

# The relationship between postoperative hypoeosinophilia and hospital stay in patients undergoing hip fracture surgery under general anesthesia or spinal anesthesia: A retrospective study

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## Research article

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# Abstract

**Background** The inflammatory immune response is related to the development and progression of many diseases. Recent studies show that eosinophils (EOSs) are involved in various inflammatory processes and even affect patient prognosis. Various anesthetics or anesthesia methods have different effects on the immune inflammatory response. This study aimed to investigate early postoperative changes in EOSs and the relationship of postoperative recovery and hypoeosinophilia in patients undergoing hip fracture surgery under general or spinal anesthesia. **Methods** We retrospectively analyzed the patients who underwent hip fracture surgery at our hospital between April 2014 and November 2017. Patients were classified according to whether they received general anesthesia or spinal anesthesia. The outcome measure was postoperative hospital stay (days), and the investigating factor was postoperative day 1 EOS levels. **Results** A total of 149 patients were included in this study, including 34 patients in the general anesthesia group and 115 patients in the spinal anesthesia group. Postoperative day 1 EOS was lower in the general anesthesia group than that in the spinal anesthesia group ( $P=0.009$ ). The correlation between postoperative hospital stay and postoperative day 1 EOS level was significant ([EOS  $1 \times 10^7/L$  increase]  $\beta=-0.39$ , 95%CI -0.74, -0.05) in the general anesthesia group, after adjusting the confounders (age, gender, American Society of Anesthesiologists [ASA] grade, intraoperative blood loss, intraoperative red blood cell [RBC] transfusion, postoperative day 1 hematocrit [HCT] and white blood cell [WBC], and postoperative complications) and the interaction terms for ASA, intraoperative blood loss, intraoperative RBC transfusion and postoperative complications. **Conclusion** EOSs were significantly decreased after surgery in general anesthesia group, Also, postoperative hospital stay was negatively correlated with postoperative day 1 hypoeosinophilia in the general anesthesia group, suggesting that patients should be closely monitored for EOS changes and postoperative complications to enable early intervention.

## Background

The inflammatory immune response is a normal or abnormal systemic response of inflammatory immune-related cells to changes in the internal and external environments. It is the fundamental pathophysiological feature of many diseases, serves as an important guide for drug therapy<sup>1</sup>, and is closely related to disease outcome. The white blood cell (WBC) count and differentials are important indicators of the inflammatory immune response. Eosinophils (EOSs), a WBC subtype, are involved in the inflammatory immune process by mediating tissue damage and promoting inflammation; however, their function is not entirely clear<sup>2,3</sup>. Studies have shown that disease-induced hypoeosinophilia is related to adverse disease outcomes<sup>2-8</sup>, probably due to activation of inflammatory responses or immune suppression<sup>9,10</sup>.

In recent years, the effects of anesthesia on the inflammatory immune response and prognosis have become a major research topic locally and abroad. Various anesthetics have been shown to have different effects on the immune response<sup>11,12</sup>. Anesthesia may directly interfere with the function of immune cells or modulate the stress response to indirectly reduce the inflammatory immune response.

For example, volatile anesthetics have an active regulatory role in the immune systems of patients with acute lung injury or ventilator-associated lung injury<sup>11,12</sup>, and local anesthetics have potential anti-inflammatory effects<sup>13</sup>. Different anesthesia methods or anesthetics cause various changes in immune cells, which affect disease prognosis and outcome, postoperative complication rates, and even tumor relapse and metastasis<sup>14,15</sup>.

Our previous study showed that the EOS count was significantly reduced (even as low as “undetectable”) in some patients after undergoing anesthesia. Therefore, we hypothesized that anesthetics may affect postoperative EOS levels and that hypoeosinophilia is related to a slow postoperative recovery. In this study, we retrospectively analyzed the relationships between preoperative and postoperative day 1 EOS levels and postoperative hospital stay in patients undergoing hip fracture surgery under general anesthesia or spinal anesthesia to investigate the effect of EOS level on postoperative recovery.

## Methods

### *Study Design*

The Medical ethics committee of Beijing Tian Tan Hospital approved the study and waived the need for informed consent. We retrospectively analyzed the clinical data of patients who underwent hip fracture surgery at Beijing Tian Tan Hospital, Capital Medical University between April 2014 and November 2017. The inclusion criterion was a single anesthesia method (general anesthesia or spinal anesthesia). The exclusion criteria were the presence of pathological fracture, multiple or combined injuries, missing any necessary data and underwent combined regional and general anesthesia.

### *Recorded Variables*

All data were collected from electronic medical records. A total of 179 patients screened. Thirty patients were excluded as described in the flowchart (Figure.1). Patient age, gender, American Society of Anesthesiologists (ASA) grade, preoperative and postoperative day 1 white blood cell (WBC) counts, EOS counts, and hematocrit (HCT), anesthesia method, blood loss (ml), intraoperative blood transfusion (ml), postoperative complications and postoperative hospital stay were recorded.

### *Definitions*

We defined postoperative complications as incision infection, pulmonary complications, cardiovascular events, cerebrovascular events and acute kidney injury. Incision infection was based on medical records. The diagnosis of pulmonary complications was based on the abnormal oxygen saturation (below 92%, inhaled air), or the positive results of X-ray and sputum culture. Cardiovascular events, including newly occurring arrhythmia, myocardial infarction and heart failure, were diagnosed by electrocardiogram and echocardiography. Cerebrovascular events, including cerebral infarction and cerebral hemorrhage, were diagnosed by neuroimaging. Acute kidney injury was defined by the increase of serum creatinine by 0.3 mg/dl (> 26.5 umol/L) or 1.5 times of the baseline value within 48 hours.

## *Statistical analysis*

Data are expressed as the mean  $\pm$  standard deviation ( $x \pm s$ ) or median (interquartile range) for quantitative variables, and as number (percentage) for qualitative variables. Comparisons between the general anesthesia group and the spinal anesthesia group were made using the Student t test or Mann-Whitney U test for quantitative variables and the chi square test for qualitative variables. Univariate regression analyses were used to examine a number of covariates potentially contributed to postoperative hospital stay, including age, gender, ASA grade, preoperative and postoperative day 1 WBC counts, EOS counts, and HCT, blood loss, intraoperative blood transfusion and postoperative complications. To estimate the magnitude of effect of postoperative day 1 EOS counts as an independent predictor of postoperative hospital stay, multivariate regression analysis was used. Covariables that regarded clinically important or showed a relation to postoperative hospital stay by univariate regression, were selected. Interaction and stratified analyses were conducted according to anesthesia method.  $P < 0.05$  was considered statistically significant. All analyses were performed using Empower (R) (<http://www.empowerstats.com>, X&Y solutions, Inc., Boston MA) and R (<http://www.Rproject.org>) software.

## **Results**

### *Demographic and perioperative data*

A total of 149 patients were included in this study. Stratification was conducted by anesthesia method. Thirty-four of them underwent general anesthesia and 115 of them underwent spinal anesthesia. No significant between-group differences were observed in following data, including gender, ASA grade, preoperative HCT, WBC, and EOS, postoperative day 1 WBC, or postoperative complications. Patient age was lower in the general anesthesia group than that in the spinal anesthesia group ( $P=0.025$ ). Intraoperative blood loss and RBC transfusion were significantly higher in the general anesthesia group than that in the spinal anesthesia group ( $P=0.010$  and  $P=0.005$ , respectively). Postoperative day 1 HCT and EOS were lower in the general anesthesia group than that in the spinal anesthesia group ( $P=0.041$  and  $P=0.009$ , respectively) (Table 1).

### *Univariate analysis of the contributing factors of postoperative hospital stay*

We performed univariate regression to analyze potential contributing factors of postoperative hospital stay. There was a significant positive correlation between postoperative hospital stay and age, ASA grade, intraoperative blood loss and RBC transfusion, postoperative day 1 WBC and EOS, postoperative complications in the all patients or subgroups stratified by anesthesia method (Table 2).

### *Multivariate analysis of postoperative hospital stay in all patients and subgroups stratified by anesthesia method*

Clinically relevant and significant factors from the univariate analysis ( $P < 0.05$ ) were incorporated into a multivariate linear analysis. In total patients, no significant correlation was found between postoperative hospital stay and postoperative day 1 EOS level after adjusting confounders, including age, gender, ASA, intraoperative blood loss, intraoperative RBC transfusion, postoperative day 1 HCT and WBC, and postoperative complications (Table 3). However, the correlation between postoperative hospital stay and postoperative day 1 EOS level was significant ([EOS  $1 \times 10^7$ /L increase]  $b = -0.39$ , 95%CI -0.74, -0.05) in the general anesthesia group, after adjusting the confounders mentioned above and the interaction terms for ASA, intraoperative blood loss, intraoperative RBC transfusion and postoperative complications. While this correlation was not observed in the spinal anesthesia group ([EOS  $1 \times 10^7$ /L increase]  $b = -0.02$ , 95%CI -0.15, 0.1;  $P$  for interaction = 0.0347)(Table 4).

## Discussion

Current studies show that hypoeosinophilia is a predictor in some infectious diseases (sepsis, systemic inflammatory response syndrome) and non-infectious diseases (acute coronary syndrome, chronic obstructive emphysema, stroke).

The inflammatory response, particularly the acute inflammatory response, can cause significant EOS changes<sup>16</sup>, and hypoeosinophilia is one of the reference diagnostic indicators of infectious and non-infectious diseases. Similar to C-reactive protein and procalcitonin, the EOS count is a serological diagnostic indicator of sepsis in the intensive care unit<sup>8</sup>. For non-infectious diseases, hypoeosinophilia is also positively related to the severity of acute ACS-induced myocardial injury; in other words, a greater myocardial infarct area corresponds to more severe peripheral hypoeosinophilia<sup>7</sup>. Hypoeosinophilia is also associated with the severity of chronic obstructive pulmonary disease. Mortality is significantly higher in patients with hypoeosinophilia at admission versus patients with normal EOS levels at admission, suggesting that EOS levels may reflect the severity of chronic obstructive pulmonary disease to some extent<sup>3</sup>. Moreover, hypoeosinophilia is a new predictor of adverse prognosis in patients with hemorrhagic or ischemic stroke, which may be associated with stroke-induced immunosuppression<sup>5,9,10</sup>.

Currently, researchers believe that anesthesia methods and anesthetics affect the immune inflammatory response to varying degrees<sup>11-13</sup>. However, no studies have investigated the effects of anesthesia methods on EOS levels. In this study, we retrospectively analyzed the clinical data of patients undergoing hip fracture surgery under different anesthesia methods to investigate the relationship between postoperative EOS changes and postoperative hospital stay.

According to the hypothesis and literature reports, this study included some measurements that might affect the association between postoperative hypoeosinophilia and postoperative hospital stay. We investigated demographic data of all participants and in subgroups stratified by anesthesia method. Preoperative EOS showed no difference between the general anesthesia group and the spinal anesthesia group, while postoperative day 1 EOS was lower in the general anesthesia group than that in the spinal anesthesia group. Because multiple drugs with varying doses were used during general anesthesia, we

thought that complex medication affected patients' inflammatory immune response and lowered postoperative EOS levels. On the other hand, fewer drugs were used during spinal anesthesia, resulting in less interference with inflammatory immune responses and thus facilitating discernment of the effect of surgical stress on postoperative day 1 EOS levels. Besides, some other variables had significant difference between two groups, such as age, intraoperative blood loss and RBC transfusion, postoperative day 1 HCT (Table 1). These differences in two groups are understandable. First, Anesthesiologists tend to choose spinal anesthesia for aged and high-risk patients. That is the reason why age was lower in the general anesthesia group than that in the spinal anesthesia group. Second, intraoperative data indicated that blood loss and RBC transfusion volume were higher in the general anesthesia group than those in the spinal anesthesia group. And consequently, postoperative day 1 HCT was found lower in the general anesthesia group than that in the spinal anesthesia group, which was considered to be related to greater intraoperative blood loss in the general anesthesia group. Similar to other literature reports, we considered that the between-group difference in blood loss in this study may be related to the anesthesia method<sup>17</sup>.

Length of postoperative hospital stay usually associates with patient age, gender, comorbidity, general physical condition, severity of surgical strikes and complications. In this study, ASA physical status as a well recognized evaluation of patient general condition was enrolled. It is also widely recognized by doctors that the severity of surgical strikes can be represent by the amount of intraoperative blood loss and transfusion. Therefore, variables related to blood loss need to be included in covariate screening. Since EOS is a subtype of WBC, perioperative WBC data should also be included in the covariates. The above variables were considered as potential confounding factors and included in univariate analysis. Variables showed significance ( $P < 0.05$ ) in univariate analysis or in the comparison of two groups were included in the multivariate analysis as covariables (Table 1 and 2).

Multivariate analysis failed to find association between post operative day 1 EOS and postoperative hospital stay in total patients ([EOS  $1 \times 10^7$ /L increase]  $b = -0.08$ , 95%CI -0.21, 0.04), after adjusting age, gender, ASA, intraoperative blood loss, intraoperative RBC transfusion, postoperative day 1 HCT and WBC, and postoperative complications (Table 3). Considering anesthesia method might be an effect modifier, we further conducted subgroup analysis and interaction test stratified by anesthesia method. After adjusting the same confounders as in total patients and the interaction term for ASA, intraoperative blood loss, intraoperative RBC transfusion and postoperative complications, we found that the correlation between postoperative day 1 EOS and postoperative hospital stay ([EOS  $1 \times 10^7$ /L increase]  $b = -0.39$ , 95%CI -0.74, -0.05) was significant in the general anesthesia, but was not ([EOS  $1 \times 10^7$ /L increase]  $b = -0.02$ , 95%CI -0.15, 0.1) in the spinal anesthesia group. Also, the interaction of anesthesia method on postoperative hospital stay related to postoperative day 1 EOS was significant ( $P$  for interaction = 0.0347) (Table 4). Therefore, combined with EOS comparison between groups, it can be considered that general anesthesia reduces postoperative EOS and hypoeosinophilia is negatively correlated with length of postoperative hospitalization.

Literatures reported that different anesthesia methods cause different postoperative inflammatory immune responses, but the detailed mechanisms are unknown<sup>18-21</sup>. In this study, the between-group difference of postoperative EOS may be related to the degree of interference with the inflammatory immune response between different anesthesia methods and drugs. Fewer drugs were used during spinal anesthesia versus general anesthesia. In this study, various regimens were used for general anesthesia, including total intravenous anesthesia and intravenous induction followed inhalation maintenance with multiple drugs, including midazolam, propofol, sufentanil, remifentanil, and sevoflurane, which exhibit varying degrees of interference with postoperative immune function; this may be the cause of postoperative hypoeosinophilia and the negative correlation between postoperative EOS level and postoperative hospital stay in the general anesthesia group. Taken together, this study suggests that patients undergoing general anesthesia should be closely monitored for hypoeosinophilia to enable early detection and intervention.

As a retrospective study, this study has some limitations. First, the sample size in the general anesthesia group was small, further subgroup analysis (e.g., inhalational anesthesia vs. intravenous anesthesia) couldn't be conducted because of the limited sample size. Second, not all patients underwent blood tests on postoperative day 2; therefore, comparing longer-term postoperative EOS levels was impossible. In the future, larger studies, preferably multicenter and prospective studies, are needed to further validate the results.

## Conclusions

Postoperative day 1 EOS levels were significantly lower in the general anesthesia group than those in the spinal anesthesia group. In the general anesthesia group, postoperative hospital stay was negatively correlated to postoperative day 1 hypoeosinophilia, suggesting that patients should be closely monitored for EOS changes and postoperative complications to enable early intervention.

## Abbreviations

EOSs: eosinophils; ASA: American Society of Anesthesiologists; RBC: red blood cell; HCT: hematocrit; WBC: white blood cell.

## Declarations

Ethics approval and consent to participate: Approved by the Medical ethics committee of Beijing Tian Tan Hospital.

Consent for publication: Not applicable.

Availability of data and material: The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: None.

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Authors' contributions:

LC: This author helped analyze the data and prepare the article.

LL: This author helped collect the data, analyze the data and prepare the article.

HY: This author helped collect the data, and prepare the article.

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WC: This author helped design the study, analyze the data and prepare the article.

All authors read and approved the final manuscript.

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## Tables

**Table 1. Patient Demographic Data of All Participants and in Subgroups Stratified by Anesthesia Method.**

	Total Patients (n=149)	General Anesthesia (n=34)	Spinal Anesthesia (n=115)	<i>P</i>
Age (y)	71.5 ± 15.3	66.3 ± 19.4	73.0 ± 13.6	0.025
Gender				0.500
Female	98 (65.77%)	24 (70.59%)	74 (64.35%)	
Male	51 (34.23%)	10 (29.41%)	41 (35.65%)	
ASA Physical Status				0.361
2	87 (58.39%)	22 (64.71%)	65 (56.52%)	
3	57 (38.26%)	10 (29.41%)	47 (40.87%)	
4	5 ( 3.36%)	2 ( 5.88%)	3 ( 2.61%)	
Preoperative				
HCT (%)	35.94 ± 6.26	35.03 ± 6.20	36.21 ± 6.28	0.345
WBC (×10 <sup>9</sup> /L)	8.67 ± 2.94	7.94 ± 2.48	8.89 ± 3.04	0.114
EOS (×10 <sup>7</sup> /L)	8.5 (3.0,16.0)	9.0 (4.0,16.5)	7.0 (3.0, 16.0)	0.892
Intraoperative				
Blood Loss (mL)	344.03 ± 432.89	512.06 ± 618.95	294.35 ± 348.53	0.010
RBC Transfusion (mL)	124.74 ± 290.56	246.06 ± 443.70	88.87 ± 216.62	0.005
Postoperative Day 1				
HCT (%)	29.02 ± 4.83	27.54 ± 4.91	29.46 ± 4.74	0.041
WBC (×10 <sup>9</sup> /L)	8.72 ± 2.59	9.04 ± 2.38	8.62 ± 2.65	0.408
EOS (×10 <sup>7</sup> /L)	1.0 (0.0, 5.0)	0.0 (0.0, 1.8)	0.0(0.0, 6.0)	0.009
Postoperative Complications				0.172
No	130 (87.25%)	32 (94.12%)	98 (85.22%)	
Yes	19 (12.75%)	2 ( 5.88%)	17 (14.78%)	
Postoperative Hospital Stay (d)	15.2 ± 6.2	13.5 ± 5.0	15.6 ± 6.4	0.076

Values are expressed as mean ± standard deviation, median (interquartile range), numbers or frequency.

ASA: American Society of Anesthesiologists; HCT:hematocrit; WBC:white blood cell; EOS:eosinophil.

**Table 2. Univariate Analysis of Possible Influencing Factors of Postoperative Hospital Stay.**

	Total Patients		General Anesthesia		Spinal Anesthesia	
	b (95%CI)	P	b (95%CI)	P	b (95%CI)	P
Age (y)	0.09 (0.02, 0.15)	0.0101	0.09 (0.01, 0.17)	0.0447	0.08 (-0.00, 0.17)	0.0580
<b>Gender</b>						
Female	0		0		0	
Male	-1.35 (-3.42, 0.73)	0.2051	-2.41 (-6.03, 1.21)	0.2018	-1.06 (-3.52, 1.39)	0.3984
<b>ASA Physical Status</b>						
2	0		0		0	
3	0.73 (-1.25, 2.71)	0.4703	0.53 (-3.29, 4.34)	0.7884	0.85 (-1.39, 3.09)	0.4607
4	10.08 (4.75, 15.41)	0.0003	1.23 (-6.17, 8.62)	0.7471	15.79 (8.88, 22.70)	<0.0001
<b>Preoperative</b>						
HCT (%)	-0.13 (-0.30, 0.03)	0.1211	-0.17 (-0.45, 0.11)	0.2374	-0.12 (-0.32, 0.08)	0.2378
WBC ( $\times 10^9/L$ )	-0.10 (-0.47, 0.27)	0.6023	-0.02 (-0.77, 0.72)	0.9516	-0.11 (-0.53, 0.31)	0.6030
EOS ( $\times 10^7/L$ )	-0.05 (-0.15, 0.06)	0.3578	-0.18 (-0.40, 0.04)	0.1126	-0.03 (-0.15, 0.09)	0.6507
<b>Intraoperative</b>						
Blood Loss (100mL)	0.32 (0.09, 0.55)	0.0072	0.08 (-0.19, 0.36)	0.5582	0.53 (0.21, 0.86)	0.0018
RBC Transfusion (100mL)	0.66 (0.33, 1.00)	0.0001	0.24 (-0.14, 0.62)	0.2175	1.17 (0.67, 1.67)	<0.0001
<b>Postoperative Day 1</b>						
HCT (%)	-0.13 (-0.34, 0.08)	0.2203	-0.11 (-0.46, 0.23)	0.5262	-0.14 (-0.38, 0.11)	0.2896
WBC ( $\times 10^9/L$ )	0.45 (0.07, 0.82)	0.0215	0.69 (0.01, 1.37)	0.0569	0.39 (-0.05, 0.83)	0.0858
EOS ( $\times 10^7/L$ )	-0.13 (-0.26, -0.00)	0.0479	-0.34 (-0.63, -0.05)	0.0305	-0.11 (-0.25, 0.04)	0.1626
<b>Postoperative Complications</b>						
No	0		0		0	
Yes	5.88 (3.05, 8.70)	<0.0001	2.13 (-5.04, 9.29)	0.5649	6.36 (3.25, 9.48)	0.0001

**Table 3. Analysis of Association of Postoperative Day 1 EOS Level with Postoperative Hospital Stay.**

	Total patients	
	b (95%CI)	P
Crude Model	-0.13 (-0.26, -0.00)	0.0479
Adjust Model I	-0.13 (-0.26, -0.00)	0.0469
Adjust Model II	-0.08 (-0.21, 0.04)	0.1803

Crude model adjust for none.

Model I adjust for: age, gender.

Model II adjust for: age, gender, ASA, intraoperative blood loss, intraoperative RBC transfusion, postoperative day 1 HCT and WBC, postoperative complications.

**Table 4. Subgroup Analysis of Association of Postoperative Day 1 EOS Level With Postoperative Hospital Stay**

	General Anesthesia		Spinal Anesthesia		<i>P</i> for interaction
	b (95%CI)	<i>P</i>	b (95%CI)	<i>P</i>	
Crude Model	-0.34 (-0.71, 0.04)	0.0828	-0.11 (-0.24, 0.03)	0.1400	0.2552
Model I	-0.39 (-0.76, -0.02)	0.0394	-0.10 (-0.23, 0.04)	0.1758	0.1347
Model II	-0.39 (-0.74, -0.05)	0.0269	-0.02 (-0.15, 0.10)	0.7440	0.0347

Crude model adjust for none.

Model I adjust for: age, gender.

Model II adjust for: age, gender, ASA, intraoperative blood loss, intraoperative RBC transfusion, postoperative day 1 HCT and WBC, postoperative complications, and the interaction terms for following variables: ASA, intraoperative blood loss, intraoperative RBC transfusion and postoperative complications.

## Figures

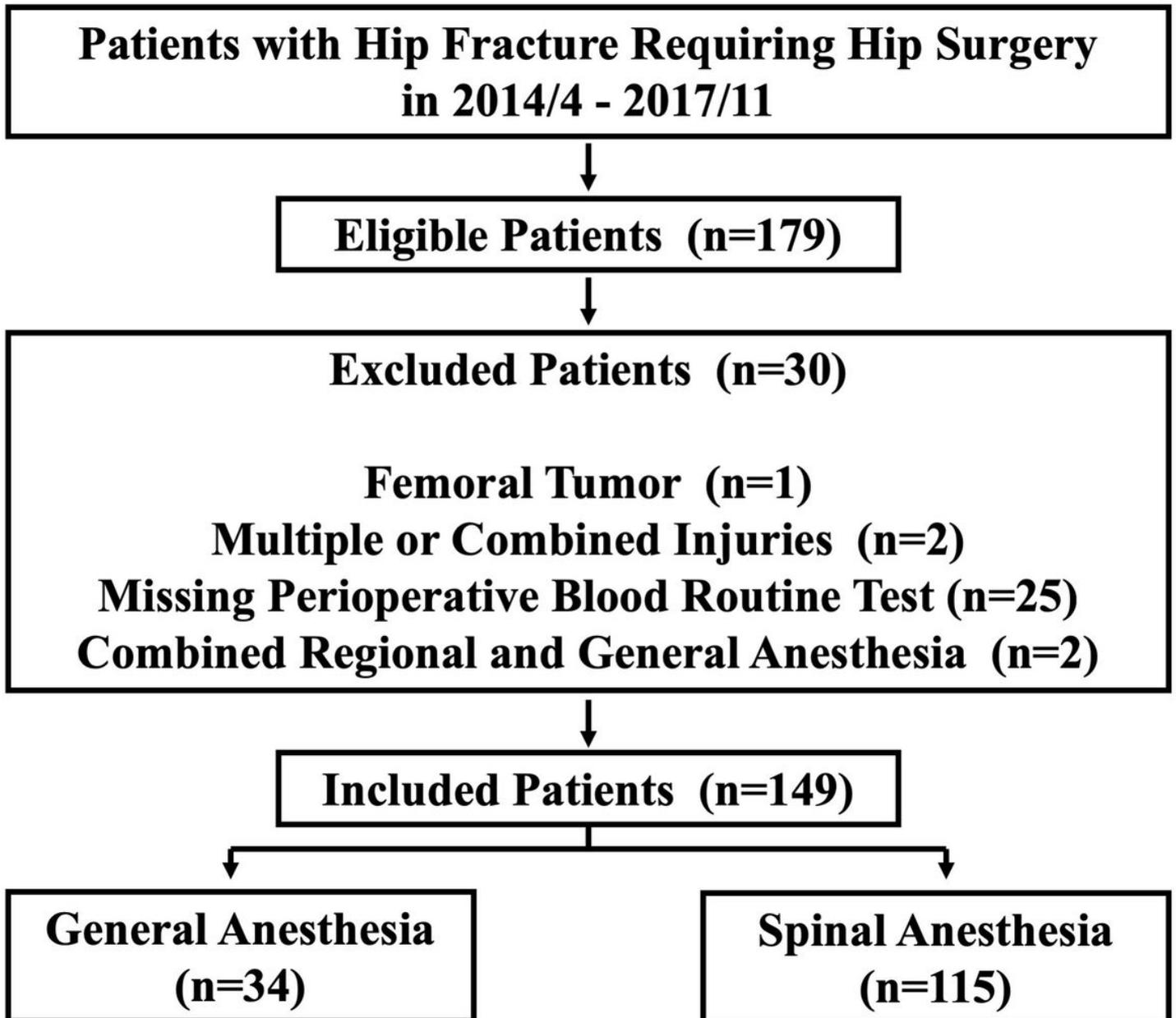


Figure 1