessions, including from the first to the second session, the second to the third session, and subsequent sessions.

Major adverse events included procedure-related 30-day mortality, major bleeding requiring intervention or operative management, stricture formation within 1 year, and 1-year overall mortality. Procedure-related mortality was defined as death occurring before complete defect closure in the absence of other attributable causes.

Endoscopic vacuum therapy technique

EVT was performed under midazolam sedation. A single- or 2-channel gastroscope (GIF-HQ290, GIF-2T240, or GIF-2TQ260M; Olympus), a nasogastric tube, and a vacuum-assisted closure kit (CuraVAC; CGBio Inc.) were used. A polyurethane sponge was trimmed to match the size and location of the cavity, typically measuring $\leq 3.0 \times 3.0$ cm. The sponge was attached to the tip of the nasogastric tube and secured with silk sutures.

During the initial endoscopic examination, the defect and extraluminal cavity were irrigated. After identification of the leakage site, the sponge-mounted tube was advanced into the esophagus, and endoscopic guidance using grasping forceps was employed to ensure accurate placement of the sponge. The external end of the tube was subsequently connected to an electronic vacuum device, applying continuous negative pressure of −80 to −100 mm Hg. The final tube position was marked at the nostrils and secured to prevent displacement.

The sponge was exchanged every 1 to 2 days, depending on the

patient's clinical condition. If endoscopic examination suggested complete closure of the defect, the sponge was removed, and esophagography or esophagogastroduodenoscopy (EGD) was performed to confirm healing.

Although the fundamental principles of EVT were applied consistently, including device selection, continuous negative pressure application, and regular sponge exchange, key procedural parameters such as negative pressure intensity, sponge exchange intervals, and total treatment duration were adjusted according to individual patient conditions, defect characteristics, and clinical responses.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics ver. 26.0 (IBM Corp.). Continuous variables are presented as mean ± standard deviation (SD) or median (range), and categorical variables as counts and percentages. The association between the number of EVT sessions and complications was evaluated by stratifying patients into 2 groups, with comparisons performed using Fisher's exact test (2-sided). Statistical significance was defined as $P < 0.05$.

Results

Clinical characteristics and endoscopic vacuum therapy–related parameters

Fourteen patients were included in the study. The mean age was 63.9 ± 6.8 years, and 12 patients (85.7%) were male. The most common etiology of perforation was stomach surgery (n = 7; 50.0%), followed by esophageal surgery (n = 5; 35.7%) and esophageal foreign body impaction (n = 2; 14.3%). Regarding underlying disease, 10 patients (71.4%) had malignant conditions and 4 patients (28.6%) had benign conditions. Leakage was most frequently diagnosed by esophagography (n = 6; 42.9%), followed by EGD (n = 3; 21.4%), chest CT (n = 3; 21.4%), and abdominal CT (n = 2; 14.3%). The overall treatment success rate was 100% (14/14), with all patients achieving defect closure without requiring surgical revision or an alternative intervention. The median number of EVT sessions was 2.5 (range, 1–6), and the mean interval from surgery to the first EVT session was 10.5 ± 8.7 days. The mean duration of EVT indwelling was 7.0 ± 2.5 days (range, 2–15 days) (Table 1).

Adverse events of endoscopic vacuum therapy

There was no 30-day mortality (0%). One patient (7.1%) experienced in-hospital mortality due to sepsis secondary to pneumonia, which was considered unrelated to the EVT procedure or gastrointestinal leakage. Adverse events occurred in a subset of patients: stricture developed in 2 patients (14.3%), and major bleeding occurred in 1 patient (7.1%) (Table 2).

Table 1. Clinical characteristics and endoscopic vacuum therapy–related parameters

Characteristic	Value
Age (yr)	63.9 ± 6.8
Sex, male	12 (85.7)
Etiology of defects	
Stomach surgery	7 (50.0)
Esophageal surgery	5 (35.7)
Foreign body	2 (14.3)
Cause	
Malignancy	10 (71.4)
Benign	4 (28.6)
Defects diagnosis method	
Esophagography	6 (42.9)
EGD	3 (21.4)
Chest CT	3 (21.4)
Abdominal CT	2 (14.3)
EVT treatment	
EVT success	14 (100.0)
Sponge exchange	2.5 (1–6)
Time to first EVT from defect event (day)	10.5 ± 8.7 (0–35)
Interval between EVT procedures	7.0 ± 2.5 (2–15)
Total EVT indwelling duration (day)	22.1 ± 14.5 (6–50)

Values are presented as mean±SD, number (%), median (range), or mean±SD (range).
EGD, esophagogastroduodenoscopy; CT, computed tomography; EVT, endoscopic vacuum therapy; SD, standard deviation.

Table 2. Adverse events after endoscopic vacuum therapy

Adverse events	No. (%)
30-day mortality	0 (0.0)
In-hospital mortality	1 (7.1)
Stricture	2 (14.3)
Massive bleeding	1 (7.1)

Risk of adverse events according to EVT sessions

Among the 14 patients, the incidence of adverse events differed according to the number of EVT sessions performed. No adverse events occurred in patients who underwent fewer than 3 EVT sessions (0/7; 0.0%), whereas 4 of 7 patients (57.1%) who underwent 3 or more EVT sessions developed adverse events (Fig. 1). The rate of adverse events was higher in the ≥ 3 EVT session group (risk ratio, 8.57; 95% CI, 0.55–134.6). Adverse events were more frequently observed in patients who underwent ≥ 3 EVT sessions than in those who underwent < 3 sessions (57.1% vs.

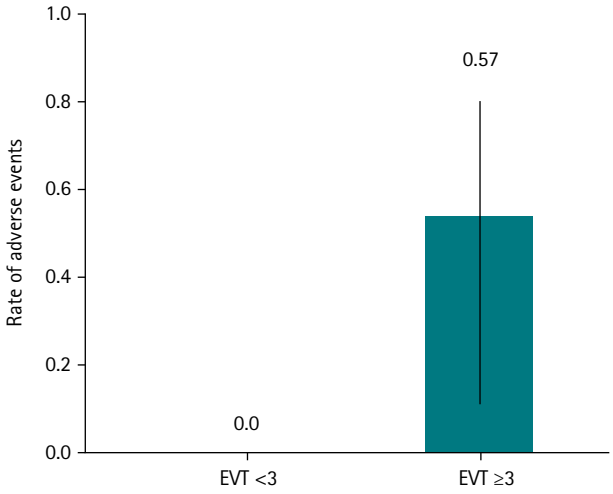

Fig. 1. Rate of adverse events according to the number of endoscopic vacuum therapy (EVT) sessions. Adverse events were more frequently observed in patients who underwent ≥3 EVT sessions than in those who underwent <3 sessions (57.1% vs. 0%), demonstrating a trend toward statistical significance (2-sided P=0.07). Error bars represent 95% confidence intervals for adverse event rates.

0%), demonstrating a trend toward statistical significance (2-sided P = 0.07).

Discussion

This retrospective study demonstrated that EVT achieved complete defect closure in all 14 patients, with no 30-day mortality. Adverse events consisted of 2 cases of stricture and 1 case of major bleeding. Notably, the risk of adverse events increased with the number of EVT sessions, as patients who underwent 3 or more sessions exhibited a substantially higher rate of adverse events. These findings support the efficacy and safety of EVT, while suggesting that patients requiring multiple sessions should be regarded as a higher-risk subgroup.

Our findings are consistent with those of previous studies reporting high technical success rates and acceptable safety profiles of EVT in the treatment of gastrointestinal transmural defects [9,10]. Most prior reports have focused primarily on overall efficacy, whereas risk factors for adverse events have been less systematically examined. In this context, the present study provides additional insight by identifying the number of EVT sessions as a potential predictor of adverse events. Patients requiring repeated EVT sessions may have larger or more complex defects, delayed tissue healing, or unfavorable clinical conditions, all of which may increase susceptibility to complications.

In the present cohort, 1 patient experienced major bleeding following EVT, necessitating subsequent embolization. Although such events are uncommon, uncontrollable hemorrhage represents a major complication associated with EVT [7,11]. The risk of bleeding may be particularly elevated in cases involving tracheoesophageal fistula, in which proximity to major vascular structures increases the potential for catastrophic outcomes [12,13]. To mitigate this risk, preprocedural evaluation of adjacent vessels using contrast-enhanced CT may be considered to identify vulnerable anatomy [14]. In selected high-risk situations, avoiding continuous negative pressure and allowing passive drainage may serve as precautionary strategies. These considerations underscore the importance of individualized risk assessment and tailored EVT application in clinical practice.

The timing of EVT initiation has been proposed as a factor that may influence treatment outcomes. However, the present study was limited in its ability to define 'early initiation' or to establish an optimal timing threshold. Previous studies have reported high success rates and relatively short EVT indwelling durations in cases of acute iatrogenic perforation, which may be attributable to prompt defect recognition and treatment initiation within 24 hours [15,16]. Owing to the limited number of cases, subgroup analyses and statistically robust conclusions could not be derived in the present study. Nevertheless, we observed a trend suggesting that longer intervals between the defect event and the first EVT session were associated with a higher risk of adverse events. These findings should be interpreted as exploratory observations that are broadly consistent with existing literature.

EVT has demonstrated high clinical and technical success rates in the management of GI transmural defects, with the added advantage of enabling simultaneous drainage of intraluminal and extraluminal collections. Nevertheless, patient discomfort related to the transnasal drainage tube and the need for repeated endoscopic procedures remain notable limitations [1,17,18]. Accordingly, increasing attention has been directed toward preventive strategies aimed at reducing postoperative defects following upper GI surgery. One such approach is preemptive EVT, which involves prophylactic application of EVT before defect formation to reduce the risk of adverse events and improve outcomes [19,20]. Recent studies have highlighted preemptive EVT as a promising strategy with potential for broader clinical adoption. Our findings suggest that earlier initiation of EVT may be associated with more favorable outcomes, although confirmation in well-designed prospective studies is required.

This study has several limitations. First, this was a single-center case series involving only 14 patients, which limits the generalizability of the findings. The small sample size may have resulted in insufficient statistical power to detect subtle between-group dif-

ferences, underscoring the need for validation in larger, multicenter prospective studies. Second, the retrospective design introduces inherent risks of selection bias, incomplete data capture, and unmeasured confounding. Third, the absence of direct comparisons with alternative treatment modalities, such as stent placement or surgical revision, precludes definitive conclusions regarding the relative efficacy of EVT. Fourth, standardized data regarding defect size and anatomical location were not consistently available, limiting assessment of the independent effects of defect-related factors on outcomes and adverse events.

In conclusion, this study suggests that EVT is an effective and safe treatment modality for gastrointestinal transmural defects, achieving complete closure in all cases with low short-term mortality. The number of EVT sessions was identified as a factor associated with complication occurrence, and a trend toward more favorable outcomes was observed with earlier EVT initiation. However, given the limited sample size, these findings should be interpreted as exploratory. Preemptive EVT may represent a promising strategy for reducing postoperative complications; however, its clinical utility and optimal indications require validation in rigorously designed prospective studies.

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Authors' contribution

Concept and design: KNS, ARC. Data analysis and interpretation: KNS, ARC, CHT, JRB. Drafting of the manuscript: ARC. Critical revision of the manuscript for essential intellectual content: KNS, ARC, CHT, JRB, EMS, SAJ. All authors have read and approved the final manuscript.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

Data cannot be shared due to issues related to the identification of vulnerable participants.

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Supplementary materials

None.

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Immunohistochemical expression of Ki-67, estrogen receptor, and human epidermal growth factor receptor 2 in p16-positive premalignant and malignant cervical squamous lesions: associations with clinicopathological parameters

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Purpose: Human papillomavirus is the dominant etiological factor underlying atypical cervical squamous epithelial cell abnormalities and cervical carcinoma. Currently, only a limited number of drugs targeting specific biomarkers in cervical cancer are available. This study aimed to assess the expression of estrogen receptor (ER), human epidermal growth factor receptor 2 (HER2), and the Ki-67 proliferative index (Ki-67) in p16-positive cervical squamous premalignant and malignant lesions, which may help clarify the potential role of targeted therapies in cervical cancer.
Methods: In p16-positive, histologically proven premalignant and malignant cervical lesions, ER, HER2, and Ki-67 expression were evaluated according to predefined criteria.
Results: p16 showed strong nuclear and cytoplasmic positivity in 54 of 56 cases. Patchy nuclear positivity was mainly observed in low-grade squamous intraepithelial lesion (LSIL) cases (2/56). Ki-67 demonstrated a variable proliferative index ranging from 5% to 95% across all cases, with higher indices predominantly observed in squamous cell carcinomas (SCC). ER positivity in LSIL, high-grade squamous intraepithelial lesion, and SCC was 100% (2/2), 66.7% (10/15), and 46.15% (18/39), respectively. HER2 expression was predominantly negative, observed in 78.6% (44/56) of cases, equivocal in 17.8% (10/56), and positive in 3.6% (2/56). Both HER2-positive cases were SCC. ER and HER2 interpretations were analyzed and were not significantly correlated with clinical or pathological parameters.
Conclusion: ER positivity decreased with progression of cervical squamous lesions, and HER2 expression was rare in cervical squamous neoplasia. No statistically significant correlation was identified between ER or HER2 expression and clinicopathological parameters. The findings of the current study may help fill gaps in the existing literature and provide essential foundational knowledge for optimizing emerging therapeutic strategies, including ER- and HER2-related therapies.

Keywords: Cervix; Estrogen receptors; HER2; p16; Squamous intraepithelial lesions; Uterine cervical neoplasms

Introduction

Worldwide, cervical cancer is the fourth most common cancer and the fourth leading cause of cancer-related death among women, as reported by GLOBOCAN (Global Cancer Observatory) [1]. Human papillomavirus (HPV) infection is a requisite etiological factor for HPV-associated cervical cancer, although it is not sufficient on its own. Other important cofactors, including certain sexually transmitted diseases, smoking, increased parity, and prolonged oral contraceptive use, are also associated with the development of cervical cancer [1].

The World Health Organization categorizes cervical squamous cell carcinomas (SCC) into HPV-associated and HPV-independent types. However, the vast majority of cervical SCCs are HPV-associated, with only rare cases reported as HPV-independent [2]. Overexpression of p16 serves as a reliable surrogate bio-

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marker for HPV infection and can be detected using immunohistochemistry [2]. Ki-67 is a marker of cellular proliferation, and increased Ki-67 expression is associated with aggressive tumor behavior and poorer clinical outcomes, making it a useful prognostic biomarker [3]. Estrogen facilitates the proliferation and differentiation of cervical epithelial cells through estrogen receptor alpha (ERα), as estrogen levels rise during the menstrual cycle, leading to hyperplastic epithelium without pathological alteration [4]. A mouse-based study demonstrated the essential role of ERα in mediating the carcinogenic effects of estrogen in the cervix. ERα-sufficient HPV transgenic mice developed progressive atypical squamous metaplasia that culminated in cervical cancer following estrogen treatment [4]. Furthermore, ERα antagonist drugs showed significant efficacy in eradicating pre-existing cervical cancers, suggesting the potential of these agents in preventing cervical cancer development [4]. Human epidermal growth factor receptor 2 (HER2) is a membrane-bound receptor with intrinsic tyrosine kinase activity and plays a key role in cellular transformation, carcinogenesis, and maintenance of malignant phenotypes [5,6]. These effects occur through activating mutations, amplification of the *HER2* gene, or overexpression of the HER2 protein, making HER2 a prime target for antitumor therapies [5,6]. The role of HER2 expression in gynecological malignancies remains under investigation, and consensus has not yet been established [5,6]. However, both preclinical models and clinical studies suggest that somatic *HER2* gene mutations in cervical cancer represent promising targets for selective inhibitors [5,6]. Uterine cervical carcinomas have a paucity of clinically effective targetable biomarkers [7]. Estrogen receptor (ER), HER2, and fibroblast activation protein have emerged as potential therapeutic or theranostic targets across several gynecologic and genitourinary malignancies [7]. Currently, only a limited number of cervical cancer-specific targetable biomarkers are available, such as pembrolizumab therapy guided by programmed cell death ligand 1 (PD-L1) expression [7].

While p16 and Ki-67 are well-established biomarkers in cervical lesions, the expression patterns and clinical significance of ER and HER2 in p16-positive cervical squamous lesions remain poorly characterized. Identification of these potentially targetable biomarkers may open new avenues for precision medicine in cervical cancer. In this study, we aimed to evaluate the expression of ER and HER2 as potential therapeutic targets, along with Ki-67 as a proliferation marker, in p16-positive cervical squamous premalignant and malignant lesions, and to assess their association with clinicopathological parameters.

Methods

Study design and setting

The present study was a cross-sectional, hospital-based study conducted over a period of 2 years in the Department of Pathology and Laboratory Medicine, in collaboration with the Department of Obstetrics and Gynecology, at All India Institute of Medical Science, Bibinagar, India. The sample size was calculated using the formula. $S = \frac{Z^2pq}{L^2}$, where S represents the sample size, Z is the Z score, p is the population proportion, q is (1−p), and L is the relative precision. Based on this calculation, the final sample size was 56.

After the study was approved by the Institutional Ethics Committee (IEC Ref No: AIIMS/BBN/IEC/JUNE/2023/284), detailed clinical data were collected, including age, age at menarche, last menstrual period, educational status, parity, age at first delivery, and presenting symptoms such as white discharge, vaginal bleeding, foul-smelling discharge, pain, history of weight loss, and clinical diagnosis.

Initial cohort

The study population comprised all patients with suspected cervical lesions who underwent biopsy or hysterectomy according to the Department of Obstetrics and Gynecology treatment protocol during the study period and were reported as having premalignant or malignant ectocervical squamous lesions. Cervical biopsy and hysterectomy specimens were received in formalin in the Department of Pathology for histopathological examination. The cases were evaluated and categorized as premalignant low-grade squamous intraepithelial lesion (LSIL)/cervical intraepithelial neoplasia (CIN) 1, high-grade squamous intraepithelial lesion (HSIL)/CIN 2 or CIN 3, or malignant lesions. Wherever applicable, pathological tumor–node–metastasis staging was performed.

In the study population of premalignant and malignant ectocervical squamous lesions, all cases were subjected to ready-to-use p16 immunohistochemical staining using a mouse monoclonal antibody (Clone JC8). For positive p16 staining, the localization pattern was assessed as nuclear, cytoplasmic, or nucleocytoplasmic. The distribution of staining was analyzed based on intensity, categorized as weak (1+), moderate (2+), or strong (3+). Positivity in 5%–25% of tumor cells was considered grade 1, 26%–50% grade 2, and ≥51% grade 3.

Exclusion criteria

Specimens that were inadequate for processing, patients who had already received or were undergoing treatment, non-squa-

mous atypical cervical lesions, and patients receiving chemotherapy or radiotherapy for any other malignancy were excluded from the study.

Final analyzed cases

All p16-positive premalignant and malignant squamous cell lesions of the cervix were further evaluated for ER, HER2, and Ki-67 immunoexpression using ready-to-use immunohistochemical markers for Ki-67 (Clone MIB-1, mouse monoclonal antibody), ER (Clone EP1, rabbit monoclonal antibody), and HER2 (Clone EP3, rabbit monoclonal antibody). Interpretation of ER and HER2 staining in cervical carcinoma followed the standard protocol used for hormone receptor assessment in breast carcinoma.

For ER analysis in CIN lesions, expression was recorded based on localization within the epithelium, specifically the lower one-third, middle two-thirds, or full thickness. Both staining intensity and the percentage of positive tumor cells were documented, and an Allred score was calculated. Scores of 0–2 were considered ER-negative, whereas scores >3 were considered ER-positive. The same Allred scoring system was applied to SCC cases.

For HER2 analysis, a score of 0 was assigned for absent staining or weak staining in <10% of tumor cells, score 1 for incomplete weak membranous staining in ≥10% of tumor cells, score 2 for complete weak to moderate membranous staining, and score 3 for complete strong membranous staining in >10% of tumor cells. Scores of 0 and 1 were considered negative, score 2 equivocal, and score 3 positive.

Ki-67, a nuclear proliferation marker, was assessed in the area of maximum expression and calculated as the percentage of atypical squamous cells demonstrating positive nuclear staining. In CIN lesions, Ki-67 expression was categorized according to involvement of the epithelium's lower one-third, middle two-thirds, or full thickness. In SCC cases, the percentage positivity was recorded and dichotomized as ≤60% or >60%, based on the approximate mean Ki-67 labeling index, for statistical analysis.

Statistical analysis

Data were analyzed using IBM SPSS for Windows ver. 28.0 (IBM Corp.). Categorical variables are presented as frequencies and percentages. Associations between categorical variables (ER/HER2 status versus clinicopathological parameters and p16/Ki-67 expression) were assessed using the Pearson chi-square test. All subgroup analyses, particularly those involving small sample sizes (e.g., LSIL, n=2), were exploratory and hypothesis-generating; therefore, nonsignificant findings were interpreted with caution in light of the study's limitations.

Results

Out of 64 cases comprising premalignant and malignant ectocervical lesions evaluated during the study period, 8 cases were p16-negative and were excluded from further analysis. The remaining 56 samples showed block positivity for p16, and in these cases, the expression patterns of ER, HER2, and Ki-67 immunomarkers, along with their associations with clinicopathological parameters, were assessed.

In the study population, age ranged from 25 to 83 years, with a mean age of 51.39 years. The mean age for LSIL, HSIL, and SCC progressively increased with lesion severity and was 36.5, 42.2, and 55.69 years, respectively. Overall, 71.4% of women were older than 45 years, indicating that cervical lesions were more commonly diagnosed in middle-aged and older women.

Early menarche (≤12 years) was observed in 62.5% of cases, and early childbearing (≤18 years) was noted in 50% of women. At presentation, 60.7% of women were postmenopausal. A high illiteracy rate of 67.9% (38/56) was observed in the study cohort. The most common presenting symptom was vaginal bleeding (96.4%), followed by white discharge and pain. Women with early menarche, early childbearing, lack of formal education, age >45 years, and postmenopausal status showed a higher frequency of SCC (Table 1).

The most common histological diagnosis was SCC (39/56), followed by HSIL (15/56). Among the 39 SCC cases, the non-keratinizing subtype was most frequent, accounting for 66.7%, including 3 well-differentiated, 22 moderately differentiated, and 1 poorly differentiated tumors (Fig. 1A, B). Among keratinizing SCC, 1 case was well-differentiated and 12 were moderately differentiated. Seven hysterectomy specimens from cases initially diagnosed as SCC on cervical biopsy were received. The greatest tumor dimension averaged 1.75±1.28 cm, with a range of 0.5–4 cm. Stromal invasion measured 1 mm and 3 mm in 1 patient each and exceeded 5 mm in 5 patients. Lymphovascular invasion and parametrial involvement were each observed in 1 patient. Pathological staging showed pT1b1 in 4 patients, pT1a1 in 2 patients, and pT2b in 1 patient. No regional lymph node or distant metastasis was identified, or such information was unavailable.

p16 demonstrated strong expression across the cohort, supporting HPV-related pathogenesis. Nuclear-cytoplasmic block-type positivity was observed in 96.4% (54/56) of cases (Fig. 1C). Patchy nuclear positivity was mainly identified in LSIL lesions (2/56). The intensity and grade of p16 expression showed an increasing trend with advancing lesion severity (Table 1).

The proliferation marker Ki-67 showed a variable proliferative index ranging from 5% to 95% (Fig. 1D). Among the 17 patients

Table 1. Distribution of cervical lesions with clinical and pathological parameters

Characteristic	LSIL	HSIL	SCC
Age (yr)			
≤45	1	8	7
>45	1	7	32
Age at menarche (yr)			
≤12	1	9	26
>12	1	6	13
Age at first delivery (yr)			
≤18	1	3	24
>18	1	12	15
Menopausal status			
Premenopausal	2	12	8
Postmenopausal	0	3	31
Education status			
Illiterate	0	5	33
Literate	2	10	6
Vaginal bleeding			
Present	2	13	39
Absent	0	2	0
Pain			
Present	0	5	29
Absent	2	10	10
White discharge			
Present	2	11	26
Absent	0	4	13
Foul-smelling discharge			
Present	0	2	8
Absent	2	13	31
Weight loss			
Present	0	1	29
Absent	2	14	10
p16 intensity			
Weak	1	0	0
Moderate	1	5	8
Strong	0	10	31
p16 grade			
Grade 1	2	1	0
Grade 2	0	4	1
Grade 3	0	10	38
Ki-67 expression			
<5%	2	4	3
6%–25%	0	1	1
26%–50%	0	2	5
51%–<75%	0	6	17
>75%	0	2	13
ER intensity in LSIL, HSIL, and SCC			
Absent	0	5	15
Weak	0	4	8
Moderate	0	3	11
Strong	2	3	5

LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; SCC, squamous cell carcinoma; Ki-67, Ki-67 proliferation index; ER, estrogen receptor.

with CIN, Ki-67 expression was limited to the lower one-third of the epithelium in 5 cases, extended to the middle two-thirds in 8 cases, and involved the full thickness in 4 cases. Among the 39 SCC cases, 53.8% (21/39) demonstrated a high proliferative index (>60%), whereas 46.2% (18/39) showed a proliferative index ≤60% (Table 1).

ER (Fig. 1E) positivity was noted in 53.6% (30/56) of cervical lesions, with expression levels ranging from 0% to >66%.

Regarding intensity, strong expression was observed in 17.9% (10/56) of cases, while 25.0% (14/56) demonstrated moderate intensity (Table 1). In CIN cases, 52.9% (9/17) showed ER expression extending up to the middle two-thirds of the epithelium (Fig. 2). A diffuse expression pattern was observed in 47.1% (8/17) of CIN cases, whereas a focal pattern was noted in 23.5% (4/17), and ER expression was absent in 29.4% (5/17) (Fig. 2). Overall, ER positivity in LSIL, HSIL, and SCC was 100%, 66.7%, and 46.15%, respectively.

HER2 expression was predominantly negative in 78.6% (44/56) of cases, equivocal in 17.8% (10/56), and positive in 3.6% (2/56) (Fig. 1F). Both HER2-positive cases were SCC and were associated with early menarche; one tumor was keratinizing and the other non-keratinizing. HER2 expression was negative in all well-differentiated and poorly differentiated tumors. Among moderately differentiated tumors, 2 cases were HER2 positive, 7 were equivocal, and 25 were negative.

ER and HER2 expression statuses were analyzed in relation to clinicopathological parameters, including age at presentation, age at menarche, menopausal status, parity, age at first delivery, clinical presentation, histological diagnosis, and degree of p16 and Ki-67 expression. The analysis demonstrated that neither ER nor HER2 status showed a statistically significant correlation with the evaluated clinical or pathological parameters. Additionally, no significant correlation was identified between ER and HER2 expression (Table 2).

Discussion

The present study included 56 cases of p16-positive cervical lesions, with an age range of 25 to 83 years. Previous studies have reported the mean age for cervical lesions to range from 34.59 to 52.28 years [8-13]. In the present study, the overall mean age was 51.39 years, and the mean age for LSIL, HSIL, and SCC progressively increased with lesion severity, measuring 36.5, 42.2, and 55.69 years, respectively. Consistent with prior observations, most LSIL cases occurred before the age of 45 years, whereas the majority of HSIL and SCC cases occurred after the age of 45 years [8,10,12,14]. The observed variation in age distribution may be

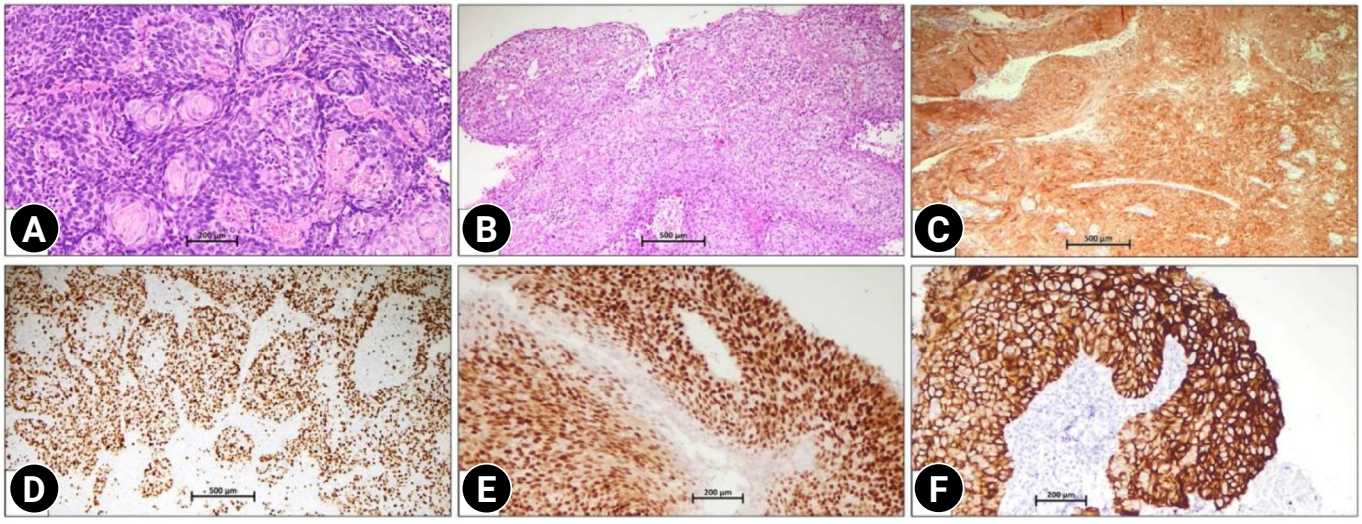

Fig. 1. (A) Keratinizing squamous cell carcinoma showing tumor cells with keratin pearl formation (hematoxylin and eosin, ×100). (B) Non-keratinizing squamous cell carcinoma showing a moderately differentiated tumor arranged in sheets and nests (hematoxylin and eosin, ×50). (C) p16 immunohistochemistry showing strong nuclear and cytoplasmic block-type positivity in squamous cell carcinoma (Clone JC8, ×100). (D) Ki-67 immunohistochemistry demonstrating a high proliferative index with nuclear positivity in >75% of tumor cells (Clone MIB-1, ×50). (E) Estrogen receptor immunohistochemistry showing strong nuclear positivity in squamous cell carcinoma, a finding that is usually uncommon (Clone EP1, ×50). (F) Human epidermal growth factor receptor 2 immunohistochemistry showing strong, complete membranous expression (score 3), a rare finding observed in only 2 cases in the present study, in squamous cell carcinoma (Clone EP3, ×100).

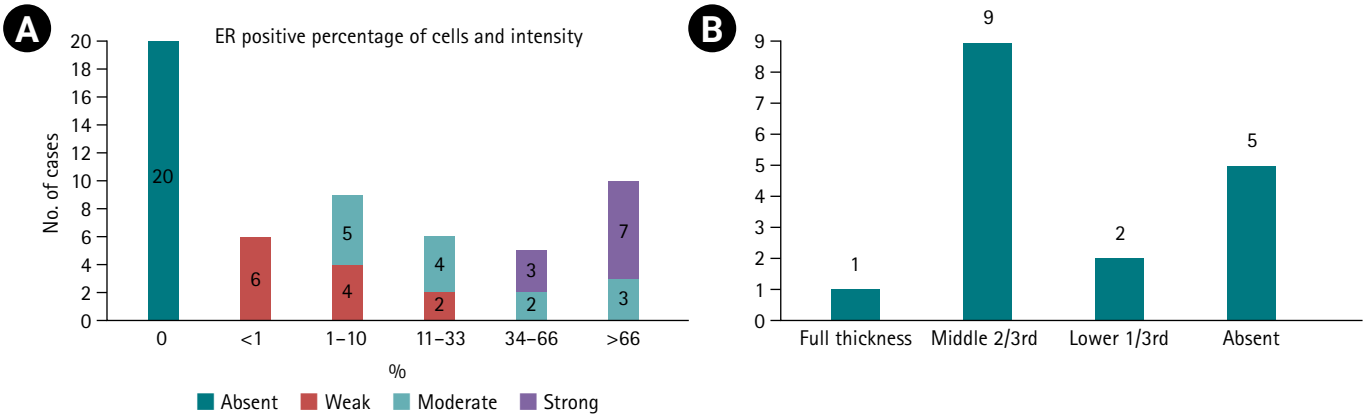

Fig. 2. (A) Estrogen receptor (ER) staining pattern shown as stacked bars representing the proportion of cases with absent, weak, moderate, or strong ER intensity and the corresponding percentage of positive cells (Allred score >3 considered positive). (B) Extent of ER expression in cervical intraepithelial neoplasia cases only (n=17), categorized by epithelial layer involvement as full thickness, middle two-thirds, lower one-third, or absent (29.4%, 5/17).

attributable to the relatively small sample size or differences in patient selection.

Bhadauria et al. [15] reported a mean age at childbearing of 18.9 years among SCC cases, whereas in the present study, the mean age at childbearing was 17.9 years across all cases. All SCC cases in the present study occurred in multiparous women and predominantly among those who attained menarche at ≤12 years or had an age at first delivery of ≤18 years. Early menarche and early age at first delivery may reflect prolonged lifetime estrogen exposure and early onset of sexual activity, respectively, while multiparity may further contribute as a risk factor for cervical dysplasia.

Carcinomas are reported more frequently in postmenopausal women, whereas precursor lesions are more common in premenopausal women [8,10,13,16,17]. In the present study, SCC predominated among postmenopausal women, while LSIL and

Table 2. Association of ER and HER2 status with clinicopathological variables

Variable	ER-negative	ER-positive	P-value	HER2 status			P-value
				Negative	Equivocal	Positive	
Age (yr)			0.799				0.660
≤45	7	9		13	2	1	
>45	19	21		31	8	1	
Age at menarche (yr)			0.905				0.258
≤12	16	20		26	8	2	
>12	10	10		18	2	0	
Menopausal status			0.906				0.948
Premenopausal	10	12		17	4	1	
Postmenopausal	16	18		27	6	1	
Parity			0.348				0.870
Multipara	26	29		43	10	2	
Nullipara	0	1		1	0	0	
Age at first delivery (yr)			1.000				1.000
≤18	13	15		22	5	1	
>18	13	15		22	5	1	
White discharge			0.950				0.632
Absent	8	9		14	3	0	
Present	18	21		30	7	2	
Foul-smelling discharge			0.250				0.791
Absent	23	23		36	8	2	
Present	3	7		8	2	0	
Vaginal bleeding			0.180				0.754
Absent	0	2		2	0	0	
Present	26	28		42	10	2	
Pain			0.906				0.410
Absent	10	12		17	5	0	
Present	16	18		27	5	2	
Weight loss			0.266				0.288
Absent	10	16		20	6	0	
Present	16	14		24	4	2	
Histological diagnosis			0.176				0.573
LSIL	0	2		1	1	0	
HSIL	5	10		13	2	0	
SCC	21	18		30	7	2	
Histological type of SCC (39 cases)			0.734				0.220
Keratinizing	8	5		8	4	1	
Non-keratinizing	13	13		22	3	1	
Histological grade of SCC (39 cases)			0.387				0.733
Well-differentiated	3	1		4	0	0	
Moderately-differentiated	18	16		25	7	2	
Poorly-differentiated	0	1		1	0	0	
p16 grade			0.099				0.932
Grade 1	0	3		2	1	0	
Grade 2	1	4		4	1	0	
Grade 3	25	23		38	8	2	

(Continued to the next page)

Table 2. Continued

Variable	ER-negative	ER-positive	P-value	HER2 status			P-value
				Negative	Equivocal	Positive	
p16 intensity			0.388				0.897
Weak	0	1		1	0	0	
Moderate	5	9		11	3	0	
Strong	21	20		32	7	2	
Ki-67 in CIN (17 cases)			0.575				1.000
Lower 1/3rd	1	4		4	1	0	
Middle 2/3rd	2	6		7	1	0	
Full	2	2		3	1	0	
SCC Ki-67 (39 cases)			0.752				0.303
≤60%	9	9		16	2	0	
>60%	12	9		14	5	2	
HER2 status			0.280				
Negative	19	25					
Equivocal	5	5					
Positive	2	0					

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; SCC, squamous cell carcinoma; CIN, cervical intraepithelial neoplasia; Ki-67, Ki-67 proliferation index.

HSIL were more frequently observed in premenopausal women. The high illiteracy rate observed in this study was comparable to that reported by Bhadauria et al. [15], which may indicate limited awareness of cancer symptoms and screening practices among illiterate populations. The most common presenting symptom was bleeding per vaginam in SCC and HSIL cases, whereas white discharge was most frequently reported in LSIL cases, findings that are consistent with those reported by Singh et al. [8] and Mehdi et al. [16]. These symptom patterns may reflect increased vascularity and epithelial disruption in dysplastic and malignant lesions.

The reported proportions of LSIL, HSIL, and SCC among cervical lesions vary widely in the literature, ranging from 4.8% to 35.7%, 20.2% to 86.5%, and 17.2% to 77.4%, respectively [5,8,9,13,14,16,18-27]. Similarly, the reported frequencies of well-differentiated, moderately differentiated, and poorly differentiated SCC range from 16% to 67.7%, 17.4% to 64%, and 9.8% to 33.2%, respectively [10,13,15-17,27,28]. Variability has also been reported with respect to histological subtype, including keratinizing and non-keratinizing SCC [13,15,17,28]. The very low number of LSIL cases and the predominance of moderately differentiated and non-keratinizing SCC observed in the present study may be attributable to the limited sample size or demographic variation within the study population.

The intensity and grading patterns of p16 staining have been variably reported in the literature, and the findings of the present study fall within these reported ranges [8,9,11,13,18,19]. HSIL and SCC predominantly showed nuclear-cytoplasmic, block-type positivity, whereas LSIL demonstrated patchy nuclear positivity, findings that are consistent with previous studies [8,16]. p16 is a tumor suppressor protein that is overexpressed in HPV-related lesions, while CIN 1 often shows variable expression with a substantial proportion of negative cases. Previous studies have reported p16-negative expression in 0%–84% of CIN 1/LSIL, 1.1%–50% of CIN 2, 0.6%–14% of CIN 3, and 0%–20% of SCC cases [8,9,13]. Grade 1 p16 expression has been reported in 10%–20.6% of CIN 1/LSIL, 6.3%–20% of CIN 2, 2.5%–10% of CIN 3, and 0%–18% of SCC cases [8,9,13]. In the present study, grade 1 expression was observed in 100% of LSIL cases and 6.7% of HSIL cases. Grade 2 expression has been reported in 0%–21% of CIN 1, 4.5%–24% of CIN 2, 1.2%–40% of CIN 3, and 0%–24% of SCC cases [8,9,13]; in the present study, 2.6% of SCC cases and 26.7% of HSIL cases showed grade 2 expression. Grade 3 expression has been reported in 0%–70% of CIN 1/LSIL, 6%–86.9% of CIN 2, 36%–95.7% of CIN 3, 100% of HSIL, and 38%–91.3% of SCC cases [8,9,13]. In the present study, grade 3 expression was observed in 66.6% of HSIL cases and 97.4% of SCC cases. These findings demonstrate a trend toward increasing p16 expression grade with lesion severity, reinforcing the utility of p16 as a biomarker of cervical lesion progression and malignancy.

LSIL lesions predominantly exhibit lower p16 expression grades, whereas HSIL and SCC show higher grades, with a progressive increase in staining intensity from LSIL to SCC [8,9,13,16,18,19,29]. In the present study, a similar progressive increase in p16 intensity was observed, ranging from predomi-

nantly negative or weak staining in CIN 1 to predominantly strong staining in SCC. Reported frequencies of weak, moderate, and strong p16 intensity range from 12.5%–50% for CIN 1/LSIL, 0%–77.8% for HSIL (CIN 2 and CIN 3), and 60%–100% for SCC [8,11,18,19]. Khamseh et al. [18] reported 87.5% negative staining in CIN 1, while 77.8% of CIN 3 cases showed moderate intensity. Li et al. [11] reported strong p16 intensity in 60% of SCC cases. Diouf et al. [19] observed 100% strong staining in SCC, with lower intensities in LSIL (50% weak) and HSIL (42.9% each moderate and strong). Singh et al. [8] reported LSIL cases with 37.5% weak and moderate staining each, HSIL with 60% strong staining, and SCC with 81% strong staining. In the present study, LSIL showed weak-to-moderate staining (50% each), HSIL showed 66.6% strong staining, and SCC showed 79.5% strong staining. Collectively, these findings underscore the value of p16 grading and intensity in distinguishing low-grade from high-grade cervical squamous lesions.

Ki-67 expression showed a gradual increase with lesion severity in the present study, consistent with previous reports, supporting its role as a valuable adjunct marker in the diagnosis and grading of cervical squamous lesions and in distinguishing high-grade lesions [8,9,16,19,21,22,25,30]. CIN 1/LSIL lesions predominantly show low Ki-67 scores (0–1), with most cases having <25% positive cells [8,9,16,19,21]. CIN 2 and CIN 3, or HSIL lesions, demonstrate progressively increased Ki-67 expression, with CIN 3 showing the highest levels [8,9,16,19,21]. Zhong et al. [9] reported that 72.8% of CIN 3 cases exhibited >50% Ki-67 positivity. SCC consistently shows the highest Ki-67 expression, with 64.7%–100% of cases demonstrating >50% positivity across studies [8,16,21]. Diouf et al. [19] reported >50% Ki-67 positivity in 100% of SCC cases, whereas LSIL cases showed <5% positivity in 50% of cases. The findings of the present study are in concordance with the existing literature, with LSIL showing minimal staining (100% score 0) and SCC demonstrating >50% positivity in 76.9% of cases.

ER expression has been reported to gradually decrease with lesion severity, ranging from 12.5% to 50% in LSIL, 0% to 23.1% in HSIL, and 0% to 38.6% in SCC [7,22,24,30-33]. Kanai et al. [30] demonstrated a progressive decrease in ER positivity from CIN 1 (50%) to CIN 3 (0%). In contrast, Tervahauta et al. [31] reported ER positivity in 12.5% of CIN 1 and 23.1% of CIN 3 cases. Nikolaou et al. [22] found ER positivity in 30.6% of CIN cases, while Fonseca-Moutinho et al. [32] reported ER positivity in 44% of CIN lesions. In SCC, ER expression has been variably reported, ranging from 0% in the study by Mosny et al. [33] to 38.6% in the study by Sun et al. [7]. In the present study, ER negativity was observed in 0% of LSIL, 33.3% of HSIL, and 53.8% of SCC cases. This observation may suggest a trend toward decreasing ER expression with increasing lesion severity in this cohort, consistent with earlier reports in which LSIL demonstrated some ER positivity and SCC often showed lower expression. ER expression intensity also decreased with lesion progression in the present study. Higher ER positivity was observed among women aged >45 years, women with early menarche, postmenopausal women, multiparous women, and women with early childbearing age. ER positivity was also slightly higher in non-keratinizing tumors compared with keratinizing tumors and increased with decreasing tumor differentiation. However, no statistically significant correlation was identified between ER expression and the evaluated clinicopathological parameters, similar to findings reported in previous studies [7,24,32].

In published studies, HER2 positivity rates in cervical squamous premalignant and malignant lesions range widely from 0% to 64%, while reported negativity rates range from 8% to 97% [5,7,10,12,15,23,25-27,31,34-38]. In the present study, only 5.1% of SCC cases were HER2 positive. Most studies have reported predominantly negative HER2 expression in cervical squamous lesions [5,7,12,15,23,34-36,38]. Gupta et al. [27] and Bajpai et al. [5] reported higher HER2 positivity in poorly differentiated SCC; however, the single poorly differentiated SCC case in our cohort was HER2 negative. Several studies have also reported no significant correlation between HER2 expression and clinicopathological parameters, findings that are concordant with our study [23,36,39]. In contrast, some authors have demonstrated a significant association between HER2 expression and histological grade, a relationship that was not observed in our cohort [10,27]. Additionally, the present study does not show a significant correlation between ER and HER2 in cervical premalignant and malignant lesions, consistent with the findings of Sun et al. [7].

The limitations of the present study include its restriction to p16-positive cases, which may limit generalizability to the broader spectrum of cervical lesions and reduce statistical power for detecting associations. Variations in immunohistochemistry protocols, scoring systems, and interpretation criteria across studies may also contribute to differences between the present findings and previously published results. Application of these findings in clinical practice will require validation through larger, multi-institutional studies and integration with emerging therapeutic approaches to better define their potential impact on patient outcomes.

In conclusion, the present study demonstrates that p16 positivity increases in both intensity and grade from LSIL to SCC. In most CIN cases, Ki-67 expression was commonly observed up to the middle two-thirds of the dysplastic epithelium. ER expression

was observed to decrease with lesion progression; however, this trend did not reach statistical significance in the present study. HER2 expression was rarely positive in cervical squamous neoplasia, suggesting limited therapeutic applicability. Overall, these findings provide valuable insights into the biological behavior of cervical squamous neoplasms and their potential relevance for targeted therapy. The results of the current study may help address gaps in the existing literature and offer foundational evidence to support further exploration of emerging strategies, including ER- and HER2-related therapeutic approaches.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

This published article includes all data generated or analyzed during this study.

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Supplementary materials

None.

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Case report

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Positional and ventilatory mechanics in the unexpected resolution of glycopyrrolate-induced tachycardia: a case report

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A 28-year-old woman developed drug-induced tachycardia in the left lateral decubitus (LLD) position following intravenous administration of glycopyrrolate. The tachycardia was unresponsive to esmolol, labetalol, and fentanyl but resolved unexpectedly after the tidal volume was reduced from 8 to 6 mL/kg. Drug-induced tachycardia or arrhythmia occurring in the LLD position under mechanical ventilation may be attenuated by adopting a low tidal volume ventilation strategy (6 mL/kg).

Keywords: Heart rate; Cholinergic antagonists; Ventilation; Anesthesia; Posture; Autonomic nervous system; Case reports

Introduction

Background

The cardiovascular system regulates heart rate (HR) and arterial blood pressure via the autonomic nervous system (ANS) in response to physiological and environmental changes. Some studies have reported that a recumbent position may influence ANS activity and hemodynamics in patients with congestive heart failure (CHF) [1,2] and might also affect healthy individuals [3].

Glycopyrrolate, a muscarinic anticholinergic commonly used preoperatively to reduce respiratory secretions, may cause systemic side effects such as mydriasis, tachycardia, prostration, anorexia, and diarrhea [4].

This case suggests that even in patients without a cardiovascular history, administration of anticholinergic agents in the left lateral decubitus (LLD) position could increase cardiac burden, potentially resulting in arrhythmia or drug-resistant tachycardia. Such complications may be mitigated by reducing the tidal volume to approximately 6 mL/kg.

Objectives

We report a case of a 28-year-old woman who developed glycopyrrolate-induced sinus tachycardia in the LLD position that was unresponsive to esmolol, labetalol, and fentanyl, but unexpectedly resolved shortly after tidal volume reduction.

Case presentation

Ethics statement

This study was approved by the Institutional Review Board (IRB) of the Korea Institute of Radiological & Medical Sciences (IRB No. 2025-10-011). The IRB approved a waiver of informed consent.

A 28-year-old woman (156.2 cm, 50.8 kg) was scheduled for curettage and bone cementing for a giant cell tumor of the right distal femur (6.7×7.3×5.9 cm). Preoperative laboratory tests revealed mild hyponatremia (126 mmol/L) and hypoglycemia (65 mg/dL), which were corrected the day before surgery (sodium: 133 mmol/L, glucose >70 mg/dL). Her past medical history, pulmonary function test results, and preoperative electrocardiogram were unremarkable.

On the day of surgery, no premedication was administered. Upon arrival in the operating room, the patient's peripheral oxygen saturation (SpO_2) was 99%, blood pressure was 110/62 mm

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Hg, and HR was 64 beats per minute (bpm). Preoxygenation was performed using face mask ventilation with 100% oxygen at a flow rate of 6 L/min. General anesthesia was induced with lidocaine 50 mg, propofol 100 mg, vecuronium 7 mg, and fentanyl 75 μg. Tracheal intubation was performed using a 7.0-mm endotracheal tube. After intubation, bilateral breath sounds were confirmed to be clear without abnormalities, and mechanical ventilation was initiated in volume-controlled ventilation mode. Anesthesia was maintained with sevoflurane 1.5% and nitrous oxide 50% in oxygen at a total flow rate of 2 L/min. Tidal volume was set at 8 mL/kg with a respiratory rate of 10 breaths/min. Ventilation and oxygenation were monitored using end-tidal CO_2 ($EtCO_2$) and SpO_2. Blood pressure was measured with a non-invasive blood pressure cuff on the left arm. A peripheral intravenous line was secured in the right arm via a 16-gauge catheter.

The patient was placed in the LLD position, and a tourniquet was applied to the right thigh. She was positioned near the left edge of the operating table. The dependent leg was well-padded, and an additional pad was placed between the legs for stability. The patient was then secured with a surgical table strap to prevent unintended movement. From that point onward, the mean arterial pressure (MAP) remained at approximately 66 mm Hg, while HR persisted at 49–55 bpm. Therefore, glycopyrrolate 0.2 mg was administered intravenously to increase the HR, as glycopyrrolate, compared with atropine, typically produces smaller increases in HR and the rate–pressure product, a hemodynamic parameter considered a reliable surrogate for myocardial oxygen demand [5]. HR increased to over 100 bpm immediately after glycopyrrolate administration (Fig. 1); thus, esmolol 20 mg was administered. However, HR continued to rise, requiring repeated doses of esmolol (30 mg × 2) without effect (Fig. 2). HR subsequently peaked at 122 bpm despite additional administration of labetalol 2.5 mg

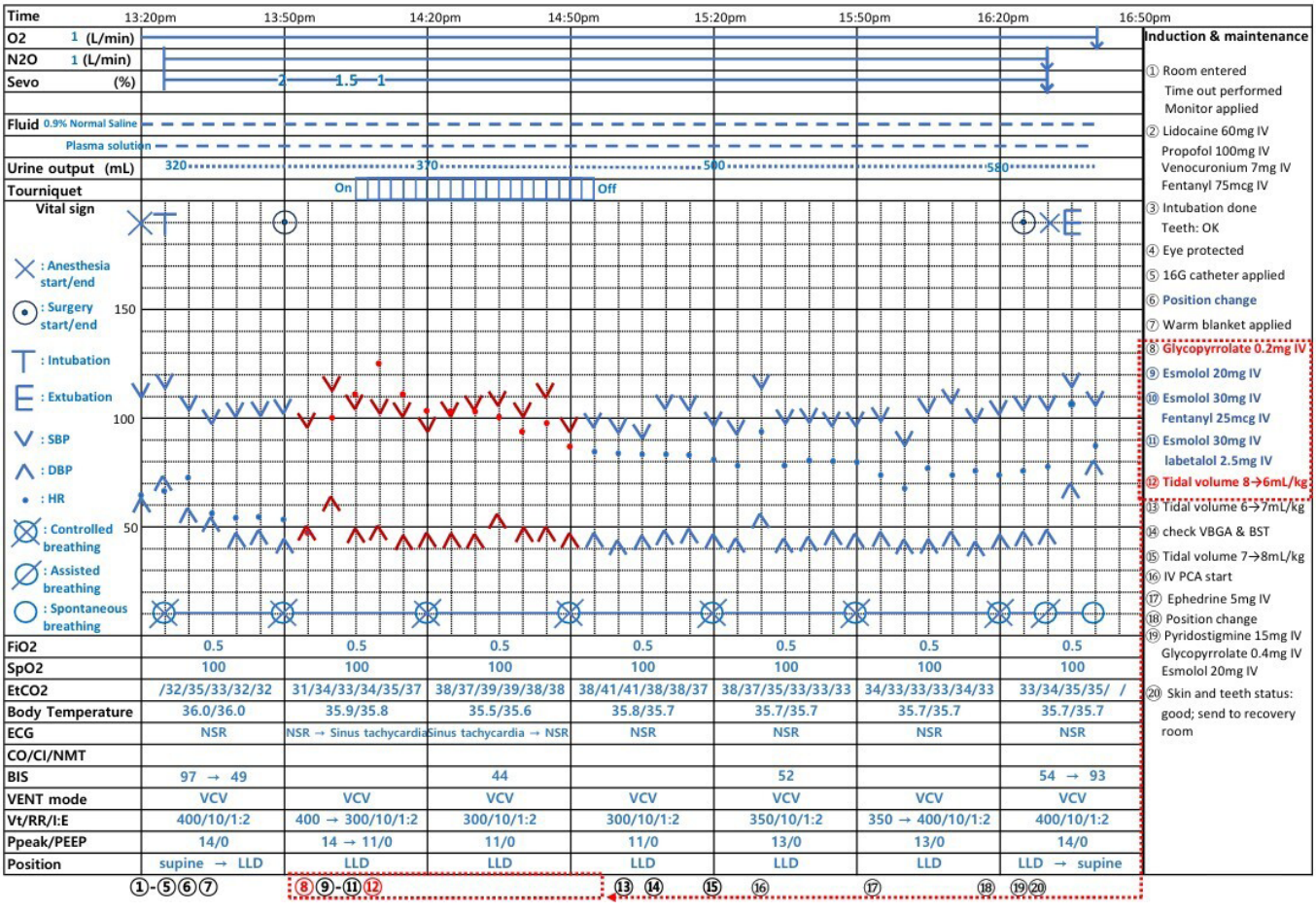

Fig. 1. Timetable of anesthetic care during the operation. BIS, bispectral index; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; ECG, electrocardiogram; HR, heart rate; IV-PCA, intravenous patient-controlled analgesia; NMT, neuromuscular transmission; NSR, normal sinus rhythm; Ppeak/PEEP, peak inspired airway pressure/positive end expiratory pressure; RR, respiration rate; VENT mode, ventilation; VCV, volume-controlled ventilation; Vt, tidal volume; $EtCO_2$, end-tidal CO_2; FiO_2, fraction of inspired oxygen; SpO_2, peripheral oxygen saturation.

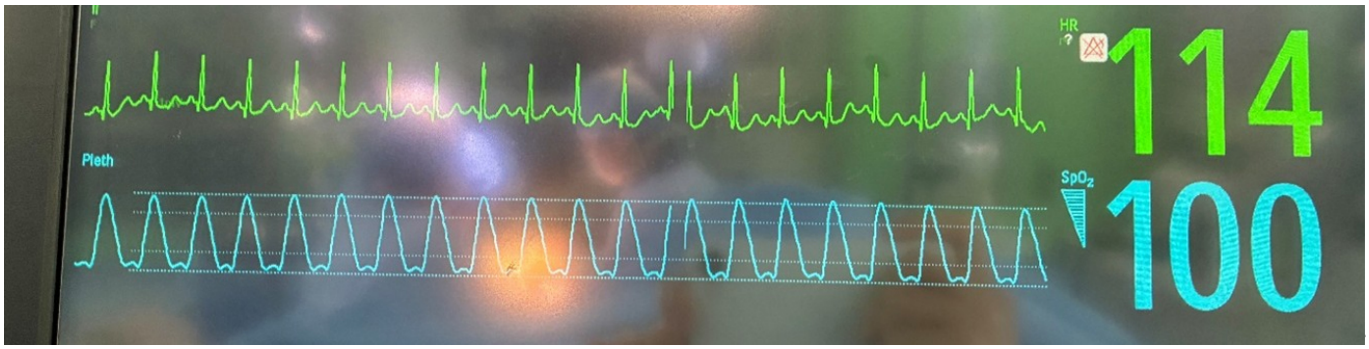

Fig. 2. Electrocardiogram demonstrating increased heart rate immediately after glycopyrrolate administration.

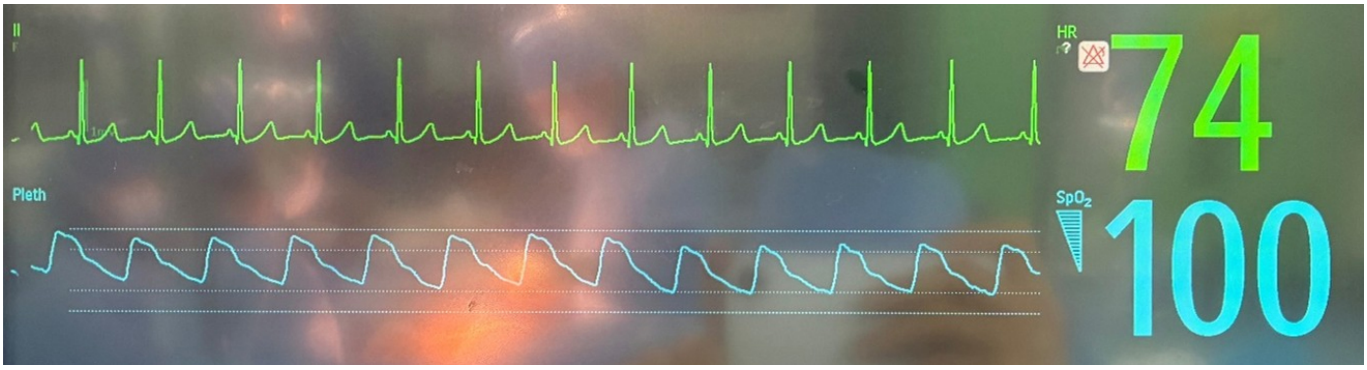

Fig. 3. Electrocardiogram demonstrating heart rate 1 hour after tidal volume reduction.

and fentanyl 25 μg, both given to attenuate the tachycardic response. During this period, systolic blood pressure was maintained at 101–110 mm Hg, diastolic blood pressure at 50–62 mm Hg, and MAP at 65–75 mm Hg. Sevoflurane was reduced to 1%, and the team notified the attending anesthesiologist, who recommended increasing tidal volume to 9–10 mL/kg to prevent hypercarbia. However, due to miscommunication, tidal volume was instead reduced to 6 mL/kg while sevoflurane was maintained at 1%; during this time, $EtCO_2$ remained at 39–41 mm Hg. Remarkably, HR promptly decreased to 109 bpm and returned below 100 bpm within 25 minutes (Fig. 3), while MAP remained near 66 mm Hg. Glycopyrrolate-induced tachycardia persisted for approximately 40 minutes. Thereafter, tidal volume was adjusted to 7–8 mL/kg to maintain a target $EtCO_2$ of approximately 35 mm Hg.

During emergence, the patient was repositioned supine, and neuromuscular blockade was reversed with glycopyrrolate 0.4 mg and pyridostigmine 15 mg. She was extubated uneventfully, with no further complications.

Discussion

In our case, after the patient was placed in the LLD position, HR initially decreased to 49–53 bpm. Chen and Kuo [3] reported that cardiac vagal tone varies by recumbent body position, based on spectral heart rate variability (HRV) indices such as normalized high-frequency power and the low-/high-frequency (LF/HF) power ratio, suggesting that autonomic modulation may differ with posture even in healthy individuals. Miyamoto et al. [1] described no significant differences in the LF/HF ratio among 3 recumbent positions (supine, LLD, and RLD) in healthy participants, indicating that cardiac autonomic activity is unaffected by posture, unlike in patients with CHF; however, Sasaki et al. [6] demonstrated that HR reduction and an increase in left ventricular end-diastolic diameter in the LLD position, without significant changes in stroke volume, cardiac output, or HRV, represent a physiological phenomenon rather than altered ANS activity.

Several mechanisms for positional effects on cardiac function have been proposed. First, gravitational effects in the LLD position may displace the heart, leading to distortion of the pulmonary veins and impaired venous return. Second, in patients with cardiomegaly, the LLD position may cause left ventricular compression against the chest wall, impairing diastolic filling. A recent case report by Feng et al. [7] further described this phenomenon, reporting severe hypotension and trepopnea in the LLD position

during preparation for spinal anesthesia. These findings suggest that the reduction in HR in the LLD position may relate to increased cardiac burden.

When HR increased after glycopyrrolate administration, the resulting sinus tachycardia was refractory to pharmacologic interventions (e.g., esmolol, labetalol, fentanyl) but resolved after tidal volume was reduced from 8 to 6 mL/kg. De Backer et al. [8] identified tidal volume as a major determinant of right ventricular (RV) afterload and stroke work, while Mahmood and Pinsky [9] demonstrated that large tidal volumes increase intrathoracic pressure swings, impairing RV ejection due to limited contractile reserve. In this case, an intermediate tidal volume (8 mL/kg), combined with positional effects, may have compromised RV function and facilitated glycopyrrolate-induced tachycardia. Cherpanath et al. [10] further reported that intermediate tidal volumes (8–10 mL/kg) cause biventricular systolic dysfunction compared with a low tidal volume (4–6 mL/kg) strategy, likely due to ventilation-induced inflammation, without affecting diastolic function. Thus, reducing the tidal volume to 6 mL/kg likely improved cardiac performance and contributed to HR normalization in this case.

In addition, Natalini et al. [11] reported that a low tidal volume ventilation strategy (6 mL/kg of ideal body weight) improved cardiac index and oxygen delivery compared with a high tidal volume strategy (12 mL/kg of ideal body weight) in patients with acute respiratory distress syndrome. These effects were attributed to a slight increase in arterial carbon dioxide tension ($PaCO_2$), which reduces systemic vascular resistance and enhances pulmonary vasoconstriction, thereby improving ventilation–perfusion matching [12].

This analysis is limited by the absence of invasive hemodynamic monitoring (e.g., an arterial line, central venous line, or Swan–Ganz catheter), as the procedure was not extensive and the patient had no significant past medical history. Nonetheless, intraoperative hypovolemia was considered unlikely because urine output remained above 0.5 mL/kg/hr, and venous blood gas analysis performed approximately 1 hour after the onset of tachycardia showed a hemoglobin level of 9.9 g/dL. As other potential causes were evaluated, attention was directed toward the possibility of a drug-induced reaction. Choi and Kim [13] reported an anaphylactic reaction following the administration of glycopyrrolate and pyridostigmine, which presented as refractory hypotension and an erythematous skin rash. In contrast, in our case, an adverse drug reaction such as glycopyrrolate-induced anaphylaxis was excluded, as no abnormal findings were observed either during emergence following administration of the reversal agent or after subsequent administration of glycopyrrolate for bradycardia. Consequently, the resolution of drug-induced tachycardia after tidal volume reduction may suggest that modulation of intrathoracic pressure improved cardiac performance, consistent with previous reports in the literature.

In conclusion, drug-induced tachycardia or arrhythmia occurring in the LLD position under mechanical ventilation may be attenuated by low tidal volume ventilation (6 mL/kg).

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Authors' contribution

Conceptualization: SJA. Data curation: SJA. Methodology/formal analysis/validation: SJA, SYL. Project administration: SJA. Funding acquisition: SJA. Writing–original draft: SJA. Writing–review & editing: SJA, SYL.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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The spirit of Ewha, carried forward through devotion: an interview with Dr. Kumie Oh, alumna of the 27th graduating class, anesthesiologist

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This interview was conducted as part of a project aimed at gaining insight into the international careers of Ewha alumnae and offering current medical students perspectives on pursuing global opportunities. The conversation took place via Zoom with alumna Dr. Kumie Oh, who graduated from Ewha Womans University College of Medicine as a member of the 27th graduating class (Fig. 1). After completing her anesthesiology residency at Loyola University Medical Center in Chicago, she served for 28 years as a faculty member in the Department of Anesthesiology and also as Director of the Division of Obstetric Anesthesia. Since her medical career in the United States began in 1987 and her faculty appointment in 1991, she has spent several decades contributing to both clinical care and medical education.

While serving as President of the Ewha Medicine Alumnae Association of North America from 2014 to 2018, Dr. Oh strengthened the alumnae network across North America and supported fundraising efforts for Ewha Seoul Hospital in Magok. Beyond her clinical career, she has continued her long-standing interest in botanical art and has participated in various international exhibitions, including those held in conjunction with the 35th and 40th class reunions.

This interview was conducted by student reporter Nahyun Kwon (Class of 2019) and was organized and written by Jiyoon Kim (Class of 2024).

Interview

EMJ: Thank you for joining me today. Could you please start by introducing yourself briefly?

Dr. Oh: Thank you for inviting me, and it is nice to meet you. My name is Kumie Oh, and I am a graduate of Ewha Medicine, 27th graduating class, in 1978. I completed my internship and anesthesiology residency at Ewha Dongdaemun Hospital and then worked as a clinical fellow at Seoul National University Hospital for 1 year. In the United States, I repeated my anesthesiology residency at Loyola University Medical Center in Chicago and later served there as a faculty member for a total of 32 years until my retirement. I am grateful for the opportunity to share my experiences as an anesthesiologist, and I also subspecialized in obstetric anesthesia during my career in the United States.

EMJ: What led you to pursue a medical career in the United States? How was the medical environment different between Korea and the United States at the time, in the mid 80's?

Dr. Oh: I graduated in 1978, shortly after the Vietnam War ended in 1975. By that time, the pathway for foreign medical graduates to work in the United States through the Educational Commission for Foreign Medical Graduates (ECFMG)-based recruitment had essentially closed. After completing my residency in Korea, I was considering remaining in academia. However, I ultimately chose to join my mother and siblings, who were already living in the United States, and to pursue a new professional challenge abroad.

In the mid-1980s, the medical environment in the United States was quite challenging for foreign medical graduates. During the war, they had been welcomed to fill physician shortages, but by the time I arrived, residency positions for foreign graduates had

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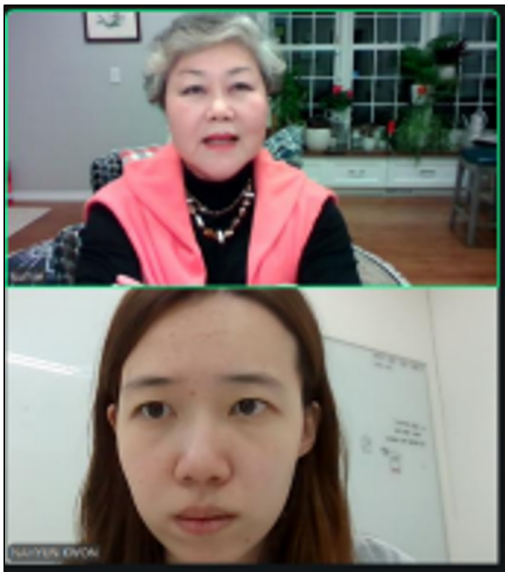

Fig. 1. On November 4, 2025, an online interview was conducted via Zoom with Dr. Kumie Oh (오구미), a graduate of Ewha Womans University College of Medicine, a member of the 27th graduating class. (A) Dr. Kumie Oh (오구미, Photograph provided by Kwon). (B) Nahyun Kwon, student reporter (Photograph provided by Kwon).

become extremely competitive. Later, I learned that most Ewha alumnae practicing in the United States had entered the system between the mid-1960s and early 1970s, before opportunities became much more limited.

EMJ: Did you face challenges related to language or cultural differences when working as a physician?

Dr. Oh: Establishing myself in the United States was not easy. I arrived in August 1985 but was unable to begin residency until July 1987. During those 2 years, I applied to more than 130 anesthesiology programs listed in the "Green Book," a directory of residency programs. Because anesthesiology was highly competitive, even among American graduates, many people advised me to switch specialties. However, I was determined to continue in my original field. During that period, I practiced English consistently and learned most effectively through immersion in clinical work. As we all know, there is no shortcut to learning a foreign language except persistent practice. Because we used English-language medical textbooks for almost every subject in medical school, medical terminology itself was not a major concern.

EMJ: What was your mindset during medical school at Ewha, and how did those experiences shape your career in the United States?

Dr. Oh: I look back on my medical school years with happiness and joy. Although the times were economically challenging for everyone, we were young, hardworking, and surrounded by like-minded, brilliant, and wonderful friends. I have continued these friendships for over 50 years. I also still maintain a close relationship with my mentor, Professor Jong-Nam Kim.

I was active in the mountaineering club, volunteered in rural clinics, and traveled on a limited budget with friends during school breaks. These are memories I treasure deeply. The mid-1970s were politically turbulent, with frequent class cancellations, yet my 5-member study group remained highly motivated. We understood that medicine is a field in which one's competence directly affects human lives. Many members of that study group later pursued academic careers, and the intellectual atmosphere of that time profoundly influenced me. Even after moving abroad, the enduring friendships formed during those years truly became a source of strength.

EMJ: Could you describe your path into internship and residency in the United States? What challenges did you encounter as an immigrant physician, and how did you overcome them?

Dr. Oh: Although my medical degree from Korea was recognized, I had to repeat both internship and residency, despite already being board-certified in anesthesiology in Korea. In addition to ECFMG certification, the Federal Licensing Examination (FLEX) was required to enter residency. A physician who had gone through the process before me advised, "Study hard, but don't lose your mind doing it."

Fortunately, I passed the FLEX on my first attempt and secured a residency position at Loyola University Medical Center. The first year of anesthesiology training is a Clinical Base Year, which involves rotating through internal medicine and other specialties. On my first day, I found myself among 50 internal medicine interns. Only 2 of us were foreign graduates: one Pakistani physician with impeccable British English, and myself, who felt bewildered by everything from the language to the hospital system.

At home, I had 2 young children, aged 1 and 5, and I was physically and emotionally exhausted. However, with my husband's support and help from family members, I persevered. Once I began my formal anesthesia training, my prior clinical experience in Korea proved to be a tremendous advantage.

EMJ: Was there any particular experience during your early adjustment period that remains unforgettable?

Dr. Oh: Before starting residency, I worked as a temporary extern at a hospital in Evanston. Because the pediatric program there had been discontinued, 2 Indian physicians in similar circumstances and I covered pediatric cases together. I vividly remember accidentally answering a question about a theophylline level in Korean because I was so nervous. At the same time, my prior anesthesia experience served me well. I was often asked to perform newborn intravenous insertions or spinal taps, which helped me

earn the nurses' trust and appreciation. These experiences taught me that despite cultural and linguistic differences, the core of patient care is universal.

EMJ: Did you encounter difficulties as a Korean woman physician in the United States? How did Korean medical training influence your practice in America?

Dr. Oh: Medicine is fundamentally a merit-based profession, so I rarely experienced discrimination based on race or gender. However, systemic differences between the 2 medical systems were quite apparent. In Korea, interns primarily carried out logistical tasks such as transporting X-rays or electrocardiograms. In contrast, interns in the United States independently formulated assessments and treatment plans and presented them during morning rounds. I often arrived at the hospital before dawn to examine my 12 assigned patients and complete their progress notes before the 8 AM rounds. Discharge summaries also took me much longer than they did for American interns. They could often finish in about 10 minutes, whereas on particularly busy days, I spent several hours completing mine. During anesthesia training, the techniques themselves were familiar, but the anesthesia machines and many of the medications were new to me. Nevertheless, my Korean training proved invaluable. On my first day, after intubating a patient with severe burns, the attending physician immediately asked, "How many years of experience do you have?" because my technique appeared advanced. At the same time, patient populations in the United States differed significantly, with higher rates of obesity, trauma, and gunshot injuries. My extensive experience caring for obstetric patients at Ewha Dongdaemun Hospital in Korea was especially helpful later, when I served as Director of Obstetric Anesthesia for more than 2 decades.

American hospitals also placed strong emphasis on collaboration rather than strict hierarchy. Lower-level trainees were expected to express their opinions, a culture that initially felt unfamiliar but ultimately fostered a deeper sense of responsibility.

EMJ: How did you build relationships with other physicians, including Korean American medical professionals?

Dr. Oh: At Loyola, there were very few Korean physicians. I eventually joined the Korean American Medical Association although it dissolved soon afterward. Most of my meaningful connections came through gatherings of the Chicago Ewha Medical Alumni, which were led by devoted senior alumnae such as Dr. Yong-Ok Cho and Dr. Jung-Sik Yoon from the Class of 1959.

EMJ: What role did alumni engagement and the Korean American community play in your life?

Dr. Oh: During my busiest years, it was difficult to participate actively, but as time passed, I became more involved. I served as secretary during the founding of the Ewha Womans University Alumnae Association of North America and later organized the annual conference in Chicago as its president. From 2014 to 2018, I also served as president of the Ewha Medicine North America Alumni Association and helped raise funds for the construction of Ewha Seoul Hospital. My connection to Ewha has always been a source of pride and personal strength.

EMJ: What efforts did you make to maintain excellence as an anesthesiologist?

Dr. Oh: Medicine requires lifelong learning. In the United States, specialists are required to renew board certification every 10 years and to accumulate continuing medical education credits every 3 years for state license renewal. Academic physicians must also remain current through conference participation, ongoing literature review, and teaching responsibilities.

I benefited greatly from activities such as weekly departmental conferences, Journal Club, daily lectures for residents, and joint conferences with obstetrics focused on high-risk obstetric patients. Above all, however, the knowledge gained from caring for the most complex and challenging patients is irreplaceable. Being selected twice by graduating anesthesia residents as "Best Teacher of the Year," in 1995 and again in 2003, remains one of my proudest professional achievements.

EMJ: How have the qualities expected of physicians changed over time? What core competencies do you believe future physicians must have?

Dr. Oh: In the past, technical skill was considered paramount, but today communication and teamwork are equally essential. When residency graduates apply for positions, department chairs often place great emphasis on an applicant's ability to collaborate effectively.

Although anesthesiology may appear to be a solitary specialty, it is fundamentally team-based. Furthermore, as technology evolves at an unprecedented pace, physicians must be prepared to adapt. My generation witnessed the transition from handwritten charts to electronic medical records, and future physicians will need to integrate artificial intelligence into nearly all aspects of medical practice.

EMJ: Did any role models or experiences shape your professional values?

Dr. Oh: Before coming to the United States, I read about Dr. Sherwood Hall, a medical missionary who introduced Korea's first Christmas Seal campaign for tuberculosis prevention. His mother, Rosetta Hall, once donated skin from her own thigh to graft onto a burn patient in Pyongyang. That story taught me the true meaning of compassion, responsibility, and love in patient care.

EMJ: Did you ever regret choosing anesthesiology? What gives

you meaning in your career?

Dr. Oh: Initially, I hoped to pursue a career in surgery. However, I am deeply grateful to the late Professor Choon-Hee Lee, former Chair of Anesthesiology at Ewha Dongdaemun Hospital, who encouraged me to consider anesthesiology. In retrospect, it proved to be the perfect choice, especially because obstetric anesthesia became my lifelong passion. The field's close relationship with surgical innovation and its central mission of alleviating pain align deeply with my values.

The official seal of the American Society of Anesthesiologists, "Vigilance," captures the essence of our role: safeguarding patient safety under anesthesia. Regional anesthesia techniques, such as spinal and epidural blocks, have significantly reduced maternal mortality. As a member of the Outreach Committee of the Society for Obstetric Anesthesia and Perinatology, I had the opportunity to help introduce epidural anesthesia in Mongolia and Georgia. These experiences reinforced my belief in contributing to a safer and more pain-free world.

EMJ: How did you balance family life with a demanding medical career?

Dr. Oh: Balancing family life with my career was extremely difficult. My children essentially grew up with minimal involvement from their mother because of my demanding workload. I still remember receiving a phone call during a particularly busy Sunday on call, while preparing anesthesia for a lung transplant, from my daughter, even though I had told her not to call me at work. Before I could fully listen, I scolded her. She then burst into tears and said, "Grandma left a pan on the stove, and the house caught fire." When I returned home the next day, I found significant damage and a flooded basement caused by the fire hoses. Despite these hardships, my children grew up safely and later told me that they were proud of me. Those words are something I will never forget. Their childhood represents the greatest sacrifice I made during my years in the United States.

EMJ: How did you find personal balance outside your professional responsibilities?

Dr. Oh: While taking my son to art lessons, I happened to discover botanical art, which I have now practiced for more than 20 years, including after my retirement. Art became a refuge from clinical stress and provided joy and creative fulfillment. I held exhibitions with classmates during our 35th and 40th reunions and also participated in several international exhibitions. It was especially meaningful to have a solo exhibition in 2024, where I was able to share my work with family and friends. Balancing professional life with artistic expression helped me maintain my emotional well-being.

EMJ: What advice would you give to physicians who feel discouraged or emotionally exhausted?

Dr. Oh: Medicine can be emotionally taxing, particularly when patient outcomes are less favorable than hoped. In those moments, my faith, friends, and family sustained me. Above all, as a believer, my unwavering trust in God became my greatest source of strength.

EMJ: What final message would you like to share with Ewha's future physicians?

Dr. Oh: Whenever I receive a warm welcome from Ewha, I feel as though I have returned home. I am proud to see Ewha Seoul Hospital establishing its place on the global stage. I hope that today's students, who are learning in an era with far richer educational resources, study diligently and grow into capable medical professionals who embody the spirit of Ewha. May our school's traditions and values continue to thrive for generations to come.

Reflection

Through our conversation with Dr. Oh, we were reminded that medicine is not merely a technical profession, but a lifelong commitment rooted in empathy, responsibility, and human understanding. Her career exemplifies the enduring dignity and compassionate leadership of Ewha alumnae, values that remain unchanged across generations.

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All the work was done by Nahyun Kwon and Jiyoon Kim.

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