

# Significance of Relative Left Ventricle Wall Thickness in Predicting Acute Kidney Injury After Video-Assisted Thoracoscopic Surgery for Lung Cancer

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## Abstract

**Aims/Background** Given the strong association between relative wall thickness (RWT) and cardiovascular dysfunction, this study aims to explore RWT as a novel cardiovascular indicator to predict the risk of acute kidney injury (AKI) after lung cancer surgery and guide clinical interventions.

**Methods** This study retrospectively analyzed 170 patients who underwent video-assisted thoracoscopic surgery (VATS) for lung cancer in Nanjing First Hospital, China, between January 2022 and December 2023. Patients were divided into AKI group (n = 52) and non-AKI group (n = 118) based on the occurrence of AKI. Univariate analysis was performed to identify factors affecting the development of AKI in patients undergoing VATS for lung cancer. Moreover, multivariate logistic regression analysis was conducted to determine influencing factors. Correlation analysis was used to analyze the relationships between variables, and receiver operating characteristic (ROC) curve analysis was conducted to assess predictive ability.

**Results** There were no statistically significant differences in gender, comorbidities, smoking history, tumor location, Tumor-Node-Metastasis (TNM) Staging System, tumor differentiation, neutrophil count, red blood cell count, white blood cell count, creatinine, urea nitrogen, intraoperative blood loss, and operation time ( $p > 0.05$ ). The comparison of age, Acute Physiology and Chronic Health Evaluation (APACHE II) score, mean arterial pressure, and RWT between the two groups showed statistically significant differences ( $p < 0.05$ ). Multivariate logistic regression analysis indicated that age, APACHE II score, mean arterial pressure, and RWT significantly influenced the development of AKI in patients undergoing VATS for lung cancer ( $p < 0.05$ ). RWT was negatively correlated with mean arterial pressure ( $r = -0.558, p < 0.05$ ), and positively correlated with age and APACHE II Score ( $r = 0.573, 0.520, p < 0.05$ ). Moreover, AKI showed a positive correlation with age, APACHE II Score, and RWT ( $r = 0.726, 0.685, 0.772, p < 0.05$ ), and a negative correlation with mean arterial pressure ( $r = -0.724, p < 0.05$ ). ROC analysis revealed that the area under the predicted curve for RWT was 0.864, and the standard error was 0.030 (95% confidence interval (CI): 0.805~0.923), with a Youden index of 0.55. At this time, the sensitivity was 87.29% and the specificity was 67.31%.

**Conclusion** RWT shows excellent predictive value for postoperative AKI in patients undergoing VATS for lung cancer.

**Key words:** echocardiography; relative left ventricle wall thickness; lung cancer; acute kidney injury

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## Introduction

Acute kidney injury (AKI) is a common and severe complication following video-assisted thoracoscopic surgery for lung cancer, particularly more pronounced in elderly patients (Balakrishna et al, 2023; Rodriguez et al, 2024). While the underlying pathogenic mechanisms are complex, cardiovascular dysfunction is considered a major contributing factor. Relative wall thickness (RWT) of the left ventricle, referred to as the ratio of left ventricular wall thickness to its chamber diameter (Gardin, 2016), is an important parameter for evaluating left ventricular structural changes and is commonly measured through echocardiography. Furthermore, RWT is closely associated with long-term risk of heart failure in patients with myocardial dysfunction and preserved left ventricular ejection fraction (LVEF). Evidence suggests that RWT may serve as a novel cardiovascular factor influencing the progression of AKI following high-risk non-cardiac surgeries (Gaasch, 1979).

Echocardiography, a non-invasive, real-time imaging method based on ultrasound echo principles, precisely visualizes cardiac chamber dimensions, thickness of walls, and morphology and function of valves (Schwarzwalder, 2019; Vitale et al, 2022; Vitale et al, 2023). Studies on the relationship between RWT and postoperative AKI in video-assisted thoracoscopic surgery (VATS) patients remained limited. However, Goeddel et al (2022) reported that an increase in RWT in patients with preserved LVEF is associated with a higher risk of developing AKI within 7 days after high-risk non-cardiac surgeries. Investigating the predictive value of RWT for AKI after VATS for lung cancer holds significant clinical importance. Understanding the association between RWT and AKI may provide personalized risk stratification, and perioperative interventions, ultimately decreasing AKI incidence and enhancing overall surgical outcomes.

We investigated the role of echocardiography in evaluating RWT as a potential indicator of AKI following thoracoscopic radical lung cancer resection. While previous studies examined the broader link between cardiovascular dysfunction and AKI, our study specifically evaluates RWT, a cardiovascular factor routinely measured through echocardiography, as a novel predictor of AKI risk after high-risk lung cancer surgeries. We aim to explore whether RWT can serve as a novel cardiovascular marker, guiding risk assessment and perioperative intervention. Ultimately, this study intends to advance the understanding of echocardiography-assessed RWT as a marker for AKI in VATS patients, providing a scientific basis for clinical decision-making and improving patient outcomes.

## Methods

### Study Participants

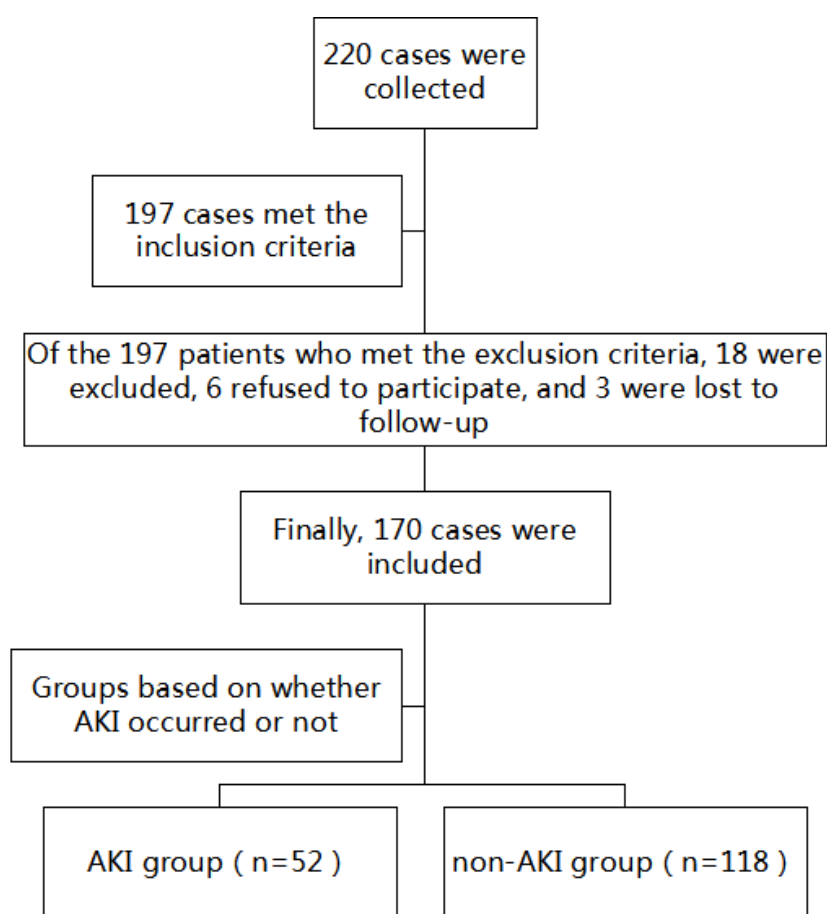
This retrospective study recruited 170 patients who underwent VATS for lung cancer at Nanjing First Hospital, China, between January 2022 and December 2023. The inclusion criteria for patient selection were set as follows: (1) Clinical diagnosis followed standard criteria and confirmed through pathological examination (Rostad et al, 1979). (2) Individual eligible for curative surgery and undergoing VATS for

lung cancer. (3) Newly diagnosed lung cancer cases. (4) No history of cardiac or aortic surgeries. (5) The patients who underwent echocardiographic examination.

The exclusion criteria included: (1) Patients who received preoperative adjuvant radiotherapy or chemotherapy. (2) Patients with impaired mental status. (3) Those with incomplete clinical or laboratory data, such as missing blood routine tests or echocardiography results. (4) Patients with severe cardiac arrhythmias, myocardial infarction, or other significant cardiac conditions.

### Stratification of the Study Subjects

Patients were divided into two groups based on the occurrence of AKI: an AKI group (n = 52) and a non-AKI group (n = 118). The diagnosis of AKI followed the Global Kidney Disease Outcomes Organization (KIDIGO) criteria (Khwaja, 2012), which include: (1) An absolute increase in serum creatinine of 0.3 mg/dL (equivalent to 26.4  $\mu$ mol/L) or more within 48 hours. (2) A relative increase in serum creatinine of 50% or above compared to baseline. (3) Urine output of less than 0.5 mL/(kg·h) for 6 hours, after excluding other factors such as urinary tract obstruction or dehydration. Patient selection and grouping procedures are shown in Fig. 1.



**Fig. 1.** A flowchart of study subjects' selection and their stratification. AKI, acute kidney injury.

### Data Collection

Clinical, laboratory, and radiological data of patients were collected using the electronic medical record system. Blood sample processing procedures involve a series of steps, such as collection, resting (if applicable), centrifugation (if applicable), aliquoting (if applicable), storage, and transportation. Standard protocols were followed in performing each step to ensure sample quality and integrity.

Ultrasound operators must undergo comprehensive training, acquire the necessary theoretical knowledge and practical skills, and obtain the required qualifications by passing relevant examinations.

Blood samples were obtained via venipuncture and analyzed as follows: Neutrophil count: Anticoagulated blood samples were processed for neutrophil quantification using an automated hematology analyzer. Red blood cell count: An appropriate amount of red blood cell diluent was added to a test tube, followed by the addition of the blood sample. They were thoroughly mixed to achieve the appropriate dilution ratio. After this, the diluted blood sample was placed into a red blood cell counting chamber, allowed to settle briefly, and analyzed using a microscope. White blood cell count: Blood samples were mixed with an appropriate white blood cell diluent. Red blood cells were lysed using specific physical methods, and the processed sample was evaluated for white blood cell count and differential analysis, either using a microscope or an automated hematology analyzer.

A Color Doppler ultrasound diagnostic system was used to comprehensively evaluate and collect multiple key cardiac indicators. Initially, during echocardiography, the parasternal long-axis view of the left ventricle was usually opted as the basic scanning plane. This scanning provides a clear view of the left ventricular structure, including the interventricular septum, posterior wall, and chamber. Then, at end-diastole, the thickness of the interventricular septum and the posterior wall of the left ventricle at the mitral chordal level was determined using the ruler function of the echocardiography system. Furthermore, the end-diastolic diameter of the left atrium was also measured, which was defined as the distance from the inner edge of the left anterior wall behind the aortic root to the inner edge of the posterior wall. Morphological abnormalities of the aortic valve, like bicuspid malformation, and its functional status, including insufficiency or stenosis, were also recorded.

Additionally, the closing function of the mitral valve was measured to examine any insufficiency or stenosis. The aortic size was assessed by calculating the ratio of the aortic cross-sectional area to body surface area (BSA) and the proximal aortic cross-sectional area to body surface area. Other crucial parameters, including left atrial diameter (LAD), left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD), were also documented. Additional measurements included the maximum aortic valve flow velocity, interventricular septum thickness in diastole (IVSd), and left ventricular posterior wall thickness in diastole (LVPWd). The RWT was determined using the following formula (Zabalgóitia et al, 1998):  $RWT = (IVSd + LVPWd)/LVEDD$ .

The Acute Physiology and Chronic Health Evaluation (APACHE II) score (Knaus et al, 1985), is a widely used approach for assessing the severity of illness and predicting the risk of death in intensive care unit (ICU) patients. The system consists of three components: the acute physiological score, the age score, and the chronic health score, with a total score ranging from 0 to 71 points. Higher scores indicate a more serious condition and a higher risk of death.

### Statistical Analysis

Data were analyzed using SPSS 27.0 (IBM Company, Chicago, IL, USA). Bartlett's test was performed to ensure homogeneity of variances. Metric data following normal distribution was represented as  $\bar{X} \pm S$  and between-group comparison was conducted using independent sample *t*-tests. Categorical data were expressed as frequencies or percentages and analyzed using the  $\chi^2$  test. Univariate and binary logistics regression analyses were used to identify factors influencing the progression of AKI in patients undergoing radical lung cancer resection through VATS. The predictive value of RWT was evaluated using receiver operating characteristic curve analysis. The correlation between variables was examined using the Pearson correlation coefficient, with statistical significance set at  $p < 0.05$ .

## Results

### Univariate Analysis of Factors Influencing Development of AKI in Patients Undergoing VATS Lobectomy for Lung Cancer

The average age of patients in the AKI group was 55–70 years, with an average of  $66.42 \pm 2.37$  years, including 27 males and 25 females. In the non-AKI group, the average age of patients was also 55–70 years, with a mean of  $64.34 \pm 2.16$  years, comprising 60 males and 58 females. There were no significant differences in baseline characteristics between the two groups ( $p > 0.05$ ). Similarly, no statistically significant differences were found between the two groups regarding gender, comorbidities, smoking history, tumor location, Tumor-Node-Metastasis (TNM) stage, tumor differentiation, neutrophil count, red blood cell count, white blood cell count, creatinine, urea nitrogen, intraoperative blood loss, and operation time ( $p > 0.05$ ). However, a comparison of age, APACHE II score, mean arterial pressure, and RWT showed statistically significant differences ( $p < 0.05$ ) (Table 1).

### Binary Logistics Regression Analysis of Factors Affecting AKI Development

Binary logistic analysis was conducted with AKI as the dependent variable (AKI = 1, non-AKI = 0), using age, APACHE II score, mean arterial pressure, and RWT as independent variables entered with their original values. We observed that age, APACHE II Score, mean arterial pressure, and RWT were significant factors influencing the occurrence of AKI in patients undergoing VATS lobectomy for lung cancer ( $p < 0.05$ ) (Table 2).

### Correlation Analysis of Variables

Pearson linear correlation analysis revealed that RWT was negatively correlated with mean arterial pressure ( $r = -0.558$ ,  $p < 0.05$ ) and positively correlated

**Table 1. Development of AKI in patients undergoing VATS lobectomy for lung cancer.**

Baseline data	AKI group (n = 52)	Non-AKI group (n = 118)	<i>t</i> / $\chi^2$ value	<i>p</i> -value
Age (years)	66.42 ± 2.37	64.34 ± 2.16	5.614	<0.001
Gender			0.017	0.897
Male	27	60		
Female	25	58		
Comorbidities (number)			0.023	0.989
0	14	32		
1	26	60		
≥2	12	26		
Smoking history			0.002	0.962
Yes	24	54		
No	28	64		
Tumor location			0.034	0.853
Left lung	23	54		
Right lung	29	64		
TNM stage			0.016	0.898
I~II	11	26		
III	41	92		
Tumor differentiation			0.068	0.795
Highly differentiated	17	41		
Poorly differentiated	35	77		
Mean arterial pressure (mmHg)	69.65 ± 5.83	73.91 ± 4.46	5.206	<0.001
Neutrophil count ( $\times 10^9/L$ )	4.63 ± 0.09	4.65 ± 0.09	1.329	0.186
Red blood cell count ( $\times 10^9/L$ )	4.49 ± 0.12	4.48 ± 0.13	0.473	0.637
White blood cell count ( $\times 10^9/L$ )	9.07 ± 0.58	8.95 ± 0.55	1.276	0.204
APACHE II score (point)	17.87 ± 2.35	16.43 ± 2.06	4.020	<0.001
RWT	0.51 ± 0.10	0.36 ± 0.09	9.675	<0.001
on admission creatinine ( $\mu\text{mol/L}$ )	86.61 ± 3.18	87.08 ± 2.95	0.934	0.351
Urea nitrogen (mmoL/L)	5.65 ± 0.30	5.69 ± 0.32	0.765	0.445
Intraoperative blood loss (mL)	322.36 ± 18.90	317.60 ± 17.20	1.613	0.109
Operation time (min)	160.64 ± 15.05	157.04 ± 14.08	1.504	0.134

AKI, acute kidney injury; VATS, video-assisted thoracoscopic surgery; TNM, Tumor-Node-Metastasis; APACHE II, Acute Physiology and Chronic Health Evaluation; RWT, relative wall thickness.

with age and APACHE II Score ( $r = 0.573, 0.520, p < 0.05$ ). Similarly, AKI exhibited a positive correlation with age, APACHE II Score, and RWT ( $r = 0.726, 0.685, 0.772, p < 0.05$ ). In contrast, RWT showed a negative correlation with mean arterial pressure ( $r = -0.724, p < 0.05$ ) (Table 3).

### ROC Curve Analysis

Receiver operating characteristic (ROC) curve analysis demonstrated the following outcomes: The area under the curve (AUC) for age was 0.732, with a standard error of 0.041 (95% CI: 0.652~0.813) and a Youden index of 0.33. At this time, the sensitivity was 67.80%, and the specificity was 65.38%. The AUC for

**Table 2. Binary logistics regression analysis of factors affecting AKI.**

Factor	B	SE	Wald	<i>p</i> -value	Exp (B)	95% CI	
						Lower limit	Upper limit
Age	0.451	0.125	12.951	<0.001	1.570	1.228	2.007
APACHE II score	0.398	0.134	8.820	0.003	1.488	1.145	1.934
Mean arterial pressure	-0.171	0.055	9.722	0.002	0.843	0.757	0.938
RWT	2.029	0.396	26.228	<0.001	7.608	3.499	16.540
Constant	-33.621	9.644	12.154	<0.001	<0.001	-	-

SE, standard error; CI, confidence interval.

**Table 3. Correlation analysis of variables.**

		Age	APACHE II score	Mean arterial pressure	RWT	AKI
Age	<i>r</i>	1	0.468	-0.522	0.573	0.726
	<i>p</i>	-	<0.001	<0.001	<0.001	<0.001
APACHE II score	<i>r</i>	0.468	1	-0.543	0.520	0.685
	<i>p</i>	<0.001	-	<0.001	<0.001	<0.001
Mean arterial pressure	<i>r</i>	-0.522	-0.543	1	-0.558	-0.724
	<i>p</i>	<0.001	<0.001	-	<0.001	<0.001
RWT	<i>r</i>	0.573	0.520	-0.558	1	0.772
	<i>p</i>	<0.001	<0.001	<0.001	-	<0.001
AKI	<i>r</i>	0.726	0.685	-0.724	0.772	1
	<i>p</i>	<0.001	<0.001	<0.001	<0.001	-

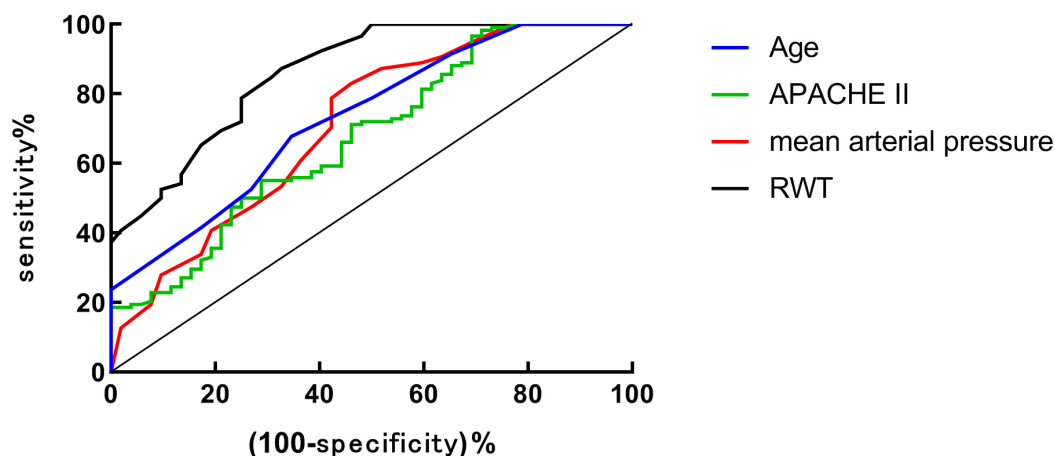
the APACHE II Score was 0.675, with the standard error being 0.045 (95% CI: 0.587~0.764) and a Youden index of 0.27. At this point, the sensitivity was 96.61%, and the specificity was 30.77%. For mean arterial pressure, the AUC was 0.714, and the standard error was 0.045 (95% CI: 0.622~0.799), with a Youden index of 0.37, where the sensitivity was 83.05%, and the specificity was 53.85%. For RWT, the AUC was 0.864, and the standard error was 0.030 (95% CI: 0.805~0.923), with a Youden index of 0.55. At this time, the sensitivity was 87.29%, and the specificity was 67.31% (Table 4 and Fig. 2).

## Discussion

Lung cancer is a highly prevalent and deadly malignancy worldwide. With the continuous advancement of medical technology, video-assisted thoracoscopic surgery (VATS) for lung cancer emerged as a crucial treatment approach, offering advantages such as minimal invasiveness and rapid recovery. However, postoperative AKI remains a severe complication, substantially increasing patients' hospital stay, medical expenses, and leading to poor prognosis or even death. Therefore, identifying effective predictive indicators for detection and management is crucial to alleviating the incidence of postoperative AKI and improving patient outcomes.

**Table 4. Receiver operating characteristic (ROC) analysis results.**

Factor	Area under curve	Standard error	95% CI	Youden	Sensitivity	Specificity
Age	0.732	0.041	0.652~0.813	0.33	67.80	65.38
APACHE II score	0.675	0.045	0.587~0.764	0.27	96.61	30.77
Mean arterial pressure	0.714	0.045	0.622~0.799	0.37	83.05	53.85
RWT	0.864	0.030	0.805~0.923	0.55	87.29	67.31



**Fig. 2. ROC curve analysis.** The ROC curve for RWT showed an area under the curve (AUC) closest to 1, indicating the highest predictive value. APACHE II, Acute Physiology and Chronic Health Evaluation; RWT, relative wall thickness of Left Ventricle.

This study investigates the predictive value of RWT, assessed through echocardiography, for postoperative AKI in patients undergoing VATS for lung cancer. In this retrospective study, we analyzed 170 patients who underwent VATS for lung cancer and identified RWT as a significant predictor of postoperative AKI, indicating its potential clinical implication.

RWT, an important echocardiography factor, indicates the proportional relationship between left ventricular wall thickness and ventricular cavity diameter. Moreover, it is closely associated with left ventricular function and myocardial remodeling (Biton et al, 2016). Previous studies (Chou et al, 1990; Gidding et al, 2010) have reported a strong link between RWT and the development of cardiovascular diseases, including hypertension, coronary heart disease, and heart failure. Our study explored the value of RWT in predicting AKI after VATS radical lung cancer resection. Comparing baseline characteristics, we observed age, APACHE II score, mean arterial pressure, and RWT as significant predictors of postoperative AKI. The increase in RWT likely indicates structural changes in the left ventricle, such as myocardial hypertrophy or fibrosis. These changes may impair the cardiac pumping function and hemodynamics, alleviating renal perfusion or renal vascular damage, thereby elevating the risk of AKI (Goeddel et al, 2022). The increase in RWT may also be associated with biological processes such as inflammation and oxidative stress, which can directly or indirectly affect kidney function and structure. The underlying biological mechanism correlating RWT and AKI may involve

interactions within the heart-kidney axis, including hemodynamic changes, release of inflammatory mediators, oxidative stress and many other aspects (Ye et al, 2020). Mean arterial pressure is a crucial indicator of cardiac pumping and vascular resistance. A reduction in the average arterial pressure requires greater effort from the left ventricle to maintain blood pumping, resulting in left ventricular wall thickening and increased RWT value (Díaz et al, 2019). Hypotension can lead to renal hypoperfusion, triggering AKI. The negative correlation between RWT and mean arterial pressure observed in this study reflects the potential effects of hypotension on heart and kidney functions.

Furthermore, ROC curve analysis indicated that the AUC for RWT was 0.864, with a standard error of 0.030 (95% CI: 0.8047~0.9228) and a Youden index of 0.55. At this time, the sensitivity was 87.29%, and the specificity was 67.31%. These observations suggest that RWT has excellent predictive value in predicting AKI after VATS radical lung cancer resection, with higher sensitivity and specificity. Therefore, RWT serves as an effective indicator to predict the occurrence of postoperative AKI in clinical practice, aiding in early diagnosis and management.

This study evaluated the predictive value of relative left ventricular wall thickness measured through echocardiography in AKI after thoracoscopic radical lung cancer surgery. Our findings enhanced our understanding of the heart-kidney interaction as well as offering a novel perspective and basis for clinical interventions. Compared to previous studies, this study provides significant implications. Firstly, this study focuses on RWT as an indicator. This retrospective analysis of a large sample set shows a strong association between RWT and AKI after VATS lung cancer radical resection. While previous studies have reported the relationship between cardiac function and AKI (Kumar and Khalpey, 2024), they often concentrated on broader cardiac function indicators, such as left ventricular ejection fraction (LVEF) (Lin et al, 2020; Pyxaras et al, 2015). As an important indicator reflecting changes in left ventricular structure, this study adds a deeper understanding of RWT's role in predicting AKI and provides a new powerful tool for the clinical assessment of AKI. Secondly, this research applies rigorous and scientific methodology. Using multiple statistical methods such as binary logistics regression analysis, correlation analysis, and ROC curve analysis, the predictive value of RWT on AKI was comprehensively evaluated, along with its association with other influencing factors. This methodological framework improves the accuracy and reliability of our results while providing a reference point for future studies in this context. Finally, our findings carry crucial implications for clinical practice. Identifying patients with increased RWT allows clinicians to adapt to earlier interventions, such as optimizing cardiac function and improving hemodynamics, thereby reducing the risk of AKI. This approach helps improve patient prognosis and quality of life and also helps to reduce unnecessary medical resource usage and medical costs. Compared to previous studies, our findings align more closely with clinical realities, providing new insights and strategies for treating postoperative complications and enhancing the care of patients undergoing lung cancer surgery.

The findings of this study demonstrate the exceptional predictive value of RWT in detecting postoperative AKI following VATS for lung cancer, providing valu-

able insights for clinical decision-making. However, there are several practical challenges to this study. Firstly, the measurement of RWT depends on echocardiographic examinations, which can be influenced by factors such as operator skills and equipment quality, possibly leading to measurement errors. Therefore, it is essential to enhance the training of echocardiography technicians and ensure rigorous quality control measures. Secondly, although RWT exhibits strong predictive capability as an individual parameter, it should be combined with other clinical indicators to offer more a comprehensive assessment of patients' risk for postoperative AKI. Lastly, this retrospective design and limited sample size may lead to potential selection bias and limit the generalizability of our findings. Therefore, future research should focus on larger-scale, prospective, multicenter studies to validate and expand the value of RWT in predicting postoperative AKI.

## Conclusion

In conclusion, this study investigated the predictive value of echocardiographic RWT in detecting postoperative AKI following VATS for lung cancer through a retrospective study design. The results indicate that RWT is a significant independent factor in predicting postoperative AKI, exhibiting high sensitivity and specificity. Therefore, RWT can serve as an effective indicator in clinical practice for predicting postoperative AKI following VATS for lung cancer. Future studies should aim to provide a deeper understanding of the role of RWT in predicting postoperative AKI and explore strategies for its combined application with other clinical indicators to guide clinical decision-making better. Additionally, enhancing the training and quality control of echocardiography personnel is crucial to improving the accuracy and reliability of RWT measurements.

### Key Points

- Age, APACHE II score, mean arterial pressure, and RWT are the factors impacting the development of AKI after VATS radical resection of lung cancer.
- RWT showed a negative correlation with mean arterial pressure, and AKI exhibited a positive correlation with age and APACHE II score. In contrast, it showed a negative correlation with mean arterial pressure.
- The area under the ROC curve for RWT was 0.864, with a sensitivity of 87.29% and a specificity of 67.31%, thereby enhancing its predictive value.
- RWT is crucial in predicting AKI after radical resection of lung cancer on VATS.

## Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding authors upon request.

## Author Contributions

XKS, LZ and YZ designed the research study. XKS and CFZ performed the research. MZB, HYZ and YZ analysed the data. XKS and YZ drafted the manuscript. LZ and HYZ revised the manuscript. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

This study was approved by the Medical Ethics Committee of the Nanjing First Hospital (The protocol number: KY20240603-KS-04) and adhered to the Helsinki Declaration for research involving human subjects. Similarly, patients or their families signed informed consent forms.

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## Conflict of Interest

The authors declare no conflict of interest.

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