

Aspiration during Rapid Sequence Induction: Prevalence and Risk Factors

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ABSTRACT

Background: Securing definitive airway with minimal complications is a challenging task for high-volume emergency departments (ED) that deal with patients with compromised airway.

Materials and methods: We conducted a prospective observational study between September 2019 and March 2020. Cohort of adults presenting to the ED requiring rapid sequence induction (RSI) were recruited to determine the prevalence and risk factors for the development of aspiration pneumonia (AP) in patients intubated in the ED.

Results: During the study period, a total of 154 patients with a mean age of 44.5 years required RSI in the ED. Male (61%) predominance was noted among the study cohorts. We did not find any association between RSI performed in the ED and the risk of developing AP. The first attempt success rate of RSI was 76.7%, and 33 (21.4%) patients had immediate adverse events following RSI. Rescue intubation was required for 11 (7.1%) patients. The prevalence of AP following RSI in the ED was 13.4%. Endotracheal tube (ET) aspirate pepsin was positive in 45 (29.2%) samples collected. The ET aspirate pepsin assay had low sensitivity (44.44%), specificity (73.53%), positive predictive value (18%), and negative predictive value (91%) in predicting the occurrence of AP. On multivariate logistic regression analysis, male gender (AOR: 7.29, 95%CI: 1.51–35.03, $p = 0.013$) and diabetes mellitus (AOR: 3.75, 95%CI: 1.23–11.51, $p = 0.02$) were found to be independent risk factors for developing AP.

Conclusion: We identified male gender and diabetes mellitus to be independent predictors of risk of developing AP after RSI in the ED. ET aspirate pepsin levels proved to be neither sensitive nor specific in the diagnosis of AP.

Keywords: Aspiration, Aspiration pneumonia, Emergency department, Endotracheal intubation, Pepsin.

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INTRODUCTION

The emergency department (ED) is considered as the face of the hospital and first line of contact to health care for the critically ill.¹ The success of resuscitation of critically ill patients reflects the standards of the ED. Endotracheal intubation is considered as the gold standard airway management in the ED for patient requiring definitive airway.² It is one of the most commonly performed invasive procedures in the ED. Due to limited time for preparation, unstable condition of the patient, and urgency of the situation, it is always considered as a high-risk procedure.³ A 12–26% intubation-related adverse events have been reported in the literature.^{4–6} RSI includes the use of an induction agent, followed by a paralytic agent to achieve optimal conditions for intubation. This drug regimen should produce sedation and neuromuscular paralysis, maintain hemodynamic stability, and prevent vomiting.⁷ Drugs with rapid onset, short duration of action, and minimal adverse effects are usually administered.

Aspiration is defined as the inhalation of either oral, pharyngeal, or gastric contents into the lower airways.⁸ This can lead to a number of syndromes based on the quantity and nature of the aspirated material, the frequency of aspiration, and the host factors that predispose the patient to aspiration and modify the response.⁸ The epidemiological study on AP is complicated due to lack of specific and sensitive marker to diagnose AP and difficulty to distinguish between aspiration syndromes (aspiration pneumonitis and AP).⁹ The diagnosis of AP is made when a patient at risk for aspiration is found to

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have a radiographic evidence of an infiltrate in a characteristic bronchopulmonary segment.¹⁰ The course of the disease is similar to that of a typical community-acquired pneumonia, but has a higher risk of developing cavitation and abscess formation, if left unrecognized or untreated.¹⁰ Pepsin is the major proteinase in the stomach secreted by the chief cells. It is normally absent in the respiratory tract. So the presence of pepsin in the respiratory tract implies that aspiration had occurred. Also, the ET aspirate will contain gastric contents if they were aspirated and this can be used to demonstrate the presence of pepsin.¹¹ In general, there is a higher risk of aspiration and developing other complications

among patients intubated in the ED compared to those in intensive care units (ICUs) and operating rooms (ORs).¹² Hence, we conducted this study to determine the prevalence and risk factors for the development of AP in patients who undergo RSI in the ED and to determine the sensitivity and specificity of pepsin to aid the diagnosis of AP.

MATERIALS AND METHODS

Study Design

A prospective observational study.

Study Setting

We conducted this study in the ED of a tertiary care hospital in South India, between September 2019 and March 2020. Our ED is a 49-bed department and is one of the busiest departments in whole country with an average caseload of 250 patients per day. We have a dedicated 6 bedded resuscitation rooms (RRs), exclusively for the management of patients who present with airway and hemodynamic compromise.

Participants

We screened all patients presenting to the ED requiring RSI during the 7-month study period.

Inclusion Criteria

All participants aged more than 18 years requiring RSI and were admitted as in-patients.

Exclusion Criteria

Patients with preexisting pneumonia, patients with direct lung injury (secondary to trauma), and those not willing to consent were excluded.

Variables

Variables, such as comorbidities, presenting complaints, indication for intubation, vital signs, drugs used as premedications, laryngoscopy blade, operator expertise, number of attempts, and Cormack–Lehane grading were compared to the risk of developing AP.

Outcome Variable

The outcome variables were defined as follows:

Aspiration pneumonia—Any of the following in patients without a diagnosis of community-acquired or healthcare-associated pneumonia, or aspiration prior to intubation: pathogenic growth in sputum culture, unexplained hypoxemia, or radiographic evidence of pneumonia in the first 48 hours after intubation.¹³

Ventilator-associated pneumonia—Radiographic evidence of pneumonia on chest x-ray, pathogenic growth in sputum culture, or unexplained hypoxia that occurred between >48 hours after intubation and <48 hours after extubation.¹³

Bias

All consecutive patients requiring RSI were screened and those consented to take part in the study were recruited.

Sample size: Based on a previous study, the incidence of AP was estimated to be 13%, with a precision of 5% and confidence level of 95%, and the sample size was calculated to be 174.¹⁴

Sample Collection

Tracheal aspirates were obtained using a standard Lueken's trap as soon as endotracheal tube position was confirmed using visualization, auscultation, and end-tidal CO₂. If no aspirate could be obtained, 3–5 mL of normal saline solution was instilled into the endotracheal tube. Each patient was ventilated for several breaths, and the sample was then collected. Tracheal aspirates were collected and marked with a study number and were sent to the biochemistry laboratory for assay.

Laboratory Test

The tracheal samples that were received in the laboratory were centrifuged at 2000 rpm for 20 minutes, and an aliquot was stored frozen at –20°C until analysis. The aliquot was then thawed and used for analysis by enzyme-linked immunosorbent assay (ELISA), from Sincere Biotech Co. Ltd., China; Catalog No: E13651380 was used for the *in vitro* quantitative determination of human pepsin antigen from tracheal aspirates. Six different standard concentrations 0, 7.5, 15, 30, 60, and 90 ng/mL were prepared. The standards and tracheal samples (50 µL) whose pepsin concentration is to be estimated were added to the antibody-coated wells. The plate with the standards and samples was incubated for 30 minutes at 37°C so as to form an antibody–antigen complex. Following the wash, 50 µL of horseradish peroxidase (HRP) conjugate was added and the plate was incubated for 30 minutes at 37°C so as to form antibody–antigen–enzyme conjugate complex. Following the wash, 100 µL of tetramethylbenzidine (TMB) chromogen substrate was added and incubated for 15 minutes at 37°C where the TMB substrate becomes blue in color with the HRP enzyme-catalyzed reaction. This reaction was terminated by the addition of a sulfuric acid solution, and the color change (yellow) was measured spectrophotometrically at a wavelength of 450 nm. The concentration of human pepsin antigen in the samples was then determined by comparing the absorbance of the samples to the standard curve.

Statistical Analysis

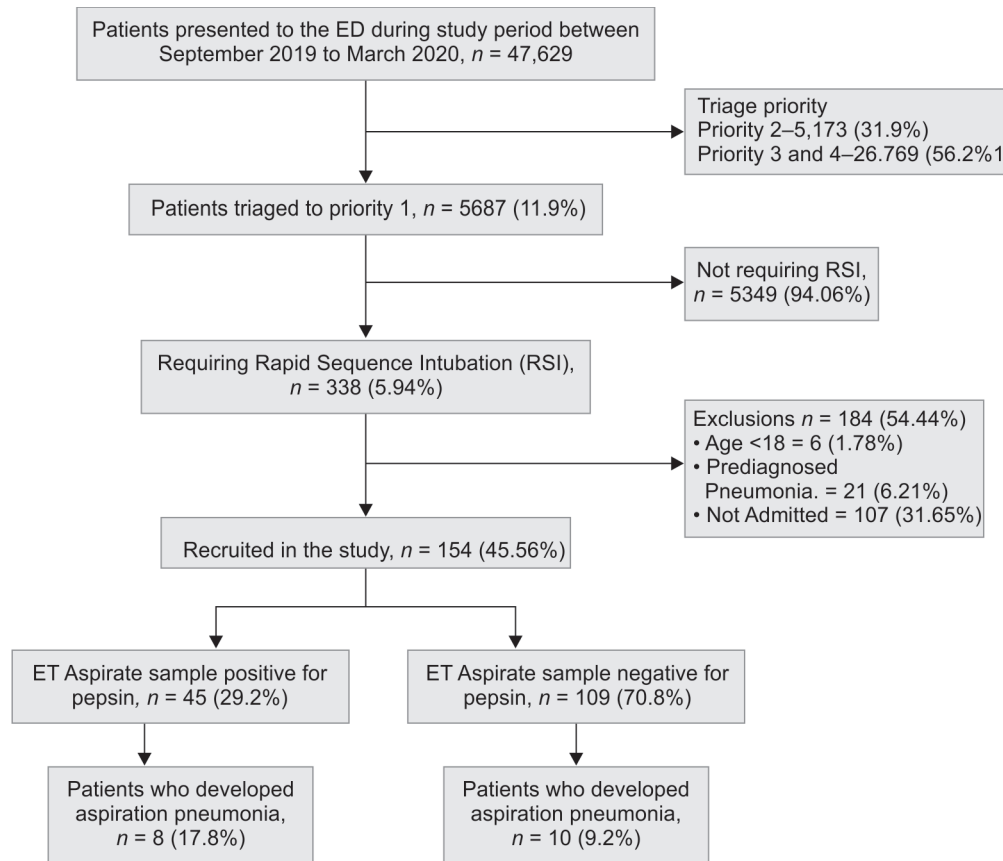
All continuous variables were expressed with mean and standard deviation, and categorical variables were expressed as frequencies and percentages. The data were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows software released 2015, version 23.0, Armonk, New York, USA. Categorical variables for the risk of developing AP were analyzed using chi-square test or Fisher's exact test. Odds ratio and their 95% confidence intervals were calculated. For all variables, a two-sided *p*-value less than 0.05 was considered statistically significant. A logistic regression analysis was done on variables, which had significance on bivariate analysis.

Ethical Considerations

Prior to the commencement of the study, approval from the Institutional Review Board (IRB) and Ethical Committee was obtained (IRB Min no: 11919 dated March 6, 2019).

RESULTS

A total of 47,629 patients presented to our ED during the study period. We screened all 338 patients requiring RSI in the ED, and 184 (54%) patients were excluded as they did not fulfill the inclusion criteria, leaving 154 patients for further analysis (Flowchart 1).



Flowchart 1: STROBE diagram

Characteristics of Study Subjects

Table 1 shows the baseline characteristics. The mean age was 44.5 ± 16.04 years. Our study cohort had a male predominance (61%).

Intubation Factors and Risk of Developing AP

Table 2 shows the premedications, laryngoscope, ET used, Cormack–Lehane grading on laryngoscopy, attempts at intubation, experience of the intubator, and the application of cricoid pressure among the study cohort. The mean time taken to perform RSI was 12.74(±9.56) minutes. Eleven (7.1%) patients required intubation by a rescue intubator. In the pre-intubation period, 14.3% of patients desaturated, requiring prolonged preoxygenation (Table 3). We observed that 15(9.7%) patients had a witnessed aspiration and 8(5.2%) patients developed hypotension during the peri-intubation period. Inadvertent placement of ET into the esophagus was observed in 3.9% of patients (Table 4).

Outcome Measures

Twenty patients died within 48 hours of intubation in the ED. These patients were excluded from the primary outcome measurement. The prevalence of AP following RSI in the ED was 13.4%(18/134). The tracheal aspirate pepsin was positive (>12.3 ng/mL) in 45(29.2%) patients. However, only 8(44.44%) patients who developed AP had positive pepsin levels. We performed an area under receiver operating characteristic (AUROC) curve for determining the sensitivity and specificity of pepsin in predicting the development of

Table 1: Baseline characteristics, n = 154

Variable	n(%)
Age, mean (SD), in years	44.49(16.17)
Gender	
Male	94(61)
Female	60(39)
Time of arrival	
12 am to 8 am	28(18.2)
8 am to 4 pm	50(32.5)
4 pm to 12 am	76(49.4)
Comorbidities	
Diabetes mellitus	45(29.2)
Hypertension	43(27.9)
Chronic kidney disease	8(5.2)
Gastroesophageal reflux disease	2(1.3)
Pregnancy	1(0.6)
Complaints	
Breathing difficulty	87(56.5)
Altered sensorium	63(40.9)
Vomiting	40(26.0)
Trauma	36(23.4)
Fever	33(21.4)
Chest pain	16(10.4)



Table 2: Rapid sequence induction parameters among the study population

Variable	n(%)
<i>Induction agent</i>	
Ketamine	53(34.4)
Midazolam	49(31.8)
No drugs	14(9.1)
Fentanyl	5(3.3)
<i>Paralyzing agent</i>	
Succinylcholine	101(65.6)
Rocuronium	35(22.7)
No drugs	16(10.4)
<i>Laryngoscope</i>	
Direct laryngoscopy	145(94.2)
Video laryngoscope	9(5.8)
<i>ET tube used</i>	
Size 7.5	64(41.6)
Size 8	46(29.9)
Size 7	39(25.3)
<i>Cormack–Lehane grading</i>	
Grade 1	91(59.1)
Grade 2	60(39.0)
Grade 3	2(1.3)
Grade 4	1(0.6)
<i>Attempts to intubate</i>	
1	118(76.6)
2	25(16.2)
3+	11(7.1)
<i>Experience of personnel</i>	
Second-year resident	59(38.3)
First-year resident	50(32.5)
Third-year resident	29(18.8)
Paramedics and interns	13(8.4)
Consultant	3(1.9)
<i>Cricoid pressure</i>	
No cricoid pressure	80(51.9)
Cricoid pressure given	74(48.1)

Table 3: Mean time to intubate, rescuer attempts, and adverse events following rapid sequence induction

Variable	n(%)
Average time to perform RSI (SD), in minutes	12.74(9.56)
Requiring rescuer attempt	11(7.1)
<i>Adverse events*</i>	
Hypoxemia in the pre-intubation period	22(14.3)
Peri-intubation vomiting	15(9.7)
Post-intubation hypotension	8(5.2)
Esophageal intubation	6(3.9)

*Adverse events between administration of induction agent and 15 minutes following successful intubation were considered

AP (Fig. 1). The ET aspirate pepsin assay had a sensitivity, specificity, positive predictive value, negative predictive, positive likelihood ratio, and negative likelihood ratio value of 44.44%, 73.53%, 18%,

91%, 1.679(CI: 0.933–3.022), and 0.756(CI: 0.494–1.156), respectively. Among the study population, 96 (62.4%) were discharged stable, while 19 (12.3%) left against and in-hospital mortality was observed in 39 (25.3%) patients.

Risk Factors for Developing AP

We performed a bivariate analysis to determine the risk factors associated with the development of AP. Male gender, diabetes mellitus, and altered sensorium had higher risk of developing AP, while using ketamine as induction agent reduces the risk of developing AP. However, on performing multivariate logistic regression analysis, with the above variables, only male gender (AOR: 7.29, 95%CI: 1.52–35.03, $p = 0.013$) and diabetes mellitus (AOR: 3.76, 95%CI: 1.23–11.51, $p = 0.020$) proved to be independent risk factors for the development of AP (Table 4).

DISCUSSION

Our study showed that the prevalence of AP secondary to endotracheal intubation in the ED was 13.4%. We did not identify any intubation factors that predisposed to the development of AP. ET aspirate pepsin assay had a very low sensitivity and specificity in predicting the occurrence of AP. The occurrence of aspiration of gastric contents following endotracheal intubation in the ED varies from 1% to 20% according to known literature.^{15–20} This variation in results may be attributed due to the lack of clear definition of AP. The end points of AP as described in previous studies too were questionable. These included (i) suspicion of aspiration, (ii) witnessed aspiration, (iii) radiographic changes, such as the presence of infiltrates, (iv) sputum cultures, and (v) arterial blood gas analysis, none of which were found to have high sensitivity or specificity for detecting aspiration.⁸

The mean age (44.5 years) of our study population was much lesser than the median age in a study done by Lanspa et al. study (77).²¹ The difference in age distribution could be attributed to the fact that in developed countries where the study was done, the life expectancy is longer; hence, the proportion of patients in their study is skewed toward older and more comorbid population. Similar to the findings of Driver et al., none of the factors associated with RSI, such as premedications, paralyzing agents, use of video and direct laryngoscope, the number of attempts to intubate, experience of the intubator, the Cormack–Lehane grading of the vocal cords, and application of cricoid pressure prior to intubation proved to be significant risk factors for the development of AP.¹³ This is perhaps attributable to the study done in a well-established teaching center with supervision, in contrast to majority of hospitals that depend on junior medical officers for managing compromised airways. Though higher use of video laryngoscopy probably resulted in a higher first-attempt success rate, it did not decrease the rate of AP.¹³ The adverse events profile in our study was similar to that seen in other studies.²²

Data from other studies have revealed that tracheal aspirate pepsin is a reliable marker to diagnose aspiration.^{11,23–25} The qualitative detection of pepsin, by demonstrating pepsin activity on exposure to pepstatin (pepsin inhibitor), proved to be highly sensitive and specific by Ufberg et al.¹¹ In our study, quantitative assessment of pepsin from ET aspirate was done and had low sensitivity. Negative pepsin assay in almost half of the patients who developed AP may be due to microaspiration that occurred following ET aspirate collection.

Table 4: Bivariate and multivariate logistic regression analysis of factors associated with the development of aspiration pneumonia

	Variables		Bivariate analysis		Multivariate analysis	
	Aspiration pneumonia n = 18(%)	No aspiration pneumonia n = 136(%)	p-value	Unadjusted OR(95%CI)	p-value	Adjusted OR(95%CI)
Male gender	16(88.9)	78(57.4)	0.01	5.95(1.32–26.89)	0.013	7.29(1.51–35.03)
Diabetes mellitus	9(50)	36(26.5)	0.039	2.78(1.02–7.55)	0.02	3.75(1.23–11.51)
Altered sensorium	12(66.7)	51(37.5)	0.018	3.33(1.18–9.43)	0.086	2.66(0.87–8.19)
Hypoxia, SpO ₂ < 94%	12(66.6)	86(63.2)	0.78	1.16(0.41–2.20)	–	–
Midazolam	9(50)	40(29.4)	0.078	2.4(0.89–6.49)	–	–
Ketamine	2(11.1)	53(37.5)	0.027	0.21(0.04–0.94)	0.061	4.57(0.93–22.42)
Succinylcholine	12(66.7)	89(65.4)	0.918	1.05(0.37–2.99)	–	–
CL Grade 2*	7(38.9)	53(39.0)	0.44	0.6(0.16–2.19)	–	–
First-attempt intubation	14(77.8)	104(76.5)	0.767	0.77(0.25–2.32)	–	–
First-year resident	4(22.2)	46(33.8)	0.323	0.56(0.17–1.80)	–	–
Cricoid pressure applied	9(50)	65(47.8)	0.86	1.09(0.41–2.92)	–	–

*CL, Cormack–Lehane grading of laryngoscopy view

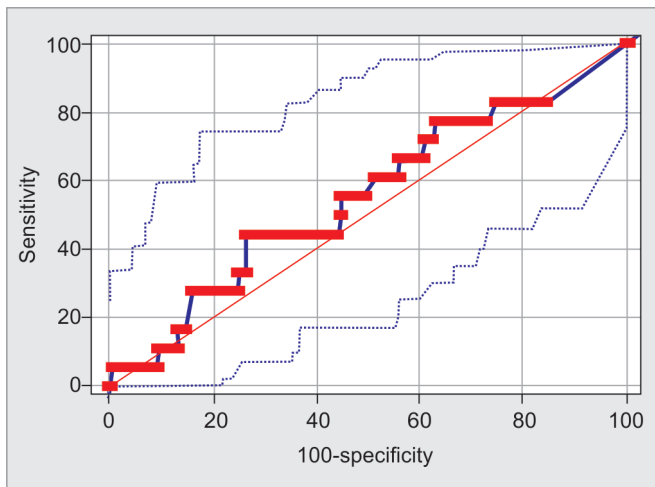


Fig. 1: AUROC curve to assess the sensitivity and specificity of ET aspirate pepsin to predict the development of AP

STRENGTHS

This was a prospective study with all consecutive patients requiring RSI being enrolled, thereby minimizing the bias. Quantitative assessment of ET aspirate pepsin levels was another strength of our study.

CLINICAL IMPLICATIONS

The ET aspirate pepsin assay used in our study was a research kit. There might be variation in results with respect to the research kits.

LIMITATIONS

In our study, we could not reach the required sample size of 174, mainly because the Human Pepsin ELISA Kit used could not be imported from China due to travel and transport disruptions during the COVID-19 pandemic.

CONCLUSION

From our study, we concluded that male gender and diabetes mellitus were independent risk factors for the development of

AP following RSI in the ED. The role of ET aspirate pepsin levels to predict the occurrence of AP did not yield promising results.

Research Quality and Ethics Statement

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting, and reproducibility guidelines set forth by the EQUATOR Network. The authors also attest that this clinical investigation was determined to require Institutional Review Board/Ethics Committee review, and the corresponding protocol/approval number is IRB Min no: 11919 dated March 3, 2019. We also certify that we have not plagiarized the contents in this submission and have done a plagiarism check.

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