

## Incidence, Risk Factors, and Clinical Outcomes of Reintubation Following Planned Extubation in a Postanesthetic Care Unit: A Case-control Study

Srisuluk Kacha<sup>1</sup>✉, Busabawan Sawangsub<sup>2</sup>, Nutchanart Bunchungmongkol<sup>1</sup>✉ and Tanyong Pipanmekaporn<sup>1</sup>✉

<sup>1</sup>Department of Anesthesiology, Faculty of Medicine, Chiang Mai University, Chiang Mai, <sup>2</sup>Srisangworn Sukhothai Hospital, Sukhothai, Thailand

**Correspondence:**  
Srisuluk Kacha, MD,  
Department of Anesthesiology,  
Faculty of Medicine, Chiang Mai  
University, Intawaroros Rd.,  
Si Phum, Muang, Chiang Mai  
50200, Thailand.  
Email: Srisuluk.ka@cmu.ac.th

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### ABSTRACT

**OBJECTIVE** This study aimed to determine the incidence, risk factors, and clinical outcomes associated with reintubation after a planned extubation (RAP) during the postoperative period.

**METHODS** A retrospective case-control study was conducted on patients with RAP in an operating theater or postanesthetic care unit. Forty-six cases between 2013 and 2017 were extracted from the anesthetic database of the Department of Anesthesiology, Faculty of Medicine, Chiang Mai University. Cases with RAP were randomly matched in a ratio of 1:4 with selected controls. Univariable and multivariable logistic regression were used for the analysis and results are presented as the odds ratio (OR) and 95% confidence interval (CI).

**RESULTS** A total of 230 patients (46 cases and 184 controls) were included. The independent risk factors of RAP included creatinine clearance (CrCl) 25–60 mL/min (OR = 3.34; 95% CI: 1.83–9.46), CrCl < 25 mL/min (OR = 4.26; 95% CI: 1.04–17.47), preoperative oxygen saturation ≤ 94% (OR = 16.78; 95% CI 3.99–70.57), and use of aminosteroid muscle relaxants (OR = 3.00; 95% CI: 1.23–7.31). The immediate outcomes of RAP were unplanned ICU admission (65.22%), major respiratory events (19.57%), and cardiovascular events (19.57%).

**CONCLUSIONS** Independent risk factors of RAP were renal insufficiency, CrCl < 60 mL/min, preoperative oxygen saturation ≤ 94%, creatinine clearance 25–60 mL/min, and use of an aminosteroid muscle relaxant. Proper evaluation and management before extubation could help prevent the occurrence of RAP.

**KEYWORDS** reintubation, PACU, postoperative outcome, anesthesia

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## INTRODUCTION

Reintubation after planned extubation (RAP) is defined as intubation that occurs after planned extubation in patients receiving general anesthesia (1). RAP can lead to unplanned intensive care admission, desaturation, hemodynamic instability, and cardiac arrest within 24 hours after reintubation. Additionally, RAP is associ-

ated with prolonged respiratory support (1–5), ventilator-associated pneumonia (6), and prolonged hospital stay (5,7). These, all of which can lead to increased morbidity and mortality (1–3,8).

Previous studies conducted in different hospitals have reported the incidence of RAP in the Postanesthetic Care Unit (PACU) ranging from

0.06% to 0.27% (3,9-12). However, according to the Thai Anesthesia Incidents Study (THAI Study), the first multi-center prospective cohort study comprising 20 hospitals (7 university, 5 tertiary, 4 secondary, and 4 primary care hospitals) across Thailand during 2003-2004, reported that the incidence of RAP was 0.027% (1). Furthermore, a study of the overall incidence of RAP from Perioperative and Anesthetic Adverse Events in Thailand (PAAd THAI) initiated by the Royal College of Anesthesiologists of Thailand (RCAT) in 2015, conducted in 22 university and non-university hospitals in Thailand was 0.0011% (5).

Independent risk factors associated with RAP can be divided into anesthesia-related, patient-related, and surgery-related factors. According to a previous retrospective cohort study report in Chiang Mai University Hospital, the incidence of RAP was 0.27% (10). In that 2009 study, the independent risk factors statistically significantly related to RAP were age over 50 years, American Society of Anesthesiologists physical status (ASA PS) 3-4, and intraabdominal surgery (10). The anesthetic management staff and other personnel in our institution have changed since that time, so the present study was conducted to explore the current incidence, relevant risk factors, possible causes, and outcomes of RAP.

## Objectives

The study aimed to determine the incidence, risk factors, possible causes, and clinical outcomes of RAP in postoperative patients.

## METHODS

This retrospective case-control study was conducted at the Department of Anesthesiology, Faculty of Medicine, Chiang Mai University. After obtaining Institutional Research Ethical Committee approval (certificate no.474/2016), adult patients who had received either elective or emergency non-cardiac surgery under general anesthesia between 2013 and 2017 were included. Patient informed consent was waived because of the retrospective nature of the study. The adverse events and causal factors related to RAP were retrieved from the electronic database, which was reviewed and summarized by

the consensus of the Quality Assurance Committee in our department. Two investigators (SK and BS) reviewed the incident cases and discussed possible causes of RAP. If there were disagreements between the reviewers, the third reviewer (TP) would make the final decision. The definition of RAP, according to the THAI study, is a patient who received general anesthesia being intubated again after extubation within 24 hours after anesthesia (1).

## Variables and clinical outcomes

Patient characteristics and demographic data (see Supplementary Data) included age, gender, body mass index (BMI), ASA PS, comorbidities, and preoperative laboratory test results.

Data on the site of the operation (thoracic surgery, intracranial surgery, head, eyes, ears, nose and throat surgery (HEENT), airway, intra-abdomen, superficial, extremities, and others), intraoperative data, and anesthetic agents were collected.

The significant events within 24 hours after surgery were recorded as immediate clinical outcomes. Immediate clinical outcomes included unplanned intensive care unit (ICU) admission, major respiratory events, cardiovascular events, and neurological events. In-hospital events that occurred within 7 days after surgery were defined as delayed clinical outcomes, e.g., prolonged ventilator support and mortality.

## Patients

### Definition of cases

All adult patients documented as RAP in the operating theater or PACU were defined as index cases.

### Selection of control

An electronic anesthetic and postanesthetic records database was reviewed to identify the control group. Control cases, patients who were successfully extubated after undergoing general anesthesia on the same operating day and time as the incidence cases, were randomly selected. Due to the low incidence of RAP, we decided to use a ratio of index to control cases of 1:4.

## Statistical analysis

Categorical data were reported as frequencies and percentages and were compared between

groups using an exact probability test. Continuous variables were presented as means and standard deviations for normally distributed data or as medians (interquartile range) for non-normal distribution. Data distribution was verified by the Shapiro-Wilk test. Comparative analysis of continuous data between the two groups was conducted using the student's t-test or the Wilcoxon rank-sum test according to the distribution of the data. Univariable logistic regression was used to determine the risk factors of RAP. All univariable risk factors with  $p < 0.2$  were selected and included in the multivariable logistic regression. Risk factors are presented as odds ratios (OR) and confidence intervals (CI).  $P < 0.05$  were considered statistically significant. STATA 14.0 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses.

The sample size was calculated based on the OR of potential risk factors for RAP from a previous study (13). A minimum of 25 cases with

RAP and 100 control cases were required with a power of 80% and  $\alpha$  error of 5%.

## RESULTS

From 2013 to 2017, 32,463 patients required general anesthesia with endotracheal intubation in Maharaj Nakhon Chiang Mai Hospital. Forty-six patients had RAP. The control group included 184 patients who had been successfully extubated who were identified by time-matching selection. The incidence of RAP was 0.14% (46 cases). The mean age of patients with RAP was 60 years, and for non-RAP patients was 51.5 years. Most patients in both groups were male (56.5% in the RAP group and 51.6% in the non-RAP group). (Table 1)

The most common sites of the operations were intra-abdomen (23.9% of the RAP group, 35.8% of the non-RAP group), extremities (23.9% of the RAP group, 23.3% of the non-RAP group), and head and neck surgery (21.7% of the RAP group, 15.8% of the non-RAP group). The number

**Table 1.** Patient characteristics and demographic data of patients with and without RAP

Variables	RAP (N=46)	Non-RAP (N=184)	p-value
Age(years) median (P25-P75)	60 (38-69)	51.5 (34-65)	0.064
< 70	35 (76.1)	157 (85.3)	
≥ 70	11 (23.9)	27 (14.7)	
Sex (n,%)			
Male	26 (56.5)	95 (51.6)	0.552
Female	20 (43.5)	89 (48.4)	
BMI (kg/m <sup>2</sup> )			
Mean±SD	23.2±5.1	23.5±4.6	0.613
ASA PS 1 (n,%)	5 (10.9)	58 (31.5)	< 0.001
ASA PS 2	15 (32.6)	95 (51.6)	
ASA PS 3	26 (56.5)	31 (16.9)	
Comorbidities (n, %)			
Hypertension	21 (45.6)	64 (34.8)	0.172
Diabetes mellitus	11 (23.9)	20 (10.9)	0.021
Respiratory disease	11 (23.9)	12 (6.5)	< 0.001
Coronary artery disease	3 (6.5)	11 (6.0)	0.89
Renal insufficiency	23 (50.0)	25 (13.6)	< 0.001
History of smoking	24 (52.2)	60 (42.6)	0.014
Laboratory (mean±SD)			
Hb (g/dL)	11.8±2.1	12.1±2.1	0.399
K (mmol/L)	4.2±0.8	4.0±0.5	0.007
Creatinine clearance	57.2 (25.3-81.8)	84.4 (63.9-110.7)	< 0.001
Median (P25-P75)			
> 60	22 (47.8)	143 (77.7)	
25-60	14 (30.4)	30 (16.3)	
< 25	10 (21.8)	11 (6.0)	

RAP, reintubation after planned extubation; BMI, body mass index; ASA PS, American Society of Anesthesiologists physical status; Hb, hemoglobin

**Table 2.** Intraoperative and anesthetic details between patients with and without RAP

Variables	RAP (N=46)	Non-RAP (N=184)	p-value
Site of operation (n, %)			
Thoracic	4 (8.7)	7 (3.8)	0.082
Intra-cranial	3 (6.5)	2 (1.1)	
HEENT	10 (21.7)	29 (15.8)	
Airway	0	11 (6.0)	
Intra-abdomen	11 (23.9)	66 (35.8)	
Superficial	6 (13.0)	16 (8.7)	
Extremities	11 (23.9)	41 (23.3)	
Others	1 (2.2)	12 (6.5)	
Type of procedure (n, %)			0.015
Elective surgery	23 (50.0)	127 (69.0)	
Emergency surgery	23 (50.0)	57 (31.0)	
Induction agents (n, %)			
Thiopental	13 (28.3)	37 (20.1)	0.072
Propofol	28 (60.9)	137 (74.5)	
Etomidate	4 (8.7)	9 (4.9)	
Inhalation	1 (2.1)	1 (0.5)	
Neuromuscular blocking agents (n, %)			
Aminosteroid compound	9 (20.0)	11 (5.9)	0.009
Rocuronium	9 (20.0)	6 (3.2)	
Pancuronium	0	5 (2.7)	
Benzylisoquinolinium compound	36 (78.2)	168 (91.3)	
Atracurium	20 (43.4)	104 (56.5)	
Cisatracurium	16 (34.8)	67 (36.4)	
Succinylcholine	0	3 (1.6)	
Reverse neuromuscular blocking agents (n, %)			
Yes	46 (100)	184 (100)	
Operation time (min)			
Median (P25-P75)	120 (85-200)	140 (90-210)	0.439
Intraoperative blood loss (ml)			
Median (P25-P75)	50 (20-200)	50 (10-200)	0.911
Intraoperative crystalloid administration (mL)	400 (280-1,000)	450 (250-875)	0.790
Median (P25-P75)			
Intubating performers (n, %)			
Anesthesiologists	4 (8.7)	1 (0.54)	< 0.001
3 <sup>rd</sup> year resident	17 (36.9)	45 (24.6)	
2 <sup>nd</sup> year resident	25 (54.4)	137 (74.5)	

HEENT, (head, eyes, ears, nose, and throat surgery)

of patients with ASA PS 3 in the RAP group (56.5%) was significantly higher than in the non-RAP group (16.9%). (**Table 2**)

Univariable logistic regression showed age equal to or higher than 70 years, hypertension, diabetes mellitus, current smokers, emergency surgery, creatinine clearance (CrCl), preoperative room air oxygen saturation (SaO<sub>2</sub>) less than 94%, and aminosteroid compound administration to be potential risk factors.

After multivariable-adjusted analysis, the independent risk factors of RAP included CrCl 25–60 mL/min (OR = 3.34; 95% (CI): 1.83–9.46), CrCl < 25 mL/min (OR = 4.26; 95% CI: 1.04–17.47), preoperative room air SaO<sub>2</sub> ≤ 94% (OR

= 16.78; 95% CI 3.99–70.57) and use of an aminosteroid muscle relaxant (OR = 3.00; 95% CI: 1.23–7.31). (**Table 3**)

Possible causes of RAP are presented in **Table S1**. In fourteen patients (30.4%) who had low-minute ventilation, hypoventilation was suspected of being a cause of RAP (**14**). In addition, 13% of the patients were re-intubated due to hemodynamic instability and upper airway obstruction. Other possible causes of RAP were mental status change, volume overload, respiratory failure, acute bronchospasm, and surgical bleeding.

The immediate outcomes of RAP were unplanned ICU admission (65.22%), major res-

**Table 3.** Univariable and multivariable logistic regression of RAP

Variables	Crude OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value
Age ≥ 70 years	1.83 (0.83-4.03)	0.135	0.54 (0.16-1.88)	0.338
Male	0.82 (0.43-1.57)	0.553		
Hypertension	1.50 (0.78-2.89)	0.223		
Diabetes Mellitus	2.44 (1.08-5.52)	0.032	1.26 (0.41-3.88)	0.691
Chronic liver disease	0.79 (0.17-3.74)	0.767		
Current smokers	2.25 (1.17-4.34)	0.015	1.67 (0.66-3.30)	0.340
Emergency surgery	2.12 (1.10-4.08)	0.025	1.05 (0.47-2.34)	0.897
Intrathoracic/abdominal surgery	0.74 (0.37-1.46)	0.379		
Cr clearance > 60	1	Reference	1	Reference
Cr clearance 25-60	2.80 (1.29-6.07)		3.34 (1.83-9.46)	0.023
Cr clearance < 25	5.83 (2.21-15.32)		4.26 (1.04-17.47)	0.044
Preoperative oxygen saturation (≤ 94%)	18.96 (5.03-71.47)	< 0.001	16.78 (3.99-70.57)	< 0.001
Aminosteroid compound administration	3.59 (1.46-8.82)	0.005	3.00 (1.23-7.31)	0.016

Cr (Creatinine) OR (Odds ratio)

piratory events (19.57%), and cardiovascular events (19.57%). (**Table 4**)

Seventy-two percent of patients in the RAP group were successfully extubated. Most (34.78%) were extubated within 24 hours in PACU and ICU. In addition, five patients in the RAP group needed mechanical ventilation after surgery for more than 48 hours. Two patients in the RAP group died within 24 hours of ICU admission. Twenty-five patients in the RAP group (54.35%) required mechanical ventilatory support for more than 24 hours. (**Table S2**)

In the RAP group, the patients were re-intubated within 30 minutes (47.83%), between 30 and 60 minutes (30.43%), and more than 60 minutes (21.74%) after extubation. RAP occurred frequently in the PACU (58.70%), operating room (36.96%), and ICU (4.35%). (**Table S3**)

## DISCUSSION

The incidence of RAP in this study was 0.14%. The independent risk factors of RAP included CrCl < 60 mL/min, preoperative room air  $\text{SaO}_2 \leq 94\%$ , and use of aminosteroid muscle relaxants. In addition, we found that patients in the RAP group had unplanned ICU admission, major respiratory events major cardiovascular events, and mechanical ventilatory support for more than 24 hours, statistically significantly higher than the incidence in the control group, 65.22%, 19.57%, 19.57%, and 54.35%, respectively.

The incidence of RAP in this study was lower than in a study by Bunchungmongkol et al.

**Table 4.** Immediate and delayed clinical outcomes after RAP

Clinical outcomes	N (%)
<b>Immediate clinical outcomes</b>	
Unplanned ICU admission	30
Major respiratory events	(65.22)
Pulmonary edema	9 (19.57)
Acute respiratory distress syndrome	8 (17.39)
Pulmonary embolism	1 (2.17)
Major cardiovascular events	1 (2.17)
Arrhythmia (atrial fibrillation)	9 (19.57)
Acute congestive heart failure	5 (10.87)
Acute myocardial ischemia	3 (6.52)
Major neurological events	1 (2.17)
Hemiparesis	4 (8.70)
Seizure	3 (6.52)
<b>Delayed clinical outcomes</b>	
Prolonged ventilator support	1 (2.17)
1-3 days	20 (43.48)
> 3 days	5 (10.87)
Death	2 (4.35)

which was conducted between 2004-2006 in our institution which reported the incidence of RAP to be 0.0027% (**10**). The incidence of RAP in our study was also lower than the results in a study in another institution in Thailand (**12**). The incidence of RAP events in that study was estimated to be 0.0017% (**12**). The lower incidence of RAP in our study was probably due to the use newer developed and shorter-acting anesthetic agents, including propofol and desflurane (**15, 16**), as well as more advanced brain function monitoring, including bispectral index (BIS), which can help anesthesiologists adjust the depth of anesthesia and improve the

recovery time.

Previous studies have reported various risk factors related to RAP (Table S2). Anesthetic-related factors identified include inappropriate fluid management (10), residual neuromuscular blockade (1,3,9,10,12), sedative effect (1,9,12), inadequate airway care (1,9,12,17), and inexperienced anesthesia personnel (5,10,18). Extreme age (age < 1 and > 70 years) (3,11,19), chronic pulmonary disease (3), preoperative hypoalbuminemia (3), renal insufficiency (3), and ASA PS status > 3 (3,10,11) were patient-related factors. Surgery-related factors were emergency surgery (3), head and neck surgery (3,11), cardiothoracic surgery (3), airway surgery (3,18,20), and operative time of more than three hours (3).

In our study, renal impairment (CrCl 25–60 mL/min, < 25 mL/min) and use of an aminosteroid neuromuscular blocking agent were the risk factors of RAP, which is in concordance with Rujirojindakul et al. (3) and Lin, H-T et al. (18).

Preoperative room air  $\text{SaO}_2$  of less than 94%, a condition commonly found in patients with preexisting chronic lung disease, was found to be related to RAP.

In previous studies, low  $\text{SaO}_2$  was also reported to be one of the most common risk factors of postoperative mechanical ventilatory support longer than 24 hours (21,22).

The RAP events mainly occurred within 30 minutes after extubation. These findings may be indicative of inappropriate evaluation of the patients before considering extubation. To reduce the risk of inappropriate evaluation, extubation criteria should be revised and their importance reinforced to all levels of resident anesthesiologists and anesthesia personnel during quality assurance activities in the department. Patients who are at risk of RAP should be extubated under the supervision of senior anesthesiologists.

Hypoventilation has been found to be one of the most common causes of RAP. Hypoventilation and desaturation in the PACU can be caused by the residual effects of neuromuscular blocking and sedative medications (23). Previous studies have reported that residual neuromuscular blockade increased the risk of RAP in PACU in cases with pulmonary com-

plications (24,25). The use of intraoperative neuromuscular monitoring could reduce the risk of residual neuromuscular blockade (26). In addition, some newer reversal agents, including sugammadex, a direct reversal agent of rocuronium and vecuronium, have been associated with a lower incidence of postoperative reintubation (20) and a lower risk of residual neuromuscular blocking effect compared to neostigmine (20,24). Despite its advantages, sugammadex was not widely administrated as a routine practice during 2013–2017 due to its higher cost compared with neostigmine. All patients in this study received neostigmine as a reversal agent. Moreover, neuromuscular monitoring was used only in selected cases due to the limited availability of this equipment in our department.

Proposed recommendations to minimize the risk of RAP include the following. First, the use of perioperative neuromuscular monitoring and sugammadex should be specified, particularly in patients at risk of RAP. Second, if a tracheal extubation is to be performed by an inexperienced anesthesia resident, it should be performed under the supervision of senior anesthesiologists or staff members. Finally, delayed extubation and mechanical ventilatory support should be considered especially for high-risk RAP patients.

## Strengths

The study's strengths include identifying potential risk factors, possible causes, and postoperative clinical outcomes of RAP which can be applied in daily anesthesia practice to increase awareness of the risk of RAP and which can help ensure in satisfactory extubation.

## Limitations

The study design is retrospective, so it is impossible to determine all patient variables and outcomes. Therefore, some potential risk factors of RAP that could influence clinical judgments might not have been identified. Additionally, as this was a single-center study, the results might not be generalizable to other institutions with different populations and clinical practices. Although we tried to recruit all cases of RAP, the sample size was small.

Further study with a larger sample size is needed to increase the accuracy of information regarding the relevant risk factors of RAP.

## CONCLUSIONS

RAP is one of the critical adverse events which can occur after anesthesia. RAP increases the rate of unplanned ICU admissions and prolongs mechanical ventilatory support. Independent risk factors of RAP include creatinine clearance  $< 60$  mL/min, preoperative oxygen saturation  $\leq 94\%$ , and use of an aminosteroid muscle relaxant. The practice of perioperative neuromuscular monitoring, the strict observance of extubation criteria and conducting extubation under the supervision of staff consultants should be encouraged, especially in the case of high-risk patients with RAP.

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## CONFLICT OF INTERESTS

The authors declare no conflicts of interest regarding the publication of this paper.

## ADDITIONAL INFORMATION

### Data availability

The data used in this study are not publicly available due to participant privacy, but are available from the corresponding author upon reasonable request.

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## Supplementary data

### Definitions of variables and clinical outcomes

#### Patients' characteristics and demographic data

The present of comorbidities were defined from the patients' preoperative evaluation and medical records.

- a. Respiratory disease was defined as chronic obstructive pulmonary disease (COPD), asthma, or interstitial lung disease.
- b. Coronary artery disease was defined as the patients who had history of coronary artery disease before surgery.
- c. Renal insufficiency was defined as creatinine clearance < 60 ml/min.

#### Immediate clinical outcomes: The significant events within 24 hours after surgery

1. Unplanned intensive care unit (ICU) admission was defined as the patients were unexpectedly admitted in the ICU after surgery.
2. Major respiratory events were included pulmonary edema, acute respiratory distress syndrome and pulmonary embolism.
3. Major cardiovascular events were included arrhythmia, acute congestive heart failure and acute myocardial ischemia.
4. Major neurological events were included hemiparesis, seizure and stroke.

#### Delayed clinical outcomes: in-hospital events occurred within 7 days after surgery.

1. Prolonged ventilator support was defined as the patients needed mechanical ventilatory support for more than 48 hours.
2. In-hospital mortality was included all-cause of death during admission within 7 days after surgery

## Supplementary tables

**Table S1 Causes of RAP**

Causes	Number (%)
Hypoventilation	14 (30.4)
Hemodynamic instability	6 (13.0)
Mental status change	4 (8.7)
Acute bronchospasm	5 (10.9)
Upper airway obstruction	6 (13.0)
Surgical bleeding	3 (6.5)
Volume overload	4 (8.7)
Respiratory failure	4 (8.7)

**Table S2 Factors Related to RAP**

<b>Factor-related</b>	<b>Number (%)</b>
<b>Patient factors</b>	32 (69.6)
- Respiratory disease	11 (34.4)
- Sepsis	6 (18.7)
- Volume overload	6 (18.7)
- Cardiovascular disease	6 (18.7)
- Neurological disease	3 (9.4)
<b>Anesthetic factors</b>	25 (54.3)
- Oversedation	14 (56.0)
- Residual neuromuscular blockade	7 (28.0)
- Inappropriate fluid management	4 (16.0)
<b>Surgical factors</b>	7 (15.2)
- Surgical complication	4 (57.1)
- Bleeding	3 (42.9)

**Table S3 Time to Reintubation and Successful Extubation after RAP**

<b>Time to reintubation</b>	<b>Number (%)</b>
Time to reintubation (min) Median (P25-P75)	30 (5-60)
<30 min	22 (47.8)
30-60 min	14 (30.4)
>60 min	10 (21.7)
<b>Place of RAP</b>	
Operating room	17 (37.0)
PACU	27 (58.7)
ICU	2 (4.3)
<b>Successful extubation after RAP</b>	
Recovery room	7 (15.2)
Within 6 hr	4 (8.7)
Within 24 hr	16 (34.8)
2-3 days	14 (30.4)
> 3 days	5 (10.9)