

RESEARCH ARTICLE

The incidence of post-intubation hypertension and association with repeated intubation attempts in the emergency department

Akihiko Inoue^{1,2*}, Hiroshi Okamoto³, Toru Hifumi⁴, Tadahiro Goto⁵, Yusuke Hagiwara⁶, Hiroko Watase⁷, Kohei Hasegawa^{5,8}, for the Japanese Emergency Medicine Network Investigators[†]



1 Department of Emergency and Critical Care Medicine, Hyogo Emergency Medical Center, Kobe, Hyogo, Japan, **2** Faculty of Medicine, Graduate School of Medicine, Kagawa University, Miki, Kita, Kagawa, Japan, **3** Center for Clinical Epidemiology, St. Luke's International University, Chuo-ku, Tokyo, Japan, **4** Emergency and Critical Care medicine, St. Luke's International Hospital, Chuo-ku, Tokyo, Japan, **5** Department of Emergency Medicine, Massachusetts General Hospital, Boston, Massachusetts, United States of America, **6** Department of Pediatric Emergency and Critical Care Medicine, Tokyo Metropolitan Children's Medical Center, Fuchu, Tokyo, Japan, **7** Department of Surgery, University of Washington, Seattle, Washington, United States of America, **8** Harvard Medical School, Boston, Massachusetts, United States of America

OPEN ACCESS

Citation: Inoue A, Okamoto H, Hifumi T, Goto T, Hagiwara Y, Watase H, et al. (2019) The incidence of post-intubation hypertension and association with repeated intubation attempts in the emergency department. PLoS ONE 14(2): e0212170. <https://doi.org/10.1371/journal.pone.0212170>

Editor: Andrea Coppadoro, San Gerardo Hospital, ITALY

Received: February 17, 2018

Accepted: January 29, 2019

Published: February 11, 2019

Copyright: © 2019 Inoue et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: There are restrictions on the availability of data due to for the data use agreement, which allows a controlled access to external researchers. The study data cannot be made publicly available because it contains protected health information of the participants and would violate the agreement with the IRBs that approved the study. The study was approved by the institutional review board of Fukui University Hospital, Fukui Prefectural Hospital, Kameda Medical Center, Kurashiki Central Hospital, Nagoya Ekisaikai Hospital, Nigata City General Hospital,

[†] Membership of the Japanese Emergency Medicine Network Investigators is provided in the Acknowledgments.

* a-inoue@hemc.jp

Abstract

Background

Studies in the non-emergency department (ED) settings have reported the relationships of post-intubation hypertension with poor patient outcomes. While ED-based studies have examined post-intubation hypotension and its sequelae, little is known about, post-intubation hypertension and its risk factors in the ED settings. In this context, we aimed to identify the incidence of post-intubation hypertension in the ED, and to test the hypothesis that repeated intubation attempts are associated with an increased risk of post-intubation hypertension.

Methods

This study is a secondary analysis of the data from a multicenter prospective observational study of emergency intubations in 15 EDs from 2012 through 2016. The analytic cohort comprised all adult non-cardiac-arrest patients undergoing orotracheal intubation without pre-intubation hypotension. The primary exposure was the repeated intubation attempts, defined as ≥ 2 laryngoscopic attempts. The outcome was post-intubation hypertension defined as an increase in systolic blood pressure (sBP) of $>20\%$ along with a post-intubation sBP of >160 mmHg. To investigate the association of repeated intubation attempts with the risk of post-intubation hypertension, we fit multivariable logistic regression models adjusting for ten potential confounders and patient clustering within the EDs.

Okinawa Chubu Prefectural Hospital, Otowa Hospital, Shonan Kamakura General Hospital, St Marianna University School of Medicine Hospital, Tokyo Bay Urayasu Ichikawa Medical Center, University Hospital, Kyoto Prefectural University of Medicine, Yokohama Rosai Hospital, Kishiwada Tokushukai Hospitals, Hyogo Emergency Medical Center, and Massachusetts General Hospital. The relevant data may be accessed upon request. Data requests from qualified investigators performing research in emergency airway management should be made to the Japanese Emergency Medicine Network Coordinating Center (Emails: jemnet@emalliance.org and khasegawa1@partners.org).

Funding: This study was supported by a grant from St. Luke's Life Science Institute. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Results

Of 3,097 patients, the median age was 69 years, 1,977 (64.0%) were men, and 991 (32.0%) underwent repeated intubation attempts. Post-intubation hypertension was observed in 276 (8.9%). In the unadjusted model, the incidence of post-intubation hypertension did not differ between the patients with single intubation attempt and those with repeated attempts (8.5% versus 9.8%, unadjusted $P = 0.24$). By contrast, after adjusting for potential confounders and patient clustering in the random-effects model, the patients who underwent repeated intubation attempts had a significantly higher risk of post-intubation hypertension (OR, 1.56; 95% CI, 1.11–2.18; adjusted $P = 0.01$).

Conclusions

We found that 8.9% of patients developed post-intubation hypertension, and that repeated intubation attempts were significantly associated with a significantly higher risk of post-intubation hypertension in the ED.

Introduction

Tracheal intubation—the definitive management for securing the airway—is one of the most invasive procedures performed in the emergency department (ED). Tracheal intubation in the ED is a high-risk procedure due to the urgency of the situation, limited time for preparation, and unstable patient's condition. Indeed, the literature has reported the incidence of intubation-related adverse events of 12%–26% in the ED [1–3]. Emerging evidence have also shown that repeated intubation attempts are associated with an increased risk of adverse events in the ED [4–8].

Among the various intubation-related adverse events in the ED (e.g., cardiac arrest, hypoxemia, esophageal intubation with delayed recognition, and hemodynamic compromise [1, 6]), most studies have investigated post-intubation hypotension and its sequelae [1, 9–11]. Within the sparse literature, studies in *non*-ED settings (e.g., operation room, intensive care unit) have reported that post-intubation hypertension is associated with myocardial ischemia [12, 13], re-rupture of aneurysmal subarachnoid hemorrhage [14], and poor outcomes in patients with severe traumatic brain injury [15], suggesting that post-intubation hypertension should also be considered as an important adverse event. While ED airway management has unique characteristics—e.g., limited patient's physiologic reserve and potentially limited resources, no study has examined its incidence or the relationship with multiple intubation attempts as a risk factor in the ED setting.

To address the knowledge gap in the literature, by using the data from a prospective multicenter study of ED airway management, we aimed to examine the incidence of post-intubation hypertension, and test the hypothesis that repeated intubation attempts are associated with a higher risk of post-intubation hypertension in the ED.

Materials and methods

Study design and setting

This study was a secondary analysis of the data from the second Japanese Emergency Airway Network (JEAN-2) Study—a multicenter prospective observational study designed to characterize the current ED airway management and outcomes across Japan. The study design,

setting, methods of measurement, and measured variables have been reported previously [3, 6, 16–19]. In brief, JEAN-2 is a consortium of 15 academic and community medical centers from different geographic regions across Japan. All 15 EDs were staffed by emergency attending physicians and had an affiliation with emergency medicine residency training program. Participating institutions included level I (n = 12) or level II (n = 3) equivalent trauma centers with a median ED census of 27,000 visits per year (range, 1,000–65,000 visits). Each ED maintained individual protocols, policies, and procedures for ED airway management. Intubations were performed by attending physicians or by resident physicians at the discretion of supervising ED attending physicians. The institutional review board of Fukui University Hospital, Fukui Prefectural Hospital, Kameda Medical Center, Kurashiki Central Hospital, Nagoya Ekisaikai Hospital, Nigata City General Hospital, Okinawa Chubu Prefectural Hospital, Otowa Hospital, Shonan Kamakura General Hospital, St Marianna University School of Medicine Hospital, Tokyo Bay Urayasu Ichikawa Medical Center, University Hospital, Kyoto Prefectural University of Medicine, Yokohama Rosai Hospital, Kishiwada Tokushukai Hospitals, Hyogo Emergency Medical Center, and Massachusetts General Hospital approved the protocol with waiver of informed consent prior to the data collection.

Study participants

In the current analysis, we included consecutive adult patients who were intubated in the ED from February 2012 through November 2016. We excluded patients with cardiac arrest, those with systolic blood pressure (sBP) of <90 mmHg before first intubation attempt, those with missing data on age or blood pressure, pediatric patients (aged <18 years), and those who underwent nasotracheal intubation or surgical cricothyrotomy.

Data collection and variables

Immediately after each intubation, intubator used a standardized data collection form to record the data, including age, sex, estimated body mass index (BMI), primary indication for intubation, methods of intubation, modified LEMON score [18], medications and dosage (e.g., sedatives, neuromuscular blockades), devices, specialty of the intubators, number of intubation attempts, adverse events, and pre- and post-intubation vital signs. Methods of intubation were categorized to rapid sequence intubation (RSI) and non-RSI. RSI was defined as intubation with virtually simultaneous administration of a sedative and rapidly acting neuromuscular blocking agent [20]. Specialty of the intubators categorized as transitional year resident (post-graduate year 1 or 2), emergency medicine resident, emergency medicine attending physician, and others. Blood pressure was measured at immediately before first intubation attempt (pre-intubation BP), immediately after successful intubation (post-intubation BP) and 30 minutes after intubation, by using noninvasive blood pressure or invasive arterial pressure monitoring.

Primary exposure

The exposure of interest was repeated intubation attempts, defined as ≥ 2 laryngoscopic attempts for a single patient encounter [7, 8, 21]. An intubation “attempt” was defined as a single insertion of the laryngoscope (or other devices) past the teeth [6].

Outcome measure

The outcome measure of interest was post-intubation hypertension, defined as a >20% increase in sBP compared to pre-intubation sBP along with a post-intubation sBP of >160 mmHg, according to prior studies [4, 22–26]. The literature has documented that these post-

intubation hypertension events are associated with poor outcome, such as myocardial ischemia [13, 27], re-rupture of aneurysmal subarachnoid hemorrhage [28], unfavorable neurological outcome [15], propagation of aortic dissection, rupture of aneurysmal thoracic or abdominal, and accelerated bleeding in trauma patients [29]. The percent change in sBP—an index of hemodynamic instability (or stability)—was calculated as $(\text{post-intubation sBP} - \text{pre-intubation sBP}) / \text{pre-intubation sBP} \times 100$ [30].

Statistical analysis

We first compared the patient characteristics and airway management characteristics according to the primary outcome (post-intubation hypertension vs. no post-intubation hypertension groups) by using Mann–Whitney *U* test for continuous variables and chi-squared test for categorical variables. Next, to test the study hypothesis that repeated intubation attempts (the primary exposure) are associated with the risk of post-intubation hypertension (the outcome), we constructed unadjusted and adjusted logistic regression models. In the multivariable model, we adjusted for potential confounders, including age, sex, BMI, indication of intubation, modified LEMON score, device of intubation, premedication, sedatives, neuromuscular blockades, and specialty of the intubator [4, 29]. As recommended by clinical epidemiologists and statisticians [31, 32], we have selected the covariates based on the clinical plausibility and *a priori* knowledge. Additionally, to account for patient clustering within the EDs, we also constructed random-effects models with binomial response using random intercepts for the EDs. To examine the robustness of our inference, in the sensitivity analyses, we used a different cut-off for the number of intubation attempts (≤ 2 vs. ≥ 3 vs. intubation attempts), modeled the number of attempts as an ordinal variable (instead of a binary variable), modeled the number of attempts as a categorical variable, and repeated the analysis in the patients who underwent RSI and in those who were intubated with sedatives (i.e., excluded patients without sedative use). All analyses were performed using STATA 14 (StataCorp, College Station, TX) and JMP statistical software (version 12; SAS Institute, Cary, NC, USA). A two-sided *P* value of <0.05 was considered statistically significant for all analyses.

Results

During the 58-month period, there were 7,908 patients who underwent emergency airway management in the EDs. Among these, 7,657 patients were recorded in the database (capture rate, 97%). We excluded 3,161 patients with cardiac arrest, 663 patients with pre-intubation sBP of <90 mmHg, 465 patients with missing data on age or BP (246 data missing on post-intubation sBP, 203 data missing on pre-intubation sBP, and 16 data missing on age), 236 pediatric patients, and 35 patients who underwent nasotracheal intubation or surgical cricothyrotomy. The remaining 3,097 patients comprised the analytic cohort (Fig 1).

Blood pressure was measured at immediately before first intubation attempt (pre-intubation sBP), immediately after successful intubation (post-intubation sBP) and 30 minutes after intubation, by using noninvasive blood pressure or invasive arterial pressure monitoring.

Overall, the median age was 69 years (IQR 53–78 years), 64.0% were men, and 84.2% of intubations involved medical emergencies (Table 1). Of these, post-intubation hypertension was observed in 8.9% of patients ($n = 276$). A comparison of the patient characteristics between the patients who developed post-intubation hypertension and those who did not were shown in Tables 1 and 2. Overall, 68.0% were successfully intubated at the first intubation attempt while 32.0% underwent repeated intubation attempts (median 2 attempts; IQR 2–3 attempts). The patient characteristics and airway management characteristics differed between the groups (S1 and S2 Tables). For example, compared to the patients with single intubation

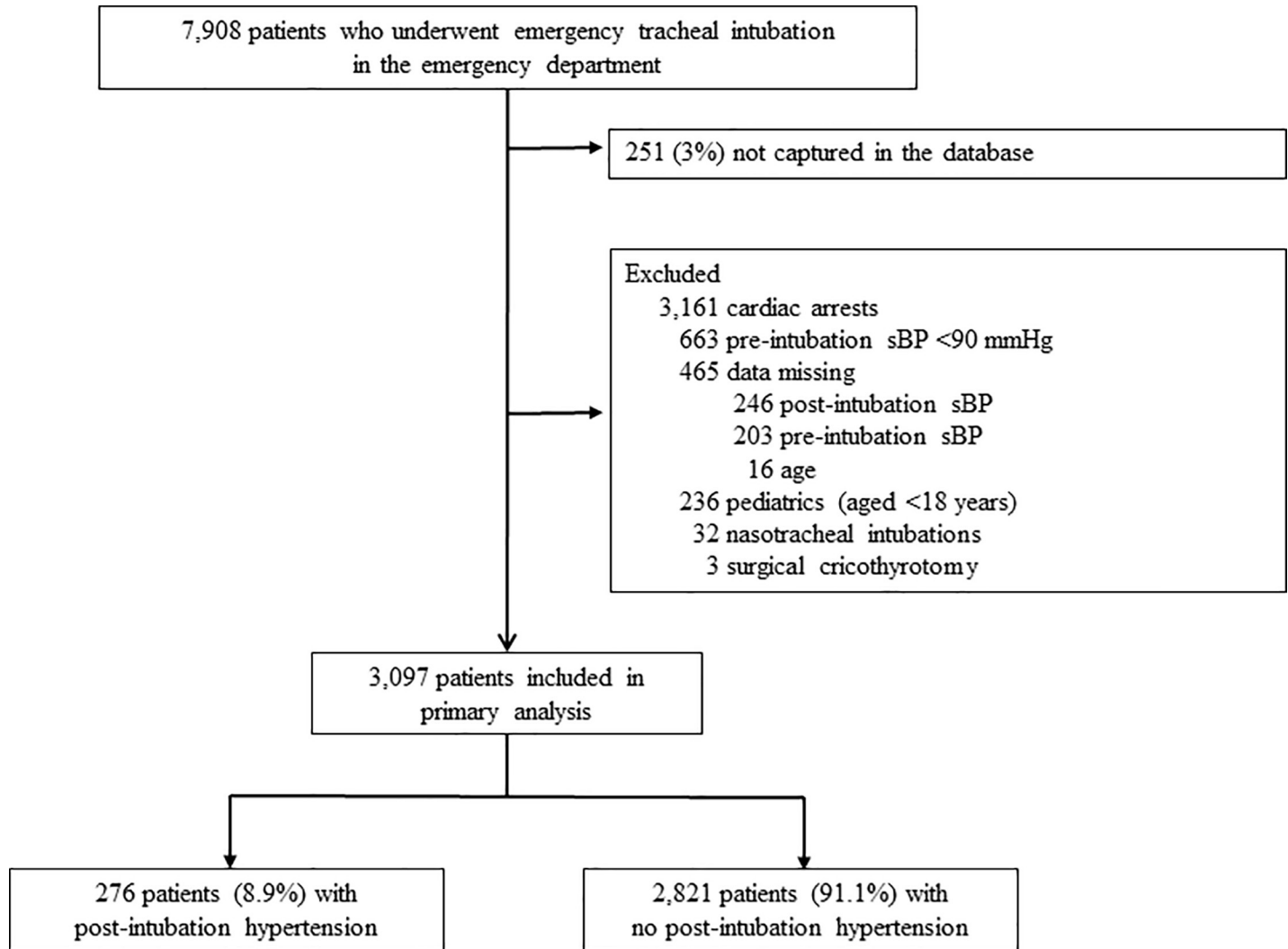


Fig 1. Patients receiving tracheal intubation in the emergency department. Abbreviation: sBP, systolic blood pressure.

<https://doi.org/10.1371/journal.pone.0212170.g001>

attempt, those with repeated attempts were more likely to be overweight or obese and intubated with a non-RSI method, and to have a predicted difficult intubation (≥ 1 modified LEMON score) (all $P < 0.05$). Additionally, these patients were less likely to be intubated by emergency medicine resident or attending physician at the first attempt ($P < 0.001$).

In the unadjusted analysis, there was no significant difference in the incidence between the patient groups (8.5% in the single intubation attempt vs. 9.8% in the repeated attempts; unadjusted $P = 0.24$; [S2 Table](#)). By contrast, after adjusting for potential confounders and patient clustering in the random-effects model, the patients who underwent repeated intubation attempts had a significantly higher risk of post-intubation hypertension (OR, 1.56; 95% CI, 1.11–2.18; adjusted $P = 0.01$; [Table 3](#)). Other factors that were associated with post-intubation hypertension were male sex, use of ketamine (compared to use of propofol), and use of neuromuscular blockers (all $P < 0.05$). Comparison of premedication and sedatives according to the use of neuromuscular blockades was shown in [S3 Table](#). The patients with neuromuscular blocker use were more likely to have received premedications (fentanyl) and sedatives (both $P < 0.05$).

Table 1. Baseline characteristics of the study population, according to the outcome.

Variables	Overall (n = 3,097)	Post-intubation hypertension (n = 276)	No post-intubation hypertension (n = 2,821)	P value
Age (yr), median (IQR)	69 (53–78)	65 [51–76]	69 [54–79]	0.009
Age ≥65 years	1,805 (58.3)	142 (51.5)	1,663 (59.0)	0.02
Male sex	1,977 (64.0)	194 (70.3)	1,783 (63.2)	0.02
Body mass index category (kg/m ²)				0.047
<18.5	366 (12.3)	22 (8.2)	344 (12.7)	
18.5–24.9	1,828 (61.3)	168 (62.7)	1,660 (61.2)	
25.0–29.9	614 (20.6)	55 (20.5)	559 (20.6)	
≥30	173 (5.8)	23 (8.6)	150 (5.5)	
Indication of intubation				
Medical encounters	2,608 (84.2)	221 (80.1)	2,387 (84.6)	0.04
Altered mental status	1,226 (39.6)	113 (40.9)	1,113 (39.5)	
Respiratory failure	920 (29.7)	59 (21.4)	861 (30.5)	
Shock	295 (9.5)	29 (10.5)	266 (9.4)	
Airway obstruction	129 (4.2)	17 (6.2)	112 (4.0)	
Other medical ^a	38 (1.2)	3 (1.1)	35 (1.2)	
Trauma encounters	489 (15.8)	55 (19.9)	434 (15.4)	0.33
Head trauma	199 (6.4)	16 (5.8)	183 (6.5)	
Shock	96 (3.1)	11 (4.0)	85 (3.0)	
Other trauma ^b	88 (2.8)	13 (4.7)	75 (2.7)	
Burn / inhalation	55 (1.8)	9 (3.3)	46 (1.6)	
Facial / neck trauma	51 (1.7)	6 (2.2)	45 (1.6)	

Abbreviation: IQR, interquartile range.

Data are expressed as number (percentage) unless otherwise indicated.

^a Defined as airway obstruction, asthma, anaphylaxis, and others.

^b Defined as multiple trauma and others.

<https://doi.org/10.1371/journal.pone.0212170.t001>

In the sensitivity analyses, the significant association between repeated intubation attempts and post-intubation hypertension persisted with the use of different definitions for repeated intubation attempts, and with limiting the samples to those with RSI and those with sedatives (Table 4). For example, compared to single intubation attempt, ≥3 intubation attempts were associated with a significantly higher risk of post-intubation hypertension with an adjusted OR of 1.93 (95%CI, 1.21–3.08; P = 0.006). In addition, even after adjusting for the dose of pre-medication and sedatives, the association between repeated intubation attempts and post-intubation hypertension remained significant (S4 Table).

Discussion

In this analysis of the data from a 15-center prospective study of 3,097 patients who underwent emergency tracheal intubation in the ED, we found that approximately 9% of patients developed post-intubation hypertension. The previous ED literature has reported an intubation-related adverse event rate of approximately 12%-26%, not including post-intubation hypertension [1–3]. Thus, the 9% incidence post-intubation hypertension would add a substantial portion of adverse events related to airway management in the ED. The data also demonstrated that repeated intubation attempts are associated with a significantly higher risk of post-intubation hypertension. The significant association persisted across several different statistical

Table 2. Airway management characteristics of the study population, according to the outcome.

Variables	Overall (n = 3,097)	Post-intubation hypertension (n = 276)	No post-intubation hypertension (n = 2,821)	P value
Method of indication				
RSI	1,675 (54.1)	189 (68.5)	1,486 (52.7)	<0.001
No RSI	1,422 (45.9)	87 (31.5)	1,335 (47.3)	
≥1 Modified LEMON	1,138 (50.6)	98 (46.5)	1,040 (51.0)	0.21
Device of intubation				0.01
Direct laryngoscope	1,998 (64.6)	157 (57.1)	1,841 (65.4)	
Video laryngoscope	1,062 (34.4)	113 (41.1)	949 (33.7)	
Other devices ^a	32 (1.0)	5 (1.8)	27 (1.0)	
Premedication (fentanyl)	975 (31.5)	108 (39.1)	867 (30.7)	0.004
Premedication (fentanyl) dose (mcg/kg), median (IQR)	1.43 (1.00–1.82)	1.43 (1.00–1.67)	1.43 (1.00–1.82)	0.32
Sedative				0.002
Midazolam	1,198 (38.7)	133 (48.2)	1,065 (37.8)	
Propofol	578 (18.7)	40 (14.5)	538 (19.1)	
Ketamine	292 (9.4)	32 (11.6)	260 (9.2)	
Others ^b	146 (4.7)	12 (4.4)	134 (4.8)	
None	879 (28.4)	59 (21.4)	820 (29.1)	
Sedative dose (mg/kg), median (IQR)				
Midazolam	0.07 (0.05–0.09)	0.07 (0.05–0.09)	0.07 (0.05–0.09)	0.95
Propofol	0.98 (0.71–1.31)	1.00 (0.67–1.67)	0.98 (0.71–1.27)	0.63
Ketamine	0.90 (0.71–1.04)	0.90 (0.73–1.36)	0.90 (0.71–1.03)	0.48
Neuromuscular blockades				<0.001
Rocuronium	1,601 (51.7)	176 (63.8)	1,425 (50.5)	
Succinylcholine	155 (5.0)	19 (6.9)	136 (4.8)	
Vecuronium	63 (2.0)	8 (2.9)	55 (2.0)	
None	1,278 (41.3)	73 (26.5)	1,205 (42.7)	
Specialty of the intubator				0.38
Transitional year resident ^c	1,195 (38.8)	107 (38.8)	1,088 (38.8)	
Emergency medicine resident ^d	1,049 (34.0)	102 (37.0)	947 (33.7)	
Emergency medicine attending physician ^e	531 (17.2)	47 (17.0)	484 (17.2)	
Other specialty ^f	308 (10.0)	20 (7.3)	288 (10.3)	
Number of intubation attempts				0.24
Repeated (≥2) intubation attempts	991 (32.0)	97 (35.1)	894 (31.7)	0.24

Abbreviations: RSI, rapid sequence intubation; IQR, interquartile range.

Data are expressed as number (percentage) unless otherwise indicated.

^a Defined as flexible bronchoscope and supraglottic devices.

^b Defined as administration of thiopental, diazepam, or combination with any of the included sedatives.

^c Defined as post-graduate year 1 or 2.

^d Defined as post-graduate years 3–5.

^e Defined as post-graduate years ≥6.

^f Defined as surgery, anesthesia, or pediatrics.

<https://doi.org/10.1371/journal.pone.0212170.t002>

assumptions. Other factors associated with the risk of post-intubation hypertension were male sex, use of ketamine (compared to the use of propofol), and use of neuromuscular blockades based on the random-effect model. To the best of our knowledge, this is the first effort that has examined the incidence of post-intubation hypertension and their risk factors in the ED.

Table 3. Unadjusted and adjusted associations between the number of intubation attempts (primary exposure) and risk of post-intubation hypertension (outcome).

Models and variables	Logistic regression model		Random-effect model	
	OR (95%CI)	P value	OR (95%CI)	P value
Unadjusted association				
Number of attempts (≥ 2 vs 1)	1.17 (0.90–1.51)	0.24	1.31 (1.00–1.71)	0.052
Adjusted association				
Number of attempts (≥ 2 vs 1)	1.50 (1.08–2.09)	0.02	1.56 (1.11–2.18)	0.01
<i>Covariates</i>				
Age ≥ 65 years (vs.18–64 years)	0.72 (0.53–0.97)	0.03	0.71 (0.53–0.96)	0.06
Male sex	1.35 (0.97–1.86)	0.07	1.36 (0.99–1.89)	0.03
Body mass index category (kg/m ²)				
<18.5	0.72 (0.42–1.21)	0.21	0.71 (0.42–1.20)	0.21
18.5–24.9	1 (reference)	-	1 (reference)	-
25.0–29.9	0.96 (0.66–1.39)	0.82	0.97 (0.67–1.41)	0.88
≥ 30	1.68 (0.96–2.92)	0.07	1.70 (0.97–2.97)	0.07
Indication				
Medical indications	1 (reference)	-	1 (reference)	-
Head and facial trauma	1.14 (0.64–2.04)	0.66	1.10 (0.61–1.98)	0.75
Other trauma	1.38 (0.84–2.25)	0.20	1.15 (0.68–1.92)	0.60
≥ 1 modified LEMON score (vs 0)	0.80 (0.59–1.08)	0.15	0.79 (0.58–1.08)	0.14
Device				
Direct laryngoscope	1 (reference)	-	1 (reference)	-
Video laryngoscope	0.98 (0.67–1.44)	0.92	0.85 (0.55–1.34)	0.49
Other devices ^a	1.53 (0.33–7.03)	0.59	1.65 (0.36–7.59)	0.52
Premedication (fentanyl vs others)				
Sedative				
Midazolam	1.51 (0.99–2.30)	0.054	1.38 (0.87–2.19)	0.17
Propofol	1 (reference)	-	1 (reference)	-
Ketamine	1.90 (1.10–3.28)	0.02	1.86 (1.04–3.32)	0.04
Others ^b	0.82 (0.33–2.03)	0.66	0.73 (0.29–1.86)	0.51
None	1.28 (0.75–2.18)	0.37	1.16 (0.67–2.00)	0.60
Neuromuscular blockade use	2.25 (1.49–3.41)	<0.001	2.05 (1.33–3.17)	0.001
Specialty of intubator				
Transitional year resident ^c	1 (reference)	-	1 (reference)	-
Emergency medicine resident ^d	1.06 (0.73–1.54)	0.77	1.15 (0.77–1.70)	0.50
Emergency medicine attending physician ^e	1.24 (0.79–1.94)	0.34	1.23 (0.78–1.94)	0.38
Other specialty ^f	0.49 (0.25–0.98)	0.04	0.53 (0.26–1.05)	0.07

Abbreviations: OR, odds ratio; CI, confidence interval.

^a Defined as flexible bronchoscope and supraglottic devices.

^b Defined as administration of thiopental, diazepam, or combination with any of the included sedatives.

^c Defined as post-graduate year 1 or 2.

^d Defined as post-graduate years 3–5.

^e Defined as post-graduate years ≥ 6 .

^f Defined as surgery, anesthesia, or pediatrics.

<https://doi.org/10.1371/journal.pone.0212170.t003>

The sparse literature has reported that post-intubation hypertension is associated with myocardial ischemia [12, 13], re-rupture of aneurysmal subarachnoid hemorrhage [14], and poor outcomes in patients with severe traumatic brain injury [15] in the non-ED setting, indicating

Table 4. Sensitivity analysis using different cut-off for number of intubation attempts and different subgroups.

Models	Adjusted associations			
	Logistic regression		Random-effect model	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Different cut-off for number of intubation attempts^a				
Number of attempts (≥ 3 vs ≤ 2)	1.69 (1.07–2.59)	0.03	1.74 (1.11–2.71)	0.02
Number of attempts (ordinal variable; OR per each incremental attempt)	1.20 (1.02–1.39)	0.02	1.26 (1.07–1.49)	0.006
Number of attempts (categorical variable)				
1	1 (reference)		1 (reference)	
2	1.34 (0.91–1.96)	0.14	1.39 (0.94–2.04)	0.10
≥ 3	1.85 (1.15–2.90)	0.01	1.93 (1.21–3.08)	0.006
Subgroup analysis				
Patients intubated with RSI ^b				
Number of attempts ≥ 2 vs 1	1.62 (1.07–2.42)	0.02	1.67 (1.10–2.53)	0.02
Patients intubated with sedatives (excluded patients with no sedative use) ^a				
Number of attempts ≥ 2 vs 1	1.72 (1.18–2.49)	0.005	1.80 (1.23–2.63)	0.003

Abbreviations: OR, odds ratio; CI, confidence interval; RSI, rapid sequence intubation.

^a Adjusted for age, sex, BMI, indication of intubation, modified LEMON score, device of intubation, premedication, sedatives, neuromuscular blockades, and specialty of the intubator.

^b Adjusted for age, sex, BMI, indication of intubation, modified LEMON score, device of intubation, premedication, sedatives, and specialty of the intubator.

<https://doi.org/10.1371/journal.pone.0212170.t004>

that post-intubation hypertension—a consequence of an imbalance between sedation and stimulation (intubation)—should also be considered as an important adverse event. Despite the apparent clinical and research importance of post-intubation hypertension, only the non-ED literature has evaluated this outcome. For example, two retrospective studies in the prehospital setting reported that the incidence of post-intubation hypertension (defined as a $>20\%$ increase in sBP or mean arterial pressure from the baseline) was approximately 80% in both 97 patients with traumatic brain injury and 115 patients with trauma [33, 34]. Another retrospective single-center study of 57 patients with unplanned extubation who were emergently reintubated reported an incidence of post-intubation hypertension (defined as $>20\%$ increase in sBP from the baseline with sBP >160 mmHg) of 14% [23]. The between-study difference in the incidence of post-intubation hypertension are likely multifactorial, such as the difference in the patient populations. Indeed, while the population of prior prehospital study comprised of patients with traumatic brain injury—which is known to carry a high risk of hypertensive responses [29], our study had a smaller proportion of traumatic head injury (6%). Additionally, the differences in the study design (retrospective vs. prospective), setting (e.g., prehospital vs. ED), methods of BP measurements, and airway practices explain, at least in part, the apparent discrepancy of incidences.

Previous studies have shown the association between repeated intubation attempts and higher risk of intubation-related adverse events (not including post-intubation hypertension) across various clinical settings [5, 6, 8]. Consistently, the current study demonstrated, for the first time, the significant association between repeated attempts and elevated risk of post-intubation hypertension. There are several plausible underlying mechanisms of this novel association. Tracheal intubation attempt—a complex procedure consisting of direct laryngoscopy [35] and passage of the tracheal tube through the vocal cords and into the trachea [36]—induces sympathetic stimulation and increases in plasma catecholamines, thereby resulting in

hemodynamic responses, such as tachycardia and elevation of blood pressure [37]. Particularly, studies have shown that an increasing force and duration at laryngoscopic attempts [38, 39] induce greater magnitude of these hemodynamic responses. The current study corroborates the earlier epidemiological and mechanistic studies, and extends them by demonstrating the associations between repeated intubation attempts and accelerated risks of post-intubation hypertension.

In the current study, other factors associated with the risk of post-intubation hypertension were male sex, use of ketamine (compared to use of propofol), and use of neuromuscular blockers. Patients with neuromuscular blockade use were more likely to have received sedatives, particularly benzodiazepines, which would have decreased the incidence of post-intubation hypertension. Regardless, because the observed association between the neuromuscular blockade use and outcome was independent from other covariates (including sedative use), it cannot be explained by the difference in sedative use. Alternatively, it is possible that the use (and choice) of neuromuscular blockades might have been related to other factors (e.g., individual intubator's skills, competencies, and practice patterns) that are also associated with the occurrence of post-intubation hypertension.

This study has several potential limitations. First, passive surveillance introduces a self-report bias, and possible underestimation of the incidence of post-intubation hypertension. It is challenging to record real-time data accurately in the ED when emergency intubation is required. However, we used a previously applied standardized data collection system with a capture rate (97%) [9, 40]. Second, the observed associations might have been biased by unmeasured confounders, such as patient's baseline cardiopulmonary reserve and between-hospital differences in the airway practice. Yet, the significant associations between repeated intubation attempts and post-intubation hypertension persisted after accounting for patient clustering within hospitals. Third, the current study did not measure post-ED clinical outcomes (e.g., in-hospital mortality, neurological outcomes). Therefore, we were unable to assess the potential heterogeneity in the impact of the observed associations between different disease conditions. For example, in patients with traumatic brain injury, post-intubation hypertension is—through improved brain perfusion—potentially favorable while this intubation-related adverse event may be harmful in other patient groups (e.g., patients with aortic dissection). Fourth, our observational data do not have the information on the methods used for blood pressure measurements—i.e., non-invasive vs. invasive monitoring. However, non-invasive monitoring is well correlated with the invasive blood pressure [41], and widely used in clinical settings. Fifth, while the multivariable models rigorously adjusted for the type of medications used, it is possible that the causal inference is confounded by other clinical factors that affected clinical decision making. Finally, the study cohort comprised patients in academic EDs across Japan; our inferences therefore might not be generalizable to other ED settings. However, the association is plausible and has been demonstrated in the other clinical settings (e.g., operating rooms), supporting the validity of our inferences.

Conclusions

In conclusion, in this analysis of a 15-center prospective study of 3,097 patients undergoing intubation in the ED, approximately 9% developed post-intubation hypertension. We also found that repeated intubation attempts were associated with a significantly higher risk of post-intubation hypertension. The observed association persisted across several different analytic assumptions. The multivariable models also demonstrated that male sex, the use of ketamine, and neuromuscular blockades were associated with a higher risk of post-intubation hypertension. For clinicians, as post-intubation hypertension is known to be related to worse

clinical outcomes, our observations not only underscore the importance of recognition and monitoring for this intubation-related adverse event, but also lend additional significant support to the concept of first-pass success in the ED.

Supporting information

S1 Table. Baseline characteristics according to the primary outcome.

(DOCX)

S2 Table. Airway management characteristics according to the primary outcome.

(DOCX)

S3 Table. Comparison of premedication and sedatives use, according to neuromuscular blockade use.

(DOCX)

S4 Table. Adjusted associations between the number of intubation attempts and risk of post-intubation hypertension, adjusting for premedication and sedatives dosage in addition to other covariates.

(DOCX)

Acknowledgments

The authors acknowledge the following research personnel at the study hospitals for their assistance with this project: Fukui University Hospital (Hiroshi Morita, MD; Takahisa Kawano, MD; Yohei Kamikawa, MD), Fukui Prefectural Hospital (Hideya Nagai, MD; Takashi Matsumoto, MD; Suguru Nonami, MD; Yusuke Miyoshi, MD), Kameda Medical Center (Sho Segawa, MD; Yuya Kitai, MD; Kenzo Tanaka, MD), Kishiwada Tokushukai Hospital (Hiromasa Yakushiji, MD), Kurashiki Central Hospital (Hiroshi Okamoto, MD), Nagoya Ekisaikai Hospital (Yukari Goto, MD), Nigata City General Hospital (Nobuhiro Sato, MD, MPH), Okinawa Chubu Prefectural Hospital (Koichiro Gibo, MD; Masashi Okubo, MD; Yukiko Nakayama, MD), Otowa Hospital (Nobuhiro Miyamae, MD), Shonankamakura General Hospital (Kaoru Hirose, MD; Taichi Imamura, MD; Azusa Uendan, MD), St. Marianna University School of Medicine Hospital (Yasuaki Koyama, MD), Tokyo Bay Urayasu Ichikawa Medical Center (Hiroshi Kamura, MD; Yoshiyuki Nakashima, MD), University Hospital, Kyoto Prefectural University of Medicine (Jin Irie, MD), and Yokohama Rosai Hospital (Seiro Oya, MD), Hyogo Emergency Medical Center (Akihiko Inoue, MD), and our many emergency physicians and residents for their perseverance in pursuing new knowledge about this vital resuscitative procedure. We also thank Koichiro Gibo, MD (Okinawa Prefectural Chubu Hospital) for his statistical support, and Yasuhiro Kuroda, MD (Kagawa University) for his support in designing and drafting the manuscript. The authors acknowledge the following Japanese Emergency Medicine Network Investigators at the study hospitals for their assistance with this study: Fukui University Hospital (Yohei Kamikawa, MD; Hideya Nagai, MD; Hiroshi Morita, MD), Fukui Prefectural Hospital (Hideya Nagai, MD; Takashi Matsumoto, MD; Suguru Nonami, MD; Yusuke Miyoshi, MD), Kameda Medical Center (Sho Segawa, MD; Yuya Kitai, MD; Kenzo Tanaka, MD; Saburo Minami, MD), Kishiwada Tokushukai Hospital (Hiromasa Yakushiji, MD), Kurashiki Central Hospital (Hiroshi Okamoto, MD; Naoto Miyauchi), Nagoya Ekisaikai Hospital (Yukari Goto, MD; Shigeki Tsuboi, MD), Nigata City General Hospital (Nobuhiro Sato, MD), Okinawa Chubu Prefectural Hospital (Koichiro Gibo, MD; Masashi Okubo, MD; Yukiko Nakayama, MD), Otowa Hospital (Nobuhiro Miyamae, MD), Shonankamakura General Hospital (Hirose Kaoru, MD; Taichi Imamura, MD; Azusa Uendan, MD),

St Marianna University School of Medicine Hospital (Yasuaki Koyama, MD), Tokyo Bay Urayasu Ichikawa Medical Center (Hiroshi Kamura, MD; Nakashima Yoshiyuki, MD; Jin Takahashi), University Hospital, Kyoto Prefectural University of Medicine (Jin Irie, MD; Nobunaga Okada, MD), and Yokohama Rosai Hospital (Seiro Oya, MD). Kohei Hasegawa, MD, MPH (Massachusetts General Hospital) is the leading investigator of this study group (Email: khasegawa1@partners.org).

Author Contributions

Conceptualization: Akihiko Inoue, Hiroshi Okamoto, Toru Hifumi, Kohei Hasegawa.

Data curation: Tadahiro Goto, Yusuke Hagiwara, Hiroko Watase.

Formal analysis: Akihiko Inoue, Tadahiro Goto.

Funding acquisition: Kohei Hasegawa.

Investigation: Akihiko Inoue, Hiroshi Okamoto, Toru Hifumi.

Methodology: Akihiko Inoue, Kohei Hasegawa.

Supervision: Hiroshi Okamoto, Toru Hifumi, Tadahiro Goto, Yusuke Hagiwara, Hiroko Watase, Kohei Hasegawa.

Writing – original draft: Akihiko Inoue, Hiroshi Okamoto, Toru Hifumi, Kohei Hasegawa.

Writing – review & editing: Akihiko Inoue, Hiroshi Okamoto, Toru Hifumi, Tadahiro Goto, Yusuke Hagiwara, Hiroko Watase, Kohei Hasegawa.

References

1. Brown CA 3rd, Bair AE, Pallin DJ, Walls RM. Techniques, success, and adverse events of emergency department adult intubations. *Ann Emerg Med.* 2015; 65(4):363–70 e1. Epub 2014/12/24. <https://doi.org/10.1016/j.annemergmed.2014.10.036> PMID: 25533140.
2. Alkhouri H, Vassiliadis J, Murray M, Mackenzie J, Tzannes A, McCarthy S, et al. Emergency airway management in Australian and New Zealand emergency departments: A multicentre descriptive study of 3710 emergency intubations. *Emerg Med Australas.* 2017; 29:499–508. Epub 2017/06/06. <https://doi.org/10.1111/1742-6723.12815> PMID: 28582801.
3. Goto Y, Goto T, Hagiwara Y, Tsugawa Y, Watase H, Okamoto H, et al. Techniques and outcomes of emergency airway management in Japan: An analysis of two multicentre prospective observational studies, 2010–2016. *Resuscitation.* 2017; 114:14–20. Epub 2017/02/22. <https://doi.org/10.1016/j.resuscitation.2017.02.009> PMID: 28219617.
4. Mort TC. Emergency tracheal intubation: complications associated with repeated laryngoscopic attempts. *Anesth Analg.* 2004; 99(2):607–13, table of contents. <https://doi.org/10.1213/01.ANE.0000122825.04923.15> PMID: 15271750.
5. Martin LD, Mhyre JM, Shanks AM, Tremper KK, Kheterpal S. 3,423 emergency tracheal intubations at a university hospital: airway outcomes and complications. *Anesthesiology.* 2011; 114(1):42–8. Epub 2010/12/15. <https://doi.org/10.1097/ALN.0b013e318201c415> PMID: 21150574.
6. Hasegawa K, Shigemitsu K, Hagiwara Y, Chiba T, Watase H, Brown CA 3rd, et al. Association between repeated intubation attempts and adverse events in emergency departments: an analysis of a multicenter prospective observational study. *Ann Emerg Med.* 2012; 60(6):749–54 e2. Epub 2012/05/01. <https://doi.org/10.1016/j.annemergmed.2012.04.005> PMID: 22542734.
7. Rognas L, Hansen TM, Kirkegaard H, Tonnesen E. Pre-hospital advanced airway management by experienced anaesthesiologists: a prospective descriptive study. *Scand J Trauma Resusc Emerg Med.* 2013; 21:58. Epub 2013/07/26. <https://doi.org/10.1186/1757-7241-21-58> PMID: 23883447; PubMed Central PMCID: PMC3733626.
8. Sakles JC, Chiu S, Mosier J, Walker C, Stolz U. The importance of first pass success when performing orotracheal intubation in the emergency department. *Acad Emerg Med.* 2013; 20(1):71–8. <https://doi.org/10.1111/acem.12055> PMID: 23574475; PubMed Central PMCID: PMC3733626.

9. Walls RM, Brown CA 3rd, Bair AE, Pallin DJ. Emergency airway management: a multi-center report of 8937 emergency department intubations. *J Emerg Med*. 2011; 41(4):347–54. Epub 2010/05/04. <https://doi.org/10.1016/j.jemermed.2010.02.024> PMID: 20434289.
10. Green RS, Edwards J, Sabri E, Fergusson D. Evaluation of the incidence, risk factors, and impact on patient outcomes of postintubation hemodynamic instability. *Cjem*. 2012; 14(2):74–82. Epub 2012/05/05. PMID: 22554438.
11. Heffner AC, Swords DS, Neale MN, Jones AE. Incidence and factors associated with cardiac arrest complicating emergency airway management. *Resuscitation*. 2013; 84(11):1500–4. Epub 2013/08/06. <https://doi.org/10.1016/j.resuscitation.2013.07.022> PMID: 23911630.
12. Edwards ND, Alford AM, Dobson PM, Peacock JE, Reilly CS. Myocardial ischaemia during tracheal intubation and extubation. *Br J Anaesth*. 1994; 73(4):537–9. Epub 1994/10/01. PMID: 7999498.
13. Sakles JC, Deacon JM, Bair AE, Keim SM, Panacek EA. Delayed complications of emergency airway management: a study of 533 emergency department intubations. *West J Emerg Med*. 2008; 9(4):190–4. Epub 2009/06/30. PMID: 19561743; PubMed Central PMCID: PMC2672279.
14. Zlotnik EI, Stolkarts IZ, Maruk IM. Rupture of an intracranial aneurysm induced by postintubation arterial hypertension. *Zh Vopr Neurokhir Im N N Burdenko*. 1984;(4):58–60. Epub 1984/07/01. PMID: 6495956.
15. CHENG C-W, WENG Y-M, LIN C-C, LIN C-KC-C. The effects of post-intubation hypertension in severe traumatic brain injury. *SIGNA VITAE*. 2013; 8(2):24–29.
16. Goto T, Gibo K, Hagiwara Y, Morita H, Brown DF, Brown CA 3rd, et al. Multiple failed intubation attempts are associated with decreased success rates on the first rescue intubation in the emergency department: a retrospective analysis of multicentre observational data. *Scand J Trauma Resusc Emerg Med*. 2015; 23:5. Epub 2015/02/24. <https://doi.org/10.1186/s13049-014-0085-8> PMID: 25700237; PubMed Central PMCID: PMC4307194.
17. Goto T, Watase H, Morita H, Nagai H, Brown CA 3rd, Brown DF, et al. Repeated attempts at tracheal intubation by a single intubator associated with decreased success rates in emergency departments: an analysis of a multicentre prospective observational study. *Emerg Med J*. 2015; 32(10):781–6. Epub 2015/01/02. <https://doi.org/10.1136/emered-2013-203473> PMID: 25552546.
18. Hagiwara Y, Watase H, Okamoto H, Goto T, Hasegawa K. Prospective validation of the modified LEMON criteria to predict difficult intubation in the ED. *Am J Emerg Med*. 2015; 33(10):1492–6. Epub 2015/07/15. <https://doi.org/10.1016/j.ajem.2015.06.038> PMID: 26166379.
19. Goto T, Gibo K, Hagiwara Y, Okubo M, Brown DF, Brown CA 3rd, et al. Factors Associated with First-Pass Success in Pediatric Intubation in the Emergency Department. *West J Emerg Med*. 2016; 17(2):129–34. Epub 2016/03/15. <https://doi.org/10.5811/westjem.2016.1.28685> PMID: 26973736; PubMed Central PMCID: PMC4786230.
20. Dronen S. Rapid-sequence Intubation: A Safe but Ill-defined Procedure. *Acad Emerg Med*. 1999; 6(1):1–2. <https://doi.org/10.1111/j.1553-2712.1999.tb00084.x> PMID: 9928967
21. Duggan LV, K.S M, Griesdale DE, T.L M, Zurba J, Deady B, et al. Complications increase with greater than one endotracheal intubation attempt: experience in a Canadian adult tertiary-care teaching center. *J Clin Anesth*. 2013; 26(2):167. <https://doi.org/10.1016/j.jclinane.2013.12.005>
22. Goldberg ME, Larijani GE. Perioperative hypertension. *Pharmacotherapy*. 1998; 18(5):911–4. Epub 1998/10/03. PMID: 9758305.
23. Mort TC. Unplanned tracheal extubation outside the operating room: a quality improvement audit of hemodynamic and tracheal airway complications associated with emergency tracheal reintubation. *Anesth Analg*. 1998; 86(6):1171–6. PMID: 9620498.
24. Mort TC. The incidence and risk factors for cardiac arrest during emergency tracheal intubation: a justification for incorporating the ASA Guidelines in the remote location. *J Clin Anesth*. 2004; 16(7):508–16. Epub 2004/12/14. <https://doi.org/10.1016/j.jclinane.2004.01.007> PMID: 15590254.
25. Goyagi T, Tanaka M, Nishikawa T. Landiolol attenuates the cardiovascular response to tracheal intubation. *J Anesth*. 2005; 19(4):282–6. <https://doi.org/10.1007/s00540-005-0347-8> PMID: 16261464.
26. Mort TC. Esophageal intubation with indirect clinical tests during emergency tracheal intubation: a report on patient morbidity. *J Clin Anesth*. 2005; 17(4):255–62. <https://doi.org/10.1016/j.jclinane.2005.02.004> PMID: 15950848.
27. Rubin DA, Schulman DS, Edwards TD, Starzl TE, Curtiss EI. Myocardial ischemia after orthotopic liver transplantation. *Am J Cardiol*. 1994; 74(1):53–6. Epub 1994/07/01. PMID: 8017307.
28. Ando T, Sakai N, Yamada H, Iwai T, Nishimura Y, Hirata T, et al. Analysis of reruptured cerebral aneurysms and the prophylactic effects of barbiturate therapy on the early stage. *Neurol Res*. 1989; 11(4):245–8. Epub 1989/12/01. PMID: 2576109.
29. Mort TC. Complications of emergency tracheal intubation: hemodynamic alterations—part I. *J Intensive Care Med*. 2007; 22(3):157–65. Epub 2007/06/15. <https://doi.org/10.1177/0885066607299525> PMID: 17562739.

30. Yokose M, Mihara T, Kuwahara S, Goto T. Effect of the McGRATH MAC(R) Video Laryngoscope on Hemodynamic Response during Tracheal Intubation: A Retrospective Study. *PLoS One*. 2016; 11(5): e0155566. Epub 2016/05/14. <https://doi.org/10.1371/journal.pone.0155566> PMID: 27171225; PubMed Central PMCID: PMC4865033.
31. Frank E, Harrell J. *Regression Modeling Strategies: with applications to linear models, logistic and ordinal regression, and survival analysis*. Springer International Publishing; 2015.
32. VanderWeele TJ, Shpitser I. A new criterion for confounder selection. *Biometrics*. 2011; 67(4):1406–13. Epub 2011/06/02. <https://doi.org/10.1111/j.1541-0420.2011.01619.x> PMID: 21627630; PubMed Central PMCID: PMC3166439.
33. Perkins ZB, Wittenberg MD, Nevin D, Lockey DJ, O'Brien B. The relationship between head injury severity and hemodynamic response to tracheal intubation. *J Trauma Acute Care Surg*. 2013; 74(4):1074–80. Epub 2013/03/21. <https://doi.org/10.1097/TA.0b013e3182827305> PMID: 23511147.
34. Perkins ZB, Gunning M, Crilly J, Lockey D, O'Brien B. The haemodynamic response to pre-hospital RSI in injured patients. *Injury*. 2013; 44(5):618–23. Epub 2012/04/10. <https://doi.org/10.1016/j.injury.2012.03.019> PMID: 22483540.
35. Takahashi S, Mizutani T, Miyabe M, Toyooka H. Hemodynamic responses to tracheal intubation with laryngoscope versus lightwand intubating device (Trachlight) in adults with normal airway. *Anesth Analg*. 2002; 95(2):480–4, table of contents. Epub 2002/07/30. PMID: 12145076.
36. Choyce A, Avidan MS, Harvey A, Patel C, Timberlake C, Sarang K, et al. The cardiovascular response to insertion of the intubating laryngeal mask airway. *Anaesthesia*. 2002; 57(4):330–3. Epub 2002/04/10. PMID: 11939990.
37. Derbyshire DR, Chmielewski A, Fell D, Vater M, Achola K, Smith G. Plasma catecholamine responses to tracheal intubation. *Br J Anaesth*. 1983; 55(9):855–60. Epub 1983/09/01. PMID: 6615672.
38. Stoelting RK. Circulatory changes during direct laryngoscopy and tracheal intubation: influence of duration of laryngoscopy with or without prior lidocaine. *Anesthesiology*. 1977; 47(4):381–4. Epub 1977/10/01. PMID: 900548.
39. Hassan HG, el-Sharkawy TY, Renck H, Mansour G, Fouda A. Hemodynamic and catecholamine responses to laryngoscopy with vs. without endotracheal intubation. *Acta Anaesthesiol Scand*. 1991; 35(5):442–7. Epub 1991/07/01. PMID: 1887747.
40. Hasegawa K, Hagiwara Y, Chiba T, Watase H, Walls RM, Brown DF, et al. Emergency airway management in Japan: Interim analysis of a multi-center prospective observational study. *Resuscitation*. 2012; 83(4):428–33. Epub 2011/12/14. <https://doi.org/10.1016/j.resuscitation.2011.11.027> PMID: 22155701.
41. Liu B, Qiu P, Chen H, Li Q. Comparison of simultaneous invasive and non-invasive measurements of blood pressure based upon MIMIC II database. *Artery Research*. 2014; 8(4):209–13. <https://doi.org/10.1016/j.artres.2014.07.001>.