BMC Anesthesiology

RESEARCH

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The impact of anesthesia methods on postoperative outcomes of lower limb surgeries in elderly patients over 90 years old: A multicenter propensity-matched study

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Abstract

Purpose This study aimed to assess the impact of different anesthesia methods on postoperative outcomes of lower limb surgeries in elderly patients over 90 years old.

Patients and methods We retrospectively reviewed the medical records of elderly patients over 90 years old who underwent lower limb surgeries at Chongqing University Center Hospital, the Affiliated Hospital of Southwest Medical University, and Chongqing General Hospital from January 2012 to December 2022. The patients were categorized into two groups based on the anesthesia method employed: the general anesthesia (GA) group and the regional anesthesia (RA) group. To minimize potential confounding, propensity score matching (PSM) was conducted in a 1:1 ratio with the caliper value set as 0.1; additionally, further univariable logistic regression was employed to compare the risk of postoperative complications and mortality between the GA and RA groups.

Results A total of 560 patients were included in our analysis, with 363 cases receiving general anesthesia (GA) and 197 cases receiving regional anesthesia (RA). After conducting propensity score matching (PSM), 139 pairs of data were successfully matched. Compared with the RA group, the GA group had a higher risk of postoperative complications (32.4% vs. 19.4%;OR,1.99; 95% CI, 1.15–3.44; $p = 0.015$), a higher risk of postoperative ICU admission (44.6% vs. 20.9%;OR,3.05; 95% CI,1.80–5.18;$p < 0.001$), but a lower risk of intraoperative blood transfusion (46% vs. 59%;OR,0.59; 95% CI,0.37–0.95;$P = 0.031$).No statistically significant differences were observed in other perioperative indices between the two groups.

Conclusion In elderly patients over 90 years old undergoing lower limb fracture surgeries, GA is associated with a higher risk of postoperative complications and ICU admission compared to RA. Furthermore, compared with RA, GA is associated with a decreased need for intraoperative blood transfusion.

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Trial registration The study was registered in the Chinese Clinical Trial Registry (ChiCTR2400083103, principal investigator: Hong Fu, 14/04/2024).

Keywords Anesthesia, Elderly, Lower limb surgery, Postoperative outcomes, Propensity matching

Background

The global population of individuals over 90 years old has reached 21 million by 2020, with an anticipated growth rate of 11-fold by the year 2100 [1]. As the population ages, the rate of lower limb fractures and degenerative diseases is increasing. More elderly patients are opting for surgery due to medical advancements and a desire for enhanced quality of life. However, they often face complications and decreased organ function, leading to high postoperative complication and mortality rates. The 30-day mortality risk post-surgery for those over 90 is 5.6%, and up to 33.9% experience complications [2]. Moreover, the risk of postoperative complications in elderly hip fracture patients ranges from 12.5 to 43%, including pneumonia, delirium, cardiac events, and deep vein thrombosis [3]. Anesthesia, as a critical component of surgery, significantly influences surgical outcomes. Therefore, it is of great significance to study the impact of anesthesia on the outcome of lower limb surgery in the elderly to improve the safety of surgery and reduce the incidence of complications.

General anesthesia (GA) and regional anesthesia (RA) are commonly used in lower limb surgeries in the elderly. The current belief is that although GA can provide high comfort and is conducive to the management of respiratory circulation, the use of general anesthetic drugs and mechanical ventilation will increase the incidence of neurological and respiratory complications. Studies have shown that GA is an independent risk factor for the occurrence of pulmonary infection complications and is highly correlated with severe postoperative outcomes [4, 5]. In contrast, RA can avoid endotracheal intubation and mechanical ventilation, providing more effective postoperative analgesia, thus reducing the risk of postoperative pulmonary infections. However, some studies believe that the anesthesia method does not affect the risk of postoperative complications and mortality in elderly patients with hip fractures [6, 7], and RA also cannot reduce the risk of myocardial infarction and mortality after non-cardiac surgery in high-risk patients for cardiac events [8]. The merits and demerits of the two anesthesia methods for the outcomes of lower limb surgeries in elderly patients have not yet reached a consensus, both domestically and internationally.

Our study concentrates on patients aged 90 and above, a demographic particularly vulnerable to the physiological stress of anesthesia and surgery. This focus is crucial for understanding the unique challenges of extreme age and for tailoring clinical practices to meet the needs of this expanding population. Notably, the incidence of pulmonary complications following GA in this age group can reach 15%, a risk nearly halved with RA [9]. The risk of postoperative pulmonary complications was 33.4% when the duration of mechanical ventilation under general anesthesia was more than 2 h [10]. These figures highlight the imperative of comparing the outcomes of GA and RA in the oldest old.

Therefore, this study was a multicenter retrospective cohort study to explore the impact of GA and RA on adverse outcomes of the elderly patients over 90 years old after lower limb surgery. The objective was to provide options for individualized anesthesia and reduce the incidence of postoperative complications and mortality in this specific patient population.

Materials and methods

Design and study subjects

This multicenter retrospective cohort study was approved by the following Institutional Review Boards (IRBs): the Ethics Committee of Chongqing University Central Hospital/ Chongqing Emergency Medical Center (RS202419), the Affiliated Hospital of Southwest Medical University(KY202401)and Chongqing General Hospital(KY S2024-022-01). The study was registered in the Chinese Clinical Trial Registry (ChiCTR2400083103). Informed consent was waived due to the retrospective nature of the study. All data were analyzed anonymously to protect patient privacy, and the study complied with the Helsinki Declaration.

The study analyzed clinical data from elderly patients over 90 years old who underwent lower limb surgeries from January 2012 to December 2022 at three centers: Chongqing University Center Hospital, The Affiliated Hospital of Southwest Medical University, and Chongqing General Hospital. Inclusion criteria included: 1. Age ≥ 90 years old. 2.Patients diagnosed with lower limb fractures and degenerative diseases requiring surgical treatment based on medical history, physical examination, and examination results. Exclusion criteria included: 1. More than 20% missing data for a patient. 2.Patients who died during surgery.

Case collection and anesthesia methods

For patients meeting the inclusion and exclusion criteria, the following information was recorded:1. Basic information: Gender, age, Barthel Index (BI) score, American Society of Anesthesiologists (ASA) classification. 2. Preoperative comorbidities: (1) cardiovascular diseases:

hypertension, coronary artery disease (CAD), heart failure, arrhythmias. (2) pulmonary diseases: chronic obstructive pulmonary disease (COPD), asthma, pneumonia, pulmonary embolism, chronic bronchitis, bronchiectasis. (3) neurological diseases: dementia, stroke, epilepsy. (4) renal diseases: chronic renal insufficiency. (5) diabetes mellitus. 3.Laboratory test results: preoperative levels of potassium (K+), sodium (Na+), hemoglobin (Hb), albumin concentration, white blood cell (WBC) count, platelet (PLT)count.4. Surgery-related: (1) type of surgery: emergency or elective. (2) anesthesia-related: Anesthesia method. (3) Intraoperative: use of vasopressor drugs (dopamine, epinephrine, norepinephrine), intraoperative blood transfusion. 5. Postoperative outcomes: Postoperative complications(postoperative cardiac complications, postoperative pulmonary complications, postoperative cerebral complications, postoperative renal insufficiency, postoperative sepsis, deep organ infections, mortality during hospitalization,), postoperative admission to the intensive care unit (ICU), duration of hospital stays, hospitalization costs. The observation endpoint is one month postoperatively.

Patients were divided into two groups, general anesthesia (GA)group and regional anesthesia (RA) group, according to the type of anesthesia used. The GA group opted for endotracheal intubation general anesthesia, while the RA group chose spinal/epidural anesthesia or peripheral nerve blockade. Patients in the RA group received a continuous infusion of dexmedetomidine at a dose of 0.2 to 0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$ during surgery. This kept the patients in a mildly sedated state, ensuring they remained relatively quiet and comfortable during the procedure without significantly suppressing their respiratory function. Additionally, patients who initially received RA but were converted to GA were classified into the GA group.

Study endpoints

The primary outcome was a composite endpoint of postoperative complications, defined as the occurrence of any one or more of the following major organ complications: cardiac complications (such as acute heart failure, arrhythmias, new-onset myocardial infarction), pulmonary complications (such as pulmonary infections, respiratory failure, pulmonary embolism), Central complications (such as cerebral infarction, cerebral hemorrhage, epilepsy), renal complications (such as acute kidney injury), postoperative sepsis, deep organ infections, mortality during hospitalization. Any one or combination of the above adverse events are considered as the occurrence of relevant complications. World Health Organization International Classification of Diseases codes (ICD-10) were used to identify various complications.

Secondary Outcome: admission to ICU, duration of hospital stays (Defined as the number of days from admission to discharge, with discharge criteria including stable vital signs, normal blood parameters, and good wound healing), total hospitalization costs (All medical-related expenses incurred during the patient's hospital stay, including diagnostic tests, medications, surgical procedures, and other healthcare services), use of vasopressor drugs during surgery, intraoperative blood transfusion.

Statistical analysis

Statistical analysis was conducted using SPSS 24.0. Propensity score matching (PSM)was used to reduce confounding, respectively to adjust for baseline differences between the two groups. Categorical data were presented as percentages and analyzed using the Chi-square test or Fisher's exact test, as appropriate. Continuous data that were normally distributed were expressed as mean ± standard deviation ($x \pm s$) and analyzed using the independent sample t-test. For continuous data that were not normally distributed, the median (P25, P75) was used, and these data were analyzed using the Mann-Whitney U test.

To identify potential confounding factors and determine which covariates needed to be included in the propensity score model, we initially conducted univariate analysis to detect variables with significant differences in baseline data between the two groups. Variables that showed significant differences in univariate analysis, as well as those potentially influencing anesthesia selection, were considered as confounding factors and were incorporated into the PSM model. PSM scores were estimated using logistic regression, and nearest-neighbor matching was performed in a 1:1 ratio with a caliper width of 0.1. The balance between the cohorts was assessed using the Standardized Mean Difference (SMD); covariates with an absolute SMD value less than 0.1 were considered well-balanced. In the matched dataset, categorical outcomes were compared using univariable logistic regression or Fisher's exact test, while quantitative outcomes were compared using Mann-Whitney U test.

Results

Patient enrolment is shown on Fig. 1. A total of 560 patients were included in this study, comprising 363 in the GA group and 197 in the RA group. In the RA group, 13% (25/197) of patients receiving peripheral nerve blockade, and 87% (172/197) receiving spinal/epidural anesthesia. These patients were recruited from three hospitals: 215 from Chongqing University Central Hospital, 209 from The Affiliated Hospital of Southwest Medical University, and 136 from Chongqing General Hospital. In the comparison of single-factor analysis, it was found that there were significant differences in the general data of the two groups of patients (including ASA classification, CAD, pneumonia, COPD, chronic

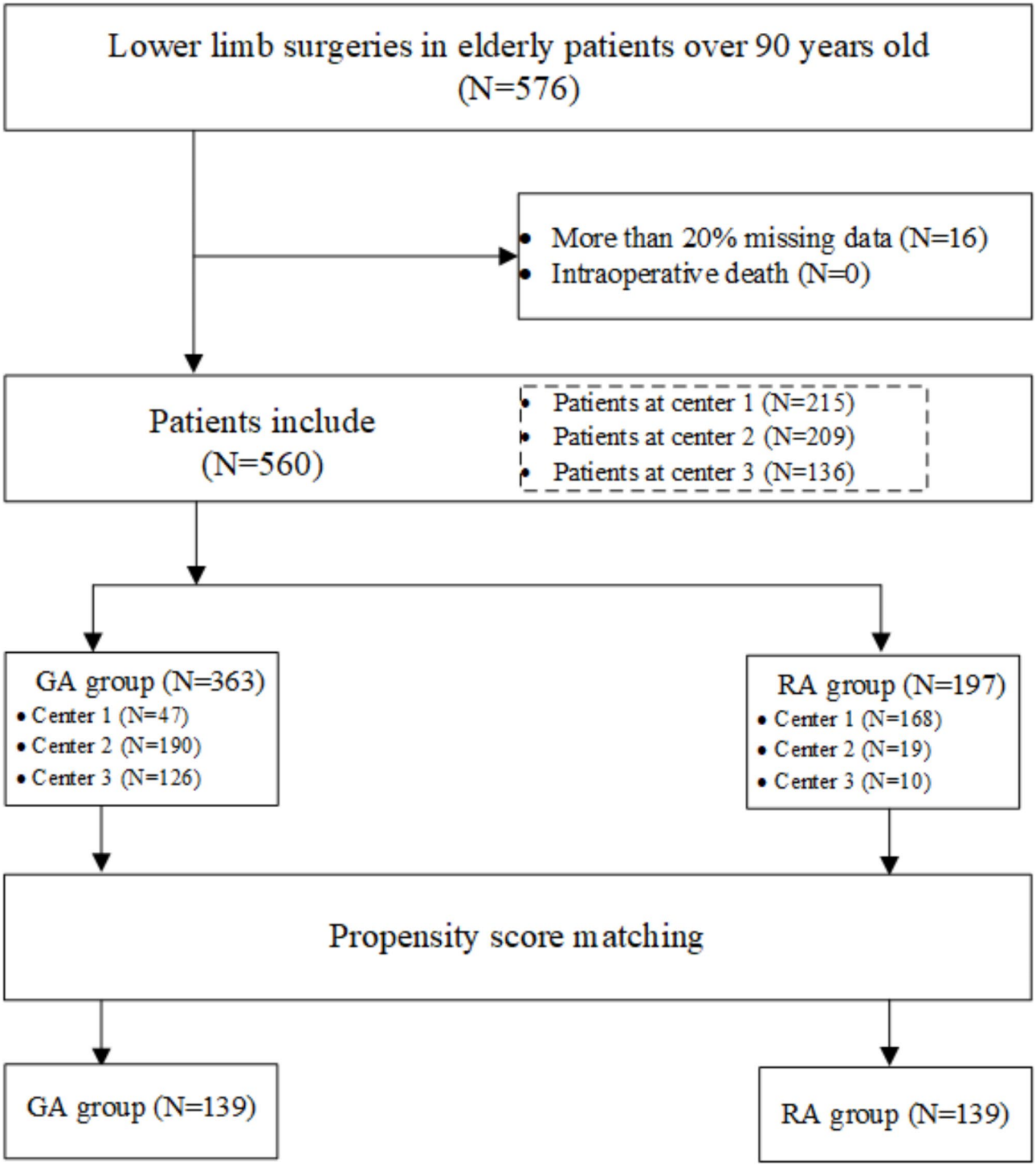

Fig. 1 Center 1 represents Chongqing University Central Hospital. Center 2 represents The Affiliated Hospital of Southwest Medical University. Center 3 represents Chongqing General Hospital

bronchitis and bronchiectasis, BI score, serum potassium level, PLT count, surgery duration, and blood loss) ($P < 0.05$), as shown in Table 1. Therefore, these variables, along with other relevant factors that may affect the choice of anesthesia (such as emergency status, asthma, dementia, renal insufficiency, etc.), were included in the propensity score matching (PSM) model to achieve intergroup balance. After PSM, the final number of patients in each group was 139. The absolute SMD of all covariates were less than 0.1, indicating good balance in baseline

Table 1 Patient characteristics before PSM between GA group and RA group

Patient characteristics	GA($n=363$)	RA($n=197$)	*P*-value
Gender (Male)	140(38.6%)	68(34.5%)	0.344 [a]
BI score	40.00(35.00–45.00)	30.00(25.00–40.00)	**0.000[d]**
Age	92.00(91.00–94.00)	92.00(91.00–94.00)	0.685 [d]
ASA classification			**0.001[a]**
≤III	282(77.7%)	165(83.7%)	--
> III	81(22.2%)	32(16.2%)	--
Emergency	25(6.9%)	10(5.1%)	0.398 [a]
Hypertension	173(47.7%)	91(46.2%)	0.740 [a]
CAD	181(49.9%)	64(32.5%)	**0.000[a]**
Heart failure	62(17.1%)	22(11.2%)	0.061 [a]
Cardiac arrhythmia	131(36.1%)	72(36.5%)	0.914 [a]
COPD	103(28.4%)	29(14.7%)	**0.000[a]**
Asthma	5(1.4%)	3(1.5%)	1.000 [b]
Pneumonia	92(25.3%)	28(14.2%)	**0.002[a]**
Pulmonary embolism	2(0.6%)	1(0.5%)	1.00 [b]
Bronchitis/Bronchiectasis	74(20.4%)	15(7.6%)	**0.000[a]**
Dementia	25(6.9%)	16(8.1%)	0.592 [a]
Epilepsy	0(0.0%)	2(1.0%)	0.123 [b]
Stroke	79(21.8%)	45(22.8%)	0.769 [a]
Renal failure	38(10.5%)	17(8.6%)	0.485 [a]
Diabetes	45(12.4%)	30(15.2%)	0.347 [a]
K^+	3.91(3.58–4.31)	4.02(3.72–4.34)	**0.035[d]**
Na^+	139.6(137.0-142.0)	139.5(137.0-141.6)	0.682 [d]
PLT	157.0(117.0-203.0)	159.0(134.0-220.0)	**0.024[d]**
WBC	7.74(6.25–9.71)	7.51(5.99–9.66)	0.365[d]
Albumin	35.76 ± 4.87	35.60 ± 4.46	0.372 [c]
Hemoglobin	104.48 ± 19.25	104.10 ± 19.60	0.852 [c]
Surgery duration	80.0(62.0-105.0)	90.0(70.0-110)	**0.039[d]**
Blood loss	100.0(50.0-400.0)	200.0(100.0-300.0)	**0.029[d]**

Notes: a: Chi-square test, b: Fisher's exact test, c: t-test, d: Mann-Whitney U test

PSM Propensity Score Matching, ***BI*** Barthel index, ***ASA*** American Society of Anesthesiologists, ***CAD*** Coronary artery disease, ***COPD*** Chronic obstructive pulmonary disease, ***WBC*** White blood cell, ***PLT*** Platelet

characteristics between the two groups, as shown in Table 2.

The primary and secondary study outcomes are summarized in Table 3. After PSM, the GA group exhibited a significantly higher risk of postoperative complications compared to the RA group (32.4% vs.19.4%; OR, 1.99; 95% CI, 1.15–3.44, $P=0.015$). Specifically, postoperative cardiac complications occurred in 10.8% of GA patients versus 3.6% of RA patients. Postoperative pulmonary complications were observed in 23.0% of the GA group and 14.4% of the RA group. Cerebral complications were rare, reported in 2.2% of GA patients, with no cases in the RA group. Postoperative renal insufficiency was observed in 2.9% of the GA group and 7.2% of the RA group. Postoperative sepsis occurred in 5.8% of GA patients and 0.7% of RA patients. One case (0.7%) was reported in the GA group, with none in the RA group. In-hospital mortality rates were 5.0% in the GA group and 2.9% in the RA group. These data are descriptive statistics and no hypothesis testing was performed.

In terms of secondary outcomes, the GA group had a significantly higher risk of ICU admission (44.6%vs.20.9%; OR, 3.05; 95% CI,1.80–5.18; $P<0.001$). The GA group had a lower risk of intraoperative blood transfusion compared to the RA group (46.0% vs. 59.0%; OR, 0.59; 95% CI,0.37–0.95; $P=0.031$). The use of vasopressors intraoperatively was similar between the two groups (64.7% vs. 54.0%, OR:1.57, 95% CI: 0.97–2.54, $P=0.068$). There were no significant differences in the duration of hospital stays (19.0 days vs. 18.0 days, $P=0.599$) or hospitalization costs (CNY49,265.83 vs. CNY52243.48, $P=0.318$) between the GA and RA groups.

Discussion

Elderly patients over 90 years old are often accompanied by osteoporosis and decreased mobility, making them prone to lower limb fractures even with minor trauma [11]. These patients, due to limited lower limb mobility, are at higher risk of complications such as hypostatic pneumonia and deep vein thrombosis from prolonged

Table 2 Patient characteristics before and after PSM between GA group and RA group

Patient characteristics	Before PSM			After PSM		
	GA(*n* = 363)	RA(*n* = 197)	SMD	GA(*n* = 139)	RA(*n* = 139)	SMD
BI score	40.00 (35.00–45.00)	30.00 (25.00–40.00)	-0.589	40.00 (30.00–45.00)	35.00 (30.00–40.00)	0.028
Age	92.00 (91.00–94.00)	92.00 (91.00–94.00)	-0.050	92.00 (91.00–94)	92.00 (91.00–94)	-0.036
ASA classification			0.065			0.000
≤III	282(77.7%)	165(83.7%)	--	103(74.1%)	115(82.7%)	--
> III	81(22.2%)	32(16.2%)	--	36(25.9%)	24(17.3%)	--
Emergency	25(6.9%)	10(5.1%)	-0.082	9(6.5%)	9(6.5%)	0.000
CAD	181(49.9%)	64(32.5%)	-0.370	59(42.4%)	58(41.7%)	-0.015
COPD	103(28.4%)	29(14.7%)	0.384	30(21.6%)	29(20.9%)	0.020
Asthma	5(1.4%)	2(1.4%)	0.12	3(2.2%)	2(1.4%)	-0.059
Pneumonia	92(25.3%)	28(14.2%)	-0.318	28(20.1%)	27(19.4%)	-0.021
Bronchitis、 Bronchiectasis	74(20.4%)	15(7.6%)	-0.480	18(12.9%)	15(10.8%)	-0.081
Dementia	25(6.9%)	16(8.1%)	0.045	11(7.9%)	8(5.8%)	-0.079
Renal failure	38(10.5%)	17(8.6%)	-0.065	13(9.4%)	14(10.1%)	0.026
K^+	3.91 (3.58–4.31)	4.02 (3.72–4.34)	0.166	4.03 ± 0.54	4.02 ± 0.44	-0.038
PLT	157.0 (117.0-203.0)	159.0 (134.0-220.0)	0.146	159.0 (112.0-219.0)	161.0 (137.0-141.9)	0.071
Surgery duration	80.0 (62.0-105.0)	90.0 (70.0-110)	0.115	80.0 (65.0-110.0)	85.0 (65.0-110.0)	0.033
Blood loss	100.0 (50.0-400.0)	200.0 (100.0-300.0)	0.075	100.0 (50.0-400.0)	100.0 (80.0-300.0)	-0.055

PSM Propensity Score Matching, ***SMD*** Standard Mean Difference, ***BI*** Barthel index

ASA American Society of Anesthesiologists, ***CAD*** Coronary artery disease, ***COPD*** Chronic obstructive pulmonary disease, ***WBC*** White blood cell, ***PLT*** Platelet

Table 3 Comparison of outcome between GA group and RA group after PSM

Outcome	GA(*n* = 139)	RA(*n* = 139)	OR (95%CI)	*P*-value
The primary outcome				
Postoperative complications	45(32.4%)	27(19.4%)	**1.99(1.15–3.44)**	**0.015**[a]
Postoperative cardiac complications	15(10.8%)	5(3.6%)		
Postoperative pulmonary complications	32(23.0%)	20(14.4%)		
Postoperative cerebral complications	3(2.2%)	0(0.0%)		
Postoperative renal insufficiency	4(2.9%)	10(7.2%)		
Postoperative sepsis	8(5.8%)	1(0.7%)		
Postoperative deep organ infections	1(0.7%)	0(0%)		
Mortality during hospitalization	7(5.0%)	4(2.9%)		
Secondary Outcome				
Admission to ICU	62(44.6%)	29(20.9%)	**3.05(1.80–5.18)**	**0.000**[a]
Intraoperative use of vasopressors	90(64.7%)	75(54.0%)	1.57(0.97–2.54)	0.068 [a]
Intraoperative blood transfusion	64(46.0%)	82(59.0%)	**0.59(0.37–0.95)**	**0.031**[a]
Duration of hospital stays(day)	19.0(11.0–26.0)	18.0(13.0–26.0)		0.599 [b]
Hospitalization costs (CNY)	49265.83(36182.56-70523.65)	52243.48(40159.39-66574.29)		0.318[b]

Notes: a: Univariate Logistic Regression, b: Mann-Whitney U test

Data for subcategories are descriptive statistics and no hypothesis testing was performed

OR Odds Ratio, ***CI*** Confidence Interval, ***ICU*** intensive care unit, ***CNY*** Chinese Yuan

bed rest. Additionally, they often have multiple systemic comorbidities, leading to a higher postoperative mortality rate. Effectively reducing postoperative complications and mortality in these elderly patients remains a major medical challenge for healthcare professionals [12–14].

The findings of this study highlight significant differences in postoperative outcomes between patients receiving GA and RA after PSM. The GA group exhibited a nearly twofold higher risk of overall postoperative complications compared to the RA group, a result that corroborates prior research suggesting that GA may exert

a more pronounced disruption on physiological homeostasis compared to RA [2, 3]. Notably, GA patients experienced higher rates of cardiac complications (10.8% vs. 3.6%), pulmonary complications (23% vs. 14.4%), and sepsis (5.8% vs. 0.7%). Although this trend was not subjected to statistical hypothesis testing, it is consistent with the notion that GA may impact postoperative outcomes [15–16].GA potentially linked to the systemic effects of general anesthetics on hemodynamic stability [17].By avoiding the use of general anesthetics, which can depress the myocardium and impair cardiac function, RA may help maintain better cardiac performance postoperatively [18]. Additionally, the incidence of postoperative sepsis was higher in the GA group than in the RA group, which may be related to the increase in invasive monitoring in elderly patients, the postoperative susceptibility to pulmonary complications, and the prevalence of preoperative combined basic diseases [19].Nonetheless, the trend observed suggests that further research with larger sample sizes is warranted to explore the relationship between anesthesia type and postoperative complications in more detail.

Furthermore, the risk of postoperative admission to ICU was significantly higher in the GA group compared to the RA group, a finding is consistent with the increased severity of postoperative complications observed in the GA group. This likely reflects the cumulative burden of complications requiring intensive monitoring, further supporting RA as a strategy to reduce critical care resource utilization. However, the risk of intraoperative blood transfusion was significantly higher in the RA group compared to the GA group, which may be related to surgical techniques and duration. In this study, the lower limb surgery method has not been further stratified, and the correlation between the incidence of intraoperative blood transfusion and anesthesia method needs to be further studied.

Cerebral complications and deep organ infections were rare but clinically significant, emphasizing the need for vigilance in high-risk GA patients [20]. Despite fewer complications, RA did not significantly reduce hospital stays or costs. This suggests that factors beyond complications, such as postoperative rehabilitation or institutional practices, may influence resource utilization.

There are still limitations, while this study utilized propensity score matching to achieve intergroup balance and benefited from a multicenter design. For example, some variables that may affect the outcomes, such as body mass index, smoking history, alcohol consumption history, coagulation-related indicators, and history of gastrointestinal diseases, were not collected. Additionally, different surgical teams may have varying requirements for anesthesia and surgical methods, and anesthesiologists may have personal preferences for anesthesia methods, which cannot be adjusted for through matching analysis. Future studies can further analyze these issues to improve the robustness of the findings.

Conclusion

In conclusion, for elderly patients over 90 years old undergoing lower limb surgery, RA may be a better choice compared to GA, as it may be associated with a lower risk of postoperative complications and ICU Admission compared to GA. This study provides an important reference value for clinical decision-makers regarding the choice of anesthesia method for elderly patients over 90 years old.

Acknowledgements

I would like to express my deepest gratitude to all those who have contributed to the completion of this study.

Author contributions

Z.Y. was responsible for the conceptualization of the study, data curation, formal analysis, validation, and was the lead writer of the original draft. X.T.and X.Duan contributed to the conceptualization, methodology, resources, and validation of the study, and were also major contributors in writing the original draft. X.Du was involved in data curation and formal analysis. J.Z. and L.F. participated in the investigation and data curation. F.H. led the conceptualization, methodology, project administration, resources, and provided supervision for the study. He also played a critical role in writing the review and editing parts of the manuscript. All authors have read and approved the final manuscript.

Funding

This work was founded by Chongqing Municipal Studios for Young and Middle- aged Top Medical Talents (ZQNYXGDRCGZS2019006).

Data availability

The raw data supporting this study cannot be made publicly available due to patient privacy concerns and institutional ethical restrictions imposed by the hospital. However, de-identified data may be shared upon reasonable request to the corresponding author, subject to approval by the ethics committee and compliance with a signed data use agreement.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Chongqing University Central Hospital/ Chongqing Emergency Medical Center (RS202419), the Affiliated Hospital of Southwest Medical University(KY202401)and Chongqing General Hospital(KY S2024-022-01). The study was registered in the Chinese Clinical Trial Registry (ChiCTR2400083103). Informed consent was waived due to its retrospective nature. All the data were analyzed anonymously to safeguard patient privacy. The study was in compliance with the Helsinki Declaration.

Conflict of interest

The authors declared no funding sources or conflicts of interest to support this article.

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Received: 10 December 2024 / Accepted: 28 March 2025
Published online: 10 April 2025

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