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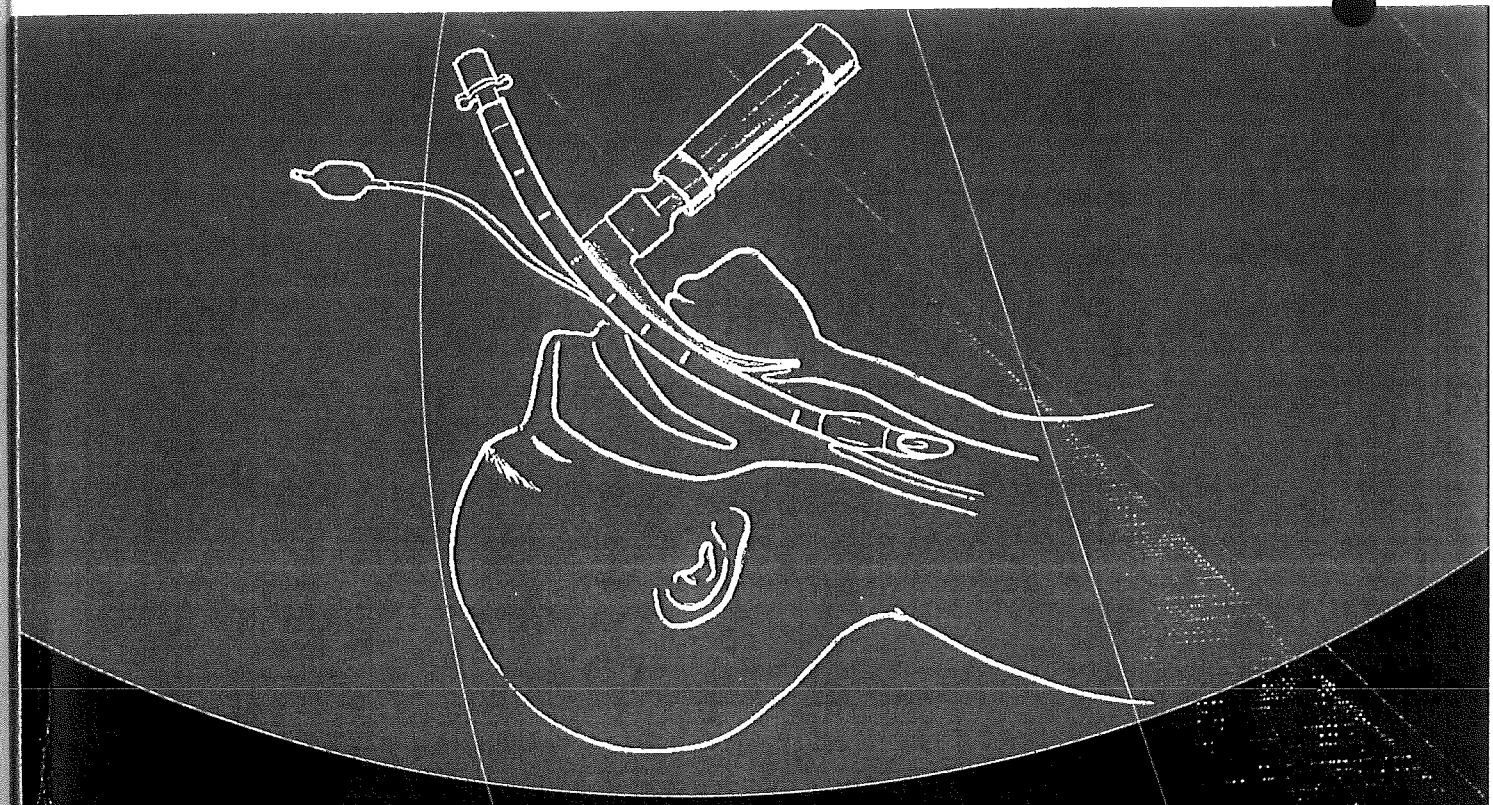

Detection of risk factors for difficult tracheal intubation. Experience gained from the national Danish Anaesthesia Database

PhD. Thesis 2010

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THE PRESENT PH.D THESIS IS BASED ON THE FOLLOWING FOUR STUDIES

STUDY I

Lundstrøm LH, Møller AM, Rosenstock C, Astrup G, Wetterslev J. *High Body Mass Index Is a Weak Predictor for Difficult and Failed Tracheal Intubation A Cohort Study of 91,332 Consecutive Patients Scheduled for Direct Laryngoscopy Registered in the Danish Anaesthesia Database.* Anesthesiology 2009; 110(2):266-274.

STUDY II

Lundstrøm LH, Møller AM, Rosenstock C, Astrup G, Gätke MR, Wetterslev J. *Avoidance of neuromuscular blocking agents may increase the risk of difficult tracheal intubation: a cohort study of 103 812 consecutive adult patients recorded in the Danish Anaesthesia Database.* British Journal of Anaesthesia 2009; 103(2):283-290.

STUDY III

Lundstrøm LH, Møller AM, Rosenstock C, Astrup G, Gätke MR, Wetterslev J. *A documented previous difficult tracheal intubation as a prognostic test for a subsequent difficult tracheal intubation in adults.* Anaesthesia 2009; 64(10):1081-1088.

STUDY IV

Lundstrøm LH, Vester-Andersen M, Møller AM, Charuluxananan S, L'Hermite J, Wetterslev J and the Danish Anaesthesia Database. *The prognostic value of the modified Mallampati-score to predict difficult tracheal intubation. A meta-analysis of studies including 177 088 patients.* Draft submitted.

CONTENTS

Preface

This thesis is conducted on the behalf of the steering committee of the Danish Anaesthesia Database. The thesis is affiliated to the Department of Anaesthesia and Intensive Care, Herlev Hospital, Copenhagen University Hospital, Denmark and the Copenhagen Trial Unit, Rigshospitalet, Copenhagen University Hospital, Denmark.

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I acknowledge all the participating anaesthetic departments, which have contributed with data to the Danish Anaesthesia Database (Appendix IV).

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Abbreviations

ASA	American Society of Anesthesiologist
BMI	body mass index
CI	confidence interval
DAD	Danish Anaesthesia Database
DOR	diagnostic odds ratio
DTI	difficult tracheal intubation
FN	false negative
FP	false positive
MAR	missing at random
MCAR	missing completely at random
MI	multiple imputation
NMBA	neuromuscular blocking agent
OR	odds ratio
PI	ponderal index
SE	standard error
sROC	summary receiver operator characteristics
TN	true negative
TP	true positive

Summary

Several studies have identified difficult airway management including a difficult tracheal intubation of patients undergoing general anaesthesia as a major cause of anaesthesia-related morbidity and mortality. Therefore it is presumed that a difficult tracheal intubation is a surrogate marker for morbidity and mortality, and by reducing the prevalence of difficult tracheal intubation then morbidity and mortality will be reduced as well. From the Danish Anaesthesia Database (DAD), we retrieved a cohort of consecutive patients planned and attempted for tracheal intubation by direct laryngoscopy. Based upon various data including an intubation score registered in the database, we aimed to evaluate four different parameters, *'Obesity'*, *'avoidance of neuromuscular blocking agents'*, *'a previous difficult tracheal intubation'* and *'the modified Mallampati-score'*, as possible risk factors for a difficult tracheal intubation.

All of these risk factors were statistically associated with a difficult tracheal intubation, but the clinical significance varied substantially. However, neither *'obesity'*, *'the modified Mallampati-score'* nor *'a previous difficult tracheal intubation'* were sufficient as stand-alone tests for prediction of difficult tracheal intubation. In multivariate analyses the impact of obesity on the risk of difficult tracheal intubation seems weak, while both *'the modified Mallampati-score'* and *'a previous difficult tracheal intubation'* demonstrated to be clinically strong risk factors for difficult tracheal intubation. The evaluation of *'avoidance of neuromuscular blocking agents'* as a risk factor differ substantially from the other assessments, as it concerns the impact of an intervention rather than of a patient-related risk factor for difficult tracheal intubation. In our assessment, *'avoiding neuromuscular blocking agents'* was demonstrated as a possible risk factor for difficult and abandoned tracheal intubation independent of other risk factors recorded in the DAD.

Several previous studies have failed to present specific risk factors that could identify difficult intubation or laryngoscopy by itself. Therefore it seems rational to focus on the development, testing and modification of multivariate models from large scale cohort studies, hereby making the prognostication operational in everyday clinical practice. From there the challenge may be to test the effectiveness of the use of such a model in order to evaluate whether it actually has the capability to reduce difficult tracheal intubation, complications, and mortality. It seems that such a

trial should and could be conducted as a cluster randomized trial of anaesthesia departments within the framework of the DAD.

Dansk resumé

Flere undersøgelser har peget på, at for patienter, der skal i generel anæstesi, udgør en vanskelig håndtering af luftvejene, herunder den vanskelige intubation, en væsentlig årsag til anæstesirelateret morbiditet og mortalitet. Man antager derfor, at en vanskelig intubation er et surrogat for morbiditet og mortalitet, således at man kan reducere omfanget af komplikationer ved at reducere forekomsten af vanskelige intubationer. Vi foretog et udtræk fra Dansk Anæstesi Database, som omfattede en kohorte af patienter, der har været i generel anæstesi og som var planlagt og forsøgt intuberet ved direkte laryngoskopi. På baggrund af en intubationsscore samt en række øvrige variable, som ligeledes var registreret i databasen, var det vores målsætning at identificere forskellige risikofaktorer for den vanskelige intubation. Vi undersøgte således fire mulige risikofaktorer: "*overvægt*", "*undladelse af brug af neuromuskulære relakserende stoffer*", "*en tidligere vanskelig intubation*" og "*den modificerede Mallampati-score*".

Alle fire parameter var statistisk højsignifikant associeret med en vanskelig intubation, men deres kliniske indbyrdes betydning som risikofaktorer for en vanskelig intubation varierede betydeligt. Hverken overvægt, den modificerede Mallampati-score eller en tidligere vanskelig intubation var tilstrækkelige som selvstændige prædiktorer for en vanskelig intubation. For overvægts vedkommende, synes risikoen for en vanskelig intubation at være beskeden. Derimod viste multivariate analyser, at både den modificerede Mallampati-score og en tidligere vanskelig intubation begge var klinisk betydende riskofaktorer for en vanskelig intubation. Vores undersøgelse af "undladelse af brug af neuromuskulære relakserende stoffer" som risikofaktor adskiller sig væsentligt fra analyserne af de øvrige risikofaktorer, idet der fokuseredes på en intervention frem for patientrelaterede faktorer. Vores undersøgelse indikerer at "undladelse af neuromuskulære relakserende stoffer" er en selvstændig risikofaktor for en vanskelig intubation og for en opgivet intubation.

I tidligere studier er det ikke lykkedes at identificere faktorer som selvstændigt kan forudsige en vanskelig intubation. Det synes således rationelt hvis der i højere grad end hidtil fokuseres på udvikling, testning og modificering af multivariate modeller udviklet på baggrund af store kohorte studier, og herved at gøre prognosticeringen operationel i en klinisk hverdag.

Efterfølgende vil udfordringen være at gennemføre forsøg, der skal vurdere effekten af en sådan model, så man kan fastslå, om man rent faktisk er i stand til at reducere antallet af vanskeligte intubationer, komplikationer og dødelighed. Sådan et forsøg kan og bør gennemføres som et cluster (afdelings) randomiseret forsøg inden for rammerne af Dansk Anæstesi Databases.

Background

Morbidity and mortality related to airway management

Patients anaesthetised with general anaesthesia are deprived of their awareness and their ability to breathe and protect their airway. Therefore it is vital, to ensure a safe airway and continued ventilation of these patients. However several studies[1-14] identify difficult or failed airway management as a major reason for mortality and morbidity related to anaesthesia. The morbidities range from sore throat, hoarseness, vocal cord lesion, pharyngeal oedema, pharyngeal necrosis[15], to more severe damages such as rupture of the pharynx, aspiration pneumonia and brain and heart injuries caused by hypoxemia or anoxaemia. These severe complications may even cause death[2-4;7;12;16]. An assessment of records from The Danish Closed Claims Register [12] from 1996 to 2004 identified 24 patients who died of causes related to anaesthesia. Of these, four were related to the airway management. Another assessment of complaints related to respiratory events in anaesthesia from 1994 to 1998 in Denmark[7] identified difficult tracheal intubation as the major cause of death. Further, the assessment highlights pulmonary aspiration of gastric contents as another cause of mortality. Other studies evaluating death related to obstetric anaesthesia have identified failed airway management as a major cause of death[4].

However, deaths caused by airway management failures seem to have decreased over the last decades[2;17;18]. A recent review of mortality in anaesthesia[2] estimates that anaesthesia-related mortality rates in developed countries are lower than 1 per 10 000 anaesthetics and that airway management accounted for the majority of the cases. However, there may be a considerable risk that these assessments underestimate the prevalence as the majority of studies were based on retrospective assessments and only evaluated a limited time span, for example, the first 24 postoperative hours[14;17], the first 3 postoperative days[10], the first 7 postoperative days[8]. Accordingly, the "dark" number of deaths associated with failed airway management may be substantial.

The Difficult Airway

There is no consensus of a standard definition of 'difficult airway' in the literature. However, in the Practice Guidelines for Management of the Difficult Airway by the American Society of

Anesthesiologist (ASA)[19], a difficult airway is defined as the clinical situation in which a conventionally trained anaesthesiologist experiences difficulty with face mask ventilation of the upper airway, difficulty with tracheal intubation or both.

The task of maintaining a safe and sufficient airway may be achieved by various different procedures. Face mask ventilation is an essential procedure. Often, mask ventilation on its own or in combination with the use of other devises like a laryngeal mask or the tracheal tube ensures sufficient airway management. Despite being a basic procedure of handling the airway, mask ventilation is an important rescue technique in a situation with difficult or failed tracheal intubation. Among studies dealing with the prediction of a difficult face mask ventilation[20-23], the ease or difficulty of mask ventilation have been categorised by using a four-point scale[24]: 1) ventilated by mask; 2) ventilated by mask with oral airway adjuvant with or without muscle relaxant; 3) difficult ventilation (inadequate, unstable, or requiring two providers) with or without muscle relaxant; 4) unable to mask ventilate with or without muscle relaxant. The most comprehensive assessment including more than 50 000 patients[21] estimated that the prevalence of difficult and impossible mask ventilation was 2.4 %. The use of supraglottic devices like the laryngeal mask occupies an increasingly important position in the management of the airway[25]. However in Denmark, around half of all patients offered general or combined anaesthesia are still undergoing tracheal intubation by direct laryngoscopy as a part of airway management[26]. Tracheal intubation is considered a safe airway, because the tube is placed and cuffed directly in the trachea of the patient. Hereby, free access and direct connection to the lower airway of the patient is ensured, and the risk of aspiration of gastric content into the lungs may be reduced.

The ASA guideline distinguishes between difficult laryngoscopy and difficult tracheal intubation. However, the guideline does not define these manoeuvres specifically. Thus, in several studies[27-62], the view of a direct laryngoscopy is classified into four grades according to the 'Cormack and Lehane' classification[63]: Grade 1) full view of the glottis; Grade 2) partial view of the glottis or arytenoids; Grade 3) only epiglottis visible; Grade 4) neither glottis nor epiglottis visible. The less frequently used 'Modified Cormack and Lehane' classification[64] has two additional grades: Grade 2a) partial view of the glottis and a Grade 2b) arytenoids or posterior part of the vocal cords only

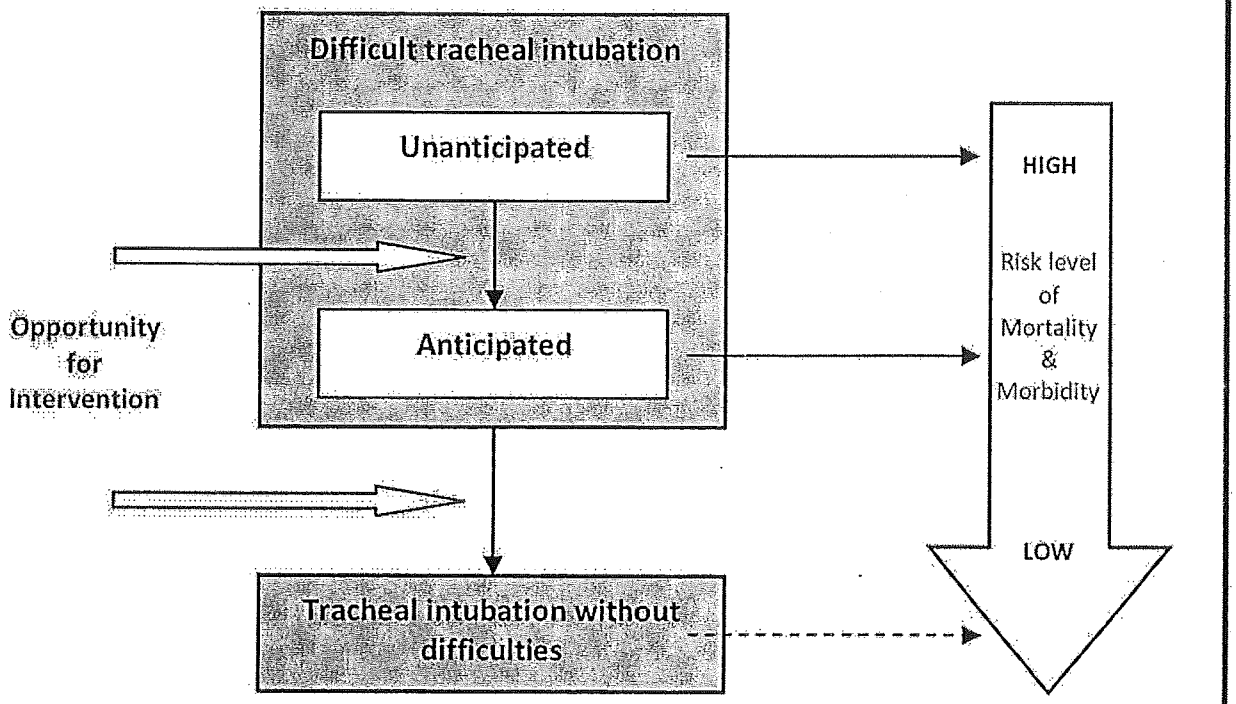
just visible. Difficult laryngoscopy is defined as (Modified) Cormack and Lehane Grades (2b), 3 and 4. Even though a difficult laryngoscopy may be a surrogate marker for difficult tracheal intubation, several studies[38;42;43;45;46;52;60-62] seem to identify difficult tracheal intubation by the Cormack and Lehane grade 3 and 4. The literature presents several studies[65-81] using various definitions of a difficult tracheal intubation. One study simply use the operator's subjective judgement as to the ease of performing an intubation by a senior anaesthesiologist[70]. Other studies combine both subjective and objective criteria[82]. Most studies use an intubation score, based solely upon objective criteria. A simple score defines a difficult tracheal intubation as a Cormack and Lehane grade 3 or 4 in combination with the use of a rubber elastic Bougie[38;42]. Other definitions include variables like the amount of time needed for intubation[83], the need of special techniques and whether intubation was attempted by a secondary/senior anaesthesiologist[66]. The most comprehensive and complicated score 'The Intubation difficulty scale' defined by Adnet et al[84] includes seven different items describing different aspects of the tracheal intubation. Thus, the score uses information on the number of attempts used, the number of operators performing the intubation, the number of alternative techniques used other than direct laryngoscopy, the observed Cormack and Lehane grade, the required lifting force during the laryngoscopy, if laryngeal pressure was needed, and information on the vocal cord mobility. The various definitions of an intubation score reflect the complexity of different elements that may be of importance for sufficient airway management. Further, these various definitions introduce heterogeneity and complicate the comparison of the numerous studies evaluating the ease and difficulty of tracheal intubation. Finally, these intubation scores were used in the assessments of both general and specific patient populations like obstetric[28;40;52;58;72;76]; obese[37;47;51;69]; acromegali[27;56]; cervical spine limit[75]; laryngeal disease[67]; thyroid surgery[68]; maxillofacial surgery[80] and patients with diabetes[59]. Despite this clinical diversity a meta-analysis[85] estimates an over-all prevalence of difficult tracheal intubation of 5.8 % (4.5 – 7.5 %, 95 % CI).

Anticipated and unanticipated difficult tracheal intubation – surrogate markers for severe complications

A surrogate outcome measure is a laboratory measurement, a physical sign, or any other intermediate substitute that may be able to predict a treatment response on a clinically meaningful outcome measure. The first step in validation is to demonstrate a correlation between

the putative surrogate and the clinical outcome, e.g., the higher prevalence of the surrogate the higher prevalence of death. However, a correlation is not sufficient to validate the surrogate. The second step is to establish if an intervention effect on the surrogate outcome accurately predicts the intervention's effect on the clinical outcome[86]. The literature does not verify that the difficult tracheal intubation is a surrogate for severe morbidity and mortality. Nonetheless, the assessments of the closed claim registers and other observational studies clearly suggest a causal relationship between a difficult or a failed tracheal intubation and severe complications and even death. In one study two thirds of all deaths that were caused by difficult tracheal intubation were unanticipated[12]. The literature distinguishes between the anticipated and the unanticipated difficult tracheal intubations, the latter is considered the clinical situation associated with the largest risk of complications. Several national and international guidelines especially focus on the unanticipated difficult tracheal intubation[19;83;87-90]. Different algorithms describe how to handle the airway, and the proposals include both technical and non-technical guidance. In contrast, the anticipated difficult tracheal intubation is considered safer, because the anaesthesiologist is able to take precautions in order to reduce the risks associated with tracheal intubation. Precautions can include allocating the task of performing the intubation to a more experienced physician or an airway expert, or employing devices other than the direct laryngoscope for airway management. There are numerous airway devices available that act either as conduits to oxygenation and ventilation (e.g., laryngeal mask airway, laryngeal tube) or as devices designed specifically to facilitate tracheal intubation (lighted stylets, videolaryngoscopes, flexible bronchoscopes)[25]. It is the general hypothesis that regardless of whether the difficult tracheal intubation is anticipated or unanticipated morbidity and mortality will decrease with a reduced risk of a difficult tracheal intubation (Figure 1).

Figure 1. Difficult tracheal intubation as a surrogate for morbidity and mortality.



The risk of difficult tracheal intubation

The risk of difficult airway management including difficult tracheal intubation is determined by multiple factors related to the patient, the anaesthetist's technical skills, non-technical skills, as well as the facilities available, and the local environment[91;92]. Therefore, there may be several approaches for reducing or removing the risk of difficult tracheal intubation. It is commonly believed the risk of complications related to the tracheal intubation is less frequent if the difficult tracheal intubation itself is anticipated. Therefore, it has been the aim of lots of studies to predict the occurrence of difficult tracheal intubation, and thereby reduce the number of unanticipated difficult tracheal intubations and thus reduce the risk of subsequent complications. Several studies have focused on different factors related to the patient. These factors have been evaluated as sole predictors or in combination. Some studies conducted multivariate risk scores[66;74;93-96], and several of the predictors have been evaluated in meta-analyses[85;97]. The performance of the tests varies considerably between studies evaluating similar tests. This may be caused by whom and how the tests were performed and the type of patient population evaluated. Patient populations vary

considerably in the listed studies. In addition to patient related factors, several other parameters may be determinants for a difficult tracheal intubation. As examples, the experience of the anesthesiologist[74;79], position of the patient (sniffing position, ramped position)[98;99], and different drugs used for induction of the anaesthesia have been evaluated[100;101].

The Danish Anaesthesia Database

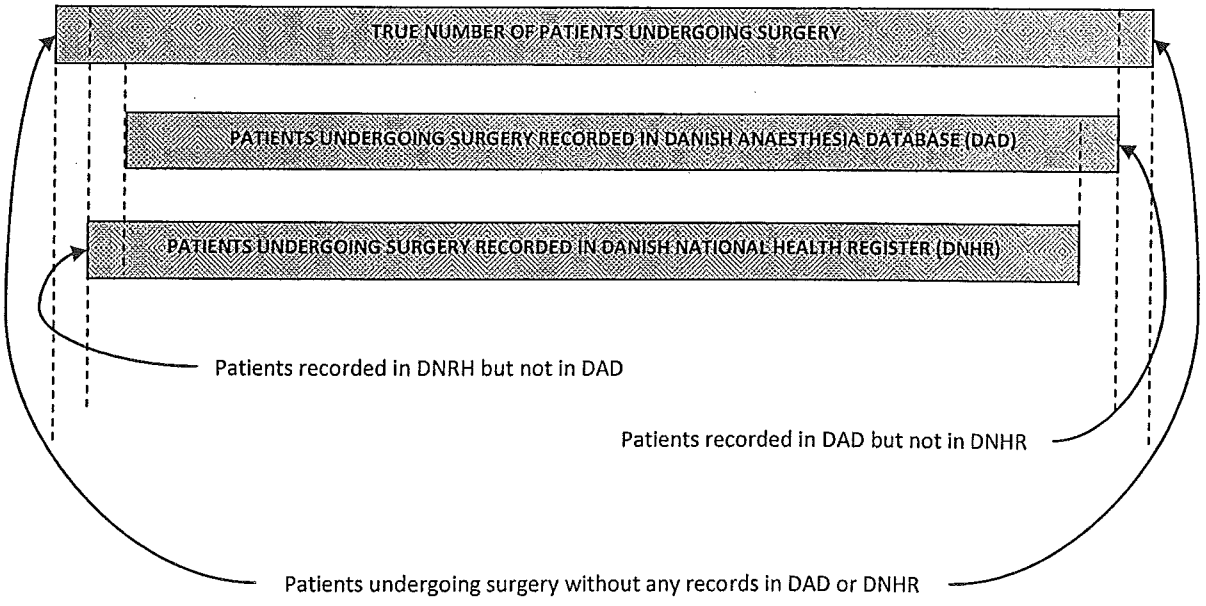
Danish Anaesthesia Database (DAD) is a national clinical quality database that contains specific quantitative anaesthetic and surgical indicators describing the perioperative period. All types of surgery are represented in the database. The departments are connected via the Internet to a central server hosted by The Unit for Clinical Quality, in the Capital Region, Denmark. Usually, the information is recorded during or immediately after each anaesthetic and surgical procedure. However, if the online hook-up to the internet is disconnected the data may have to be registered later. The aim is to report data consecutively to the DAD. The interface of the database is interactive and changes depending on the type of anaesthesia and surgery that is registered. All registered parameters are predefined and the interface to register the airway-evaluation, plan, and management is the same for all the registration sites as well as the rules of validation and the on-line user manual. Each patient entered into the database is registered with a unique identifying number from the centralised Danish civil register. This unique identifier enables registration of each patient during the statistical analysis and prevents duplicates of anaesthesia reports thereby avoiding errors in reporting due to a wrong sampling unit. Furthermore, the unique identifier makes it possible to retrieve information on patients anaesthetised and registered more than once during the period of observation.

Coverage, completeness and quality of data

Fourteen Danish anaesthesia departments in 2005, and 25 departments in 2006-07, prospectively reported data to the DAD version 2. Patients anaesthetised in these departments probably represent less than half of all patients anaesthetised in Denmark during 2006-7 as around 50 anaesthesia departments were operating during this period. Unfortunately the exact coverage is not known, because the true number of patients undergoing surgical procedures is concealed (Figure 2). Further, there are no global estimations of the number of pertinent records registered

in the Danish National Health Register (DNHR) (a comprehensive register of all citizens' health records) which are not registered in the DAD. On the opposite, there are a number of estimations for the coverage of specific populations. In a survey of 6,143 patients undergoing hip fracture surgery, the records retrieved from the DAD corresponded to 98.5 % coverage of the records in the Danish National Health Register. Similarly, of 1 472 records of patients undergoing tracheal intubation by direct laryngoscopy who died within 2 weeks after surgery, the coverage was 99.0 %. This indicates that 1-1.5 % of the records in the DAD were not retrievable from the Danish National Health Register. However, the number of patients registered in DNHR which cannot be retrieved in DAD is unknown. The DAD still awaits the possibility to make a valid estimate of this number. The expectation is that this will be possible within a couple of years.

Figure 2: Coverage of patients recorded in the Danish Anaesthesia Database.



Quality of data entry is controlled during the process of registration in the DAD, all registered parameters are predefined and user manuals are available in both paper and as an integrated on-line manual in the DAD. Further, the designs of the categories of the registered parameters of the DAD are exclusive and exhaustive. As an example, the modified Mallampati-score is divided into

six categories: 1 = class I; 2 = class II; 3 = class III; 4 = class IV; 5= unknown; 6 = is already tracheal intubated. Because of multiple numbers of clinical evaluators of many parameters of many patients in an everyday clinical set up, we cannot ensure controlled and uniform evaluation and registration of all parameters for all patients. There are no large formalised evaluations of the data validity registered in the database. However, in a small retrospective assessment, a total of 102 consecutive anaesthetic patient files from Herlev Anaesthesia Department from October 2005 were evaluated and compared with corresponding records in the DAD. Two anaesthetic patient charts did not have a corresponding record in the DAD, thus a total of 100 anaesthetic patient files of patients undergoing general or combined anaesthesia had a matching record in the DAD. We did this small assessment, because we knew that approximately 11 % of all records of the Mallampati-score in DAD was categorised as 'unknown'. Therefore, we compared the patient charts and the data in the DAD to evaluate the number of patients who were registered with or without a Mallampati-score (Table 1).

Table 1. Registration of Mallampati-score in anaesthetic charts and the Danish Anaesthesia database.

		Mallampati-score registered in DAD		
		Yes	No	
Mallampati-score registered in charts	Yes	78	2	80
	No	9	11	20
		87	13	100

In this small sample, the missing value (categorised as; '5 = unknown') of a Mallampati-score in the DAD were 13 % (7.3 – 19.6, 95 % CI) while 20 % (13.2 – 27.8, 95 % CI) of the patient charts did not report the score. A total of 45 % (9 of 20) of the patients who did not have any records of a Mallampati-score in the anaesthetic patient chart were registered with a Mallampati-score in the DAD. On the contrary, 15 % (2 of 13) were recorded in the DAD without a Mallampati-score even though the matching anaesthetic patient chart contained a Mallampati-score. This may indicate that the patient charts should not be considered the gold standard when evaluating the coverage of the DAD concerning the Mallampati-score. The Mallampati-score is the covariate encumbered with the highest degree of missing value in the database probably because the registration of 'unknown' is allowed. On the other hand allowing a score of 'unknown' discourages the practise of 'inventing' values which may occur if the anaesthesia personnel were obliged to register a specific

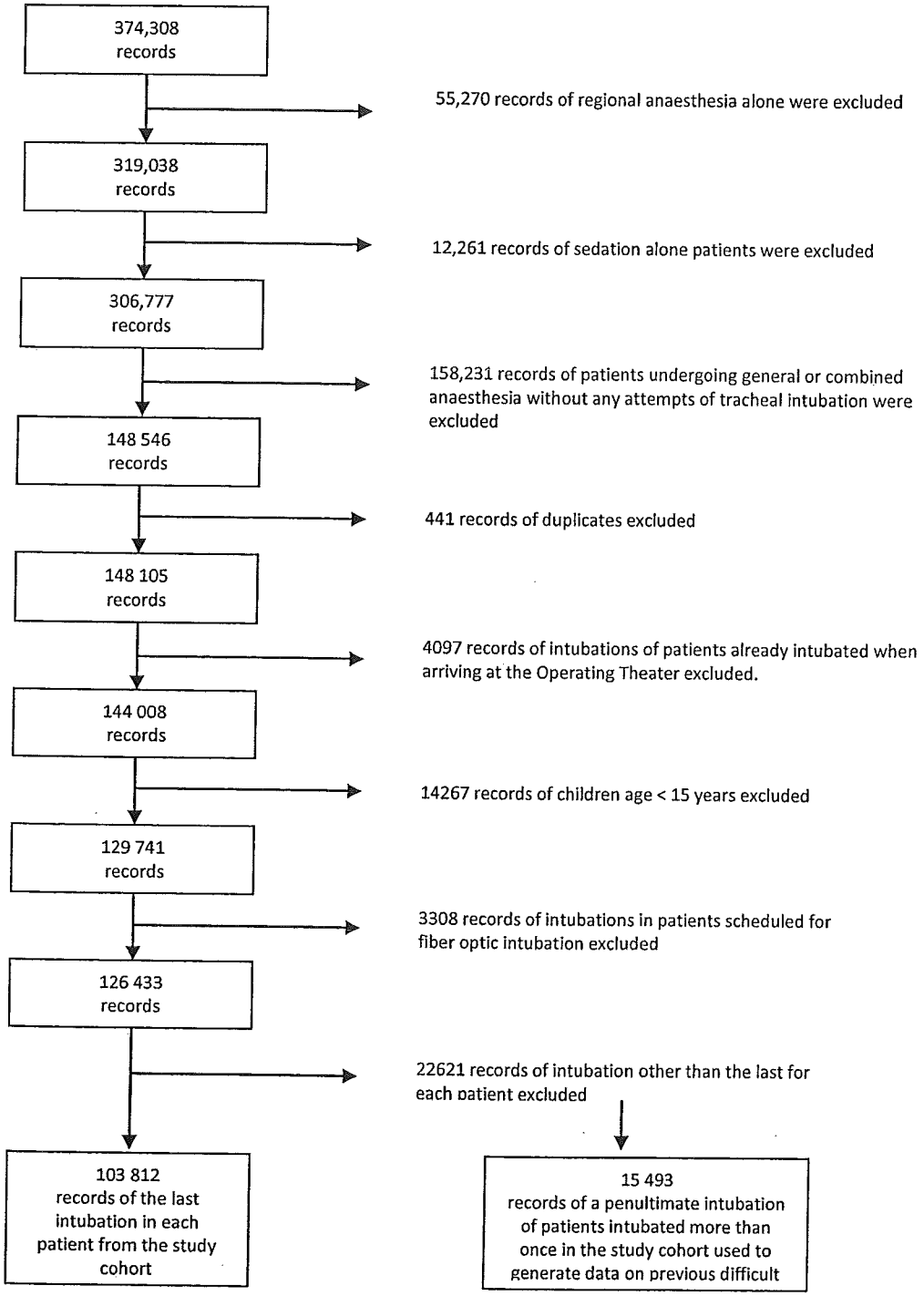
Mallampati-score for each patient in the database. Mostly, the completeness of parameters is high, as for other parameters the missing values are less than 2 % due to the fact that the DAD record can not be delivered to the central server without the obligatory fields filled in.

As a supplementary assessment, we focused on the 78 patients (Table 1) registered with both a Mallampati-score in the patient chart and in the DAD. Of these, the Mallampati-score differs by 5 %, as in 4 of 78 patients there was a disagreement between the registered Mallampati-score in the patient file and the DAD. There may be several reasons for this. It is likely that the disagreements were caused by an incorrect entry in the DAD. The disagreement may also be caused by the evaluation of the Mallampati-score being performed by two different evaluators. The score registered in the patient file may be performed days ahead of surgery. Therefore, the anaesthesiologist performing the airway handling and induction of anaesthesia may have re-evaluated the Mallampati-score. This may be supported by a study[102] that evaluated the reliability of the Mallampati-score. In this study the inter-observer-reliability was poor (kappa = 0.31).

The cohort retrieved from the Danish Anaesthesia Database

In three of the studies included in the current thesis, we retrieved a cohort from the DAD of patients undergoing anaesthesia from January 2005 to December 2007. We excluded records of patients exclusively undergoing regional anaesthesia or sedation. Records of patients undergoing general or combined anaesthesia without any attempts of tracheal intubation were also excluded. A total number of 148 546 records including patients undergoing general or combined anaesthesia primarily scheduled for tracheal intubation were retrieved. We further excluded patients who had already been tracheal intubated when arriving at the operating room, patients aged less than 15 years and those primarily scheduled to undergo flexible or rigid fiberoptic tracheal intubation. There were no records of the reason for these patients to be allocated to fiberoptic tracheal intubation; some may have been allocated to this procedure due to educational purposes rather than anticipated difficult tracheal intubation. Tracheal intubation was performed or attempted in 103 812 eligible patients. However, records of 126 433 intubations exist as some patients underwent tracheal intubation by direct laryngoscopy for anaesthesia on more than one occasion. Of these patients, 88 313 underwent tracheal intubation only once while 15 499 patients had been

Figure 3: Selection of the study cohort.



Selection of the study cohort. Recorded intubations were excluded as explained in the figure. The subgroup of 15 499 records representing the penultimate intubations of patients intubated more than once were merged to the corresponding last intubation for the specific patient, and thereby information for the covariate previous difficult intubation was created. Thus, 88 313 patients were only tracheal intubated once, 15 499 patients were intubated on two or more times occasions. Of these information of a previous intubation score was missing for 6 patients.

anaesthetised on more than one occasion, and therefore had two or more records of tracheal intubation by direct laryngoscopy. For these 15 499 patients both the last and the penultimate record of tracheal intubation were retrieved for the assessment (Figure 3). The fourth study is based on a section of this cohort starting January 2005 until the end of September 2007. Data were retrieved with the same methodological approach, and the cohort in this study included 91 332 patients. Of these patients 13 135 had been anaesthetised on more than one occasion.

In the Danish Anaesthesia Database a predefined four-point intubation score is used. It is based upon the number of attempts, change from direct laryngoscopy to a more advanced technique, intubation by a different operator or abandoned intubation (Table 2).

Table 2. The Danish Anaesthesia Database tracheal intubation score.

All patients in whom the primary airway management was planned and attempted for tracheal intubation by direct laryngoscopy were scored as follows:

Score = 1	Intubated by direct laryngoscopy by the first anaesthetist and in two attempts maximally.
Score = 2	Intubated by direct laryngoscopy by the first anaesthetist but with more than two attempts or intubated by a supervising anaesthetist after one or more failed attempts at intubation.
Score = 3	Intubated by a method other than direct laryngoscopy.
Score = 4	Intubation abandon after multiple attempts, no tracheal tube was inserted.

The predefined difficult tracheal intubation was defined as an intubation score > 1

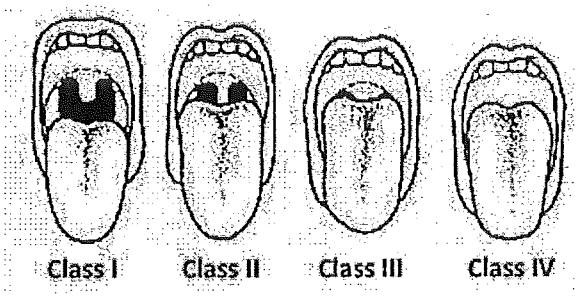
Furthermore, in one of the included studies[103] we introduced a 'Failed tracheal intubation by direct laryngoscopy' defined as an intubation score > 2 as an alternative outcome. This includes a change from direct laryngoscopy to a more advanced technique and the situation where tracheal intubation was abandoned. Both of these outcomes may be more clinically significant than the predefined definition of a difficult tracheal intubation.

The following data, other than the intubation score and Mallampati-score, were obtained from the DAD: age, sex, height, weight, classification of ASA physical status, history of a previous difficult

intubation, priority of surgery, time of surgery, the use of neuromuscular blocking agents and the modified Mallampati-score were used in the studies.

The modified Mallampati-score was registered as defined by Samsoon and Young[63] (Figure 4). The on-line user guide prescribes the patients to be placed in a sitting position with the head in a neutral potion and the assessment must be performed without phonation.

Figure 4. The modified Mallampati Score



The view was graded as follows:

Class I = soft palate, fauces, uvula, and pillars visible
Class II = soft palate, fauces, and uvula visible
Class III = soft palate and base of the uvula visible
Class IV = soft palate not visible at all

Handling missing data with multiple imputation

Analysing exclusively 'complete cases' or 'complete variables' invariably leads to biased results[104;105]. Intuitively this may be obvious because if a patient with one missing value is excluded then all of the information from all other variables are discarded. Simulation studies that simulate 'missingness' from a complete data set, show that complete case or complete variable analyses, which omit cases or variables with missing data, are biased compared with analyses of the original complete data set. However, bias occurring from complete case or complete variable analyses can be limited if the missingness is simulated to occur completely at random (MCAR) (Random sample of the full data set). The MCAR assumption can be tested by Little's test[105]. If the test for MCAR is statistically significant then all information can be used to predict the most likely distribution of the missing data, given that the non-missing data assumes missingness at random (MAR). The MAR assumption is that missingness is dependent of the observed data. A randomly

performed imputation (selection) for a missing value can then be performed from such a distribution under the MAR assumption. Performing the imputation multiple times preserves the most likely uncertainty of the imputation and makes it possible to confer this uncertainty to the aggregated or pooled results of the imputed data sets without creating an illusion of undue certainty. However, data may be missing not at random if the missingness is dependent on non-observed data in such a situation even multiple imputation may fail to deliver unbiased results although it seems that even then MI may provide less biased results.

We therefore described the prevalence and pattern of missing values among all covariates in the original data set. Afterwards, multiple imputations for missing values under the MAR assumption were performed according to the methods described in Appendix II.

Aims

Several studies have identified difficult airway management including difficult tracheal intubation of patients undergoing general anaesthesia as a major cause of anaesthesia-related morbidity and mortality. Therefore, it is presumed, that difficult tracheal intubation is a surrogate for morbidity and mortality, and by reducing the prevalence of difficult tracheal intubation morbidity and mortality will be reduced as well. In the literature there is no consensus of how to define a difficult tracheal intubation. Despite this heterogeneity, more studies have contributed efforts to identify different risk factors of difficult tracheal intubation. By identifying risk factors, in some cases it may be possible to prevent difficult tracheal intubation. In other cases, by identifying different risk factors it may be possible to distinguish between anticipated and unanticipated difficult tracheal intubations. It is hypothesized that an anticipated difficult tracheal intubation is safer, because it enables the anaesthesiologist to take precautions that reduces the complications related to difficult tracheal intubation.

From the Danish Anaesthesia Database, we retrieved a cohort of consecutive patients for whom tracheal intubation by direct laryngoscopy was planned and attempted. Based upon various data including an intubation score registered in the database, the aim was to evaluate four different parameters, *'obesity'*, *'avoidance of neuromuscular blocking agents'*, *'a previous difficult tracheal intubation'* and *'the modified Mallampati-score'*, as possible risk factors for difficult tracheal intubation. Thus, the aims of current thesis are:

1. To assess if and how obesity measured by body mass index is associated with difficult tracheal intubation. To compare body mass index and weight to decide if there are differences in their association with a difficult tracheal intubation, and finally to evaluate the accuracy of obesity as a stand-alone clinical test to predict difficult tracheal intubation.

2. To evaluate whether avoiding the use of neuromuscular blocking drugs for general anaesthesia including intubation by direct laryngoscopy is a risk factor for difficult intubation and failure of tracheal intubation. Also, to evaluate the use of non-depolarizing drugs compared with depolarizing drugs as a risk factor for difficult intubation.

3. To evaluate the diagnostic accuracy of a previous difficult tracheal intubation and a previous failed tracheal intubation by direct laryngoscopy documented in DAD as a stand-alone tests for the prediction of a subsequent difficult tracheal intubation and a failed tracheal intubation by direct laryngoscopy, respectively. Furthermore, in a multivariate regression model to evaluate previous failed intubation by direct laryngoscopy documented in DAD as a risk factor risk factor for a subsequent failed tracheal intubation by direct laryngoscopy.

4. To assess the performance of the modified Mallampati-score as a prognostic test of a difficult tracheal intubation based on a meta-analysis of retrievable observational studies including the large cohort from the Danish Anaesthesia Database.

5. Based upon the cohort of 103 812 patients retrieved from the Danish Anaesthesia Database in an additionally assessment we will evaluate if a difficult tracheal intubation or a failed tracheal intubation by direct laryngoscopy statistically are associated with death.

Presentation of the studies

Study I

'High Body Mass Index Is a Weak Predictor for Difficult and Failed Tracheal Intubation'

Introduction

Previous studies have failed to identify high body mass index (BMI) as a risk factor for difficult tracheal intubation (DTI). The aim here was to assess whether obesity measured by BMI is associated with DTI. We evaluated the different levels of BMI used to categorize obesity and evaluate if the risk of DTI is greater in patients with high BMI. We compared BMI and weight to decide if there are differences in their association with a DTI and evaluated the accuracy of obesity as a stand-alone clinical test to predict a DTI.

Methods

The patients were retrieved as previously described. Logistic regression was performed (Appendix III). The accuracy of BMI as diagnostic and prognostic test was evaluated (Appendix I).

Results

The results of a univariate analysis of BMI stratified in six categories demonstrated the odds ratio for DTI increased with BMI. Based on the p-values and the odds ratios, the BMI was divided into three categories: BMI < 25, 25 ≤ BMI < 35 and 35 ≤ BMI. In a multivariate logistic regression analysis adjusted for other significant covariates, BMI ≥ 35 or more and 25 < BMI ≤ 35 were statistically significant risk factors of DTI with an OR of 1.34 (95 % CI 1.19 –1.51, P < 0.0001) and 1.11 (95 % CI 1.04 –1.18, P < 0.0016), respectively.

We performed a multivariate logistic regression analysis including both BMI and weight. According to a non-significant P value weight was excluded and hereby leaving BMI as the only independent significant risk factor for DTI.

Evaluating the performance of a BMI ≥ 35 as a prognostic test for the prediction of difficult tracheal intubation by direct laryngoscopy demonstrated a sensitivity of 0.07 (0.07 – 0.08, 95 %

CI), a specificity of 0.94 (0.94 – 0.94, 95 % CI), a predictive value of a positive test of 0.06 (0.06 – 0.07, 95 % CI), a predictive value of a negative test of 0.95 (0.95 – 0.95, 95 % CI), a positive likelihood ratio of 1.26 (1.14 – 1.40, 95 % CI) and negative likelihood ratio of 0.98 (0.98 – 0.99, 95 % CI).

Conclusion and discussion

In our large cohort, increasing obesity was demonstrated as a risk factor for DTI independent of other risk factors registered in the DAD. The impact of BMI ≥ 35 on the frequency of DTI was limited compared to other known risk factors. As sole predictors of DTI, the accuracy of BMI assessed as dichotomous tests performed poorly, and obesity measured by BMI cannot in itself identify patients at risk of DTI. BMI appears to be a better measure than weight itself to describe obesity as a risk for DTI.

Even though high BMI only is a weak predictor for difficult and abandoned tracheal intubation, obesity has been identified as a risk for difficult mask ventilation[20], which is an important rescue technique in these situations. The airway management of obese patients may also be associated with accelerated oxygenic desaturation[106] and difficult emergency tracheotomy[90]. Therefore, the knowledge of obesity being a risk factor for DTI simultaneously with difficult mask ventilation may be important despite the rather low impact on the frequency of DTI.

Obesity may create anatomical difficulties for the intubation caused by the decreased mobility and enlargement of structures in the throat and around the neck. Therefore, it seems rational to hypothesize that obesity in terms of BMI may be independently associated with DTI. BMI may be a confounder for other and more closely related risk factors for DTI. E.g., the neck circumference may be a better and more relevant predictor than BMI, but again the current literature does not provide an adequate answer to this question[47;69;94]. Other indices like the Ponderal index (PI) may be a more physically correct measure for obesity[107]. The PI calculated as a relationship between mass and height is similar to the BMI, however the mass is normalized with the third power of body height rather than the second power: ($PI = (mass * hight^{-3})$, $(unit = kilogram * meter^{-3})$). It has been suggested that we might have found better correlation between the ponderal index and DTI

than between BMI and difficult tracheal intubation[107;108]. We performed a multivariate regression analysis of the cohort from the DAD to determine if it is possible to include both BMI and PI in the same model. This analysis left PI as the only independent significant risk factor for DTI, suggesting that PI may be a better predictor of DTI than BMI. Nevertheless, the association between PI and DTI was only marginally stronger than between BMI and DTI[109]. Thus, in a clinical context the PI does not seem to be a more convincing diagnostic tool to predict a DTI.

Study II

'Avoidance of neuromuscular blocking agents may increase the risk of difficult tracheal intubation'

Introduction

The use of neuromuscular blocking agents (NMBA) to facilitate tracheal intubation is a widely accepted procedure. However, because of unwanted side effects such as anaphylaxis, residual relaxation, interference with the patients' electrolyte status or simply because of prolonged muscle relaxation during short-duration surgery, the use of NMBA may be undesirable. The conditions for tracheal intubation, possible side effects, and postoperative discomfort like sore throat, hoarseness, vocal cord lesion, pharyngeal oedema, pharyngeal necrosis have been evaluated in randomised trials comparing different regimes of anaesthesia induction and comparing the use of NMBA with the avoidance of NMBA[100;110-119] These studies indicate that avoiding NMBA may be a risk factor for difficult tracheal intubation.

Methods

The patients were retrieved as previously described. Logistic regression was performed (Appendix III).

Results

Among the 103 812 patients retrieved from the Danish Anaesthesia Database, the frequency of patients undergoing tracheal intubation without the use of NMBA increased over the 3 years of observation from 17.5 % in 2005 to 25.8 % in 2006 and to 31.6 % in 2007. The univariate analysis of the dichotomized covariate of the use/avoidance of NMBA demonstrated an OR for difficult tracheal intubation of 1.52 (1.43–1.61, $P < 0.0001$). A subsequent multivariate analysis demonstrated an OR for a DTI of 1.48 (1.39–1.58, $P < 0.0001$) with 'avoidance of NMBA'. Exploring the model for interactions identified a statistically significant interaction of NMBA with surgical priority ($P < 0.0001$). This means that the association between DTI and the use of NMBA is dependent on surgical priority and vice versa. Therefore, we introduced a new covariate combining the use/avoidance of NMBA and levels of surgical priority and repeated the multivariate analysis with this covariate having four levels. Among the patients undergoing non-

scheduled surgery, the OR of DTI was 3.10 (2.69–3.57, P < 0.0001) for those anaesthetized without the use of NMBA. In those undergoing scheduled surgery, the OR of DTI was 1.26 (1.18–1.35, P < 0.0001) for those anaesthetized without the use of NMBA.

The dichotomized covariate avoidance of NMBA (as opposed to the use of NMBA) was statistically significantly associated with 'abandoned tracheal intubation'. In a multivariate analysis, the odds ratio of 'abandoned tracheal intubation' was 1.72 (1.21–2.43, P < 0.0001) for 'avoidance of NMBA' compared to the use of NMBA.

We repeated our analysis with the use of NMBA stratified into three classes as 'depolarizing drugs with or without non-depolarizing drugs', 'non-depolarizing drugs only', or 'none'. Our multivariate analysis demonstrated an OR for DTI of 1.74 (1.59 – 1.90, P < 0.0001) with avoidance of NMBA and of 1.26 (1.16 – 1.37, P < 0.0001) for 'non-depolarizing drug only'.

Conclusion and discussion

In our cohort, avoiding neuromuscular blocking drugs may be a risk factor for difficult and abandoned tracheal intubation independent of other risk factors recorded in the Danish Anaesthesia Database. We identified a statistical interaction between the covariates such that the impact of avoiding NMBA on DTI differed with surgical priority. Regardless of surgical priority, the risk of DTI was highest in patients anaesthetized and intubated without the use of NMBA. Among patients intubated using NMBA, a multivariate analysis identified that patients anaesthetized with only non-depolarizing NMBA to be more at risk for DTI than those anaesthetized with depolarizing NMBA alone.

Our assessment does not contain data on whether patients were intubated using a rapid sequence induction or not. Including more covariates, especially records of rapid sequence induction, in our investigation may have changed the result, and may have ultimately removed 'non-depolarizing NMBA' as an independent risk factor for DTI. Confounding by indication is well-known to introduce bias in the results in any non-randomised study involving interventions. Unknown confounding variables may be important for airway management. Therefore, our results could be biased by

numerous variables that are not recorded in the Danish Anaesthesia Database. As an example, a limitation of this study was that risk factors such as the thyromental distance, ability of mouth opening, range of neck movement, or jaw protrusion ability were not registered in the DAD and therefore impossible to retrieve for our multivariate analysis. A considerable part of the OR for difficult intubation attributable to avoidance of NMBA may accordingly have been caused by residual confounding due to lack of registration of important covariates.

Because confounding by indication is a major problem as well in observational studies describing the effect of interventions, systematic reviews with meta-analysis or more randomized clinical trials comparing the avoidance and use of NMBA for intubation and examining patient-centred and important outcomes would be very valuable.

Study III

'A documented previous difficult tracheal intubation as a prognostic test for a subsequent difficult tracheal intubation in adults'

Introduction

A previous DTI has been identified as a risk factor for a future DTI. However, the information of a previous DTI has been partly or totally reported by the patient, and therefore documented information may only be partly retrieved for their assessments[66;93]. The Danish Anaesthesia Database contains documented information about patients in whom tracheal intubation was performed more than once. The aim was to evaluate the diagnostic accuracy of a documented previous DTI and a previous failed tracheal intubation by direct laryngoscopy as a stand-alone test for the prediction of a subsequent DTI or a failed tracheal intubation by direct laryngoscopy, respectively. Furthermore, in a multivariate regression model we evaluated a documented previous failed intubation by direct laryngoscopy as a risk factor of a subsequent failed tracheal intubation by direct laryngoscopy.

Methods

The patients were retrieved as previously described. Further, we changed the cut off level of the intubation score in the Danish Anaesthesia Database and hereby, we introduced a failed tracheal intubation by direct laryngoscopy as an additional outcome measure in our assessments. The previous failed tracheal intubation by direct laryngoscopy was dichotomised with same methodological approach as the previous DTI.

Logistic regression was performed (Appendix III) and the accuracy of a previous DTI and a previous failed tracheal intubation by direct laryngoscopy as diagnostic and prognostic tests was evaluated (Appendix I).

Results

Table 3. The accuracy of previous difficult tracheal intubation as a dichotomous stand-alone test for the prediction of a subsequent difficult tracheal intubation.

Total cohort 103 812 patients		Outcome: **Difficult tracheal intubation**		
		Yes	No	Total
Test: **Previous difficult tracheal intubation**	Yes	170	528	698
	No	5163	97 865	103 024
	Total	5329	98 393	103 722

		95 % confidence intervals
Sensitivity	0.03	(0.03 - 0.04)
Specificity	0.99	(0.99 - 1.00)
Predictive value of positive test	0.24	(0.21 - 0.28)
Predictive value of negative test	0.95	(0.95 - 0.95)
Positive likelihood ratio	5.94	(5.01 - 7.05)
Negative likelihood ratio	0.97	(0.97 - 0.98)

The total number of patients differs because of missing values.

Evaluating the performance of a previous failed tracheal intubation by direct laryngoscopy as a prognostic test for the prediction of a subsequent failed tracheal intubation by direct laryngoscopy demonstrated a sensitivity of 0.04 (0.03 – 0.05, 95 % CI), a specificity of 1.00 (1.00 – 1.00, 95 % CI), a predictive value of a positive test of 0.30 (0.24 – 0.36, 95 % CI), a predictive value of a negative test of 0.98 (0.98 – 0.98, 95 % CI), a positive likelihood ratio of 22.09 (16.92 – 28.86, 95 % CI) and negative likelihood ratio of 0.96 (0.96 – 0.97, 95 % CI).

In a multivariate logistic regression model adjusted for other significant covariates, a previous failed tracheal intubation by direct laryngoscopy was a statistically significant risk factor of a subsequent failed tracheal intubation by direct laryngoscopy with an OR of 16.6 (11.9–23.2, 95 % CI, $p < 0.0001$).

Conclusion and discussion

Our assessments demonstrate that a previous DTI or a previous failed tracheal intubation by direct laryngoscopy as stand-alone tests, are inadequate predictors of subsequent difficult or failed

tracheal intubations by direct laryngoscopy respectively. Still, a dichotomous test of a previous documented DTI enables us to predict 24 % of the patients who will subsequently undergo a DTI. Further, a previous failed tracheal intubation by direct laryngoscopy was able to predict 30 % of the patients with a subsequent failure.

The sensitivities of the two tests were only 0.03 and 0.04, respectively. These remarkably low estimates are the result of retrieving a cohort including patients with no previous record in the Danish Anaesthesia Database. The 15 499 patients with a documented previous record of an intubation score are of most interest. However, these patients only represent a selected subgroup of the total cohort. A selection, which may appear artificial, considering the fact that they are retrospectively selected, as we only know which of the patients that have been intubated more than once when the cohort is finally analysed. Thus in a real clinical situation the physician will also meet patients scheduled for tracheal intubation without a documented previous intubation score or even without a previous intubation at all. Therefore the clinical situation will be one of three:

1) 'The patient previously underwent a difficult tracheal intubation'
2) 'The patient previously underwent a tracheal intubation without problems'
3) 'There is no documented information of a previous tracheal intubation of the patient'

If we exclude the 88 313 patients with absence of any documented information of previously tracheal information, it results in a false increased sensitivity with distorted specificity and positive- and negative likelihood ratios will also be distorted. This is demonstrated in the table below, where the accuracy of a stand-alone test for the subgroup of 15 499 patients is presented.

In our multivariate regression model, the problems will be similar. By only using the subgroup of the 15 499 patients, there is a major risk of introducing selection bias. Furthermore, using more than 100 000 patients for our assessment will strengthen the statistical power of our estimates including the corresponding narrow confidence intervals.

Table 4. The accuracy of previous difficult tracheal intubation as a dichotomous stand-alone test for the prediction of a subsequent difficult tracheal intubation.

Subgroup 15 499 patients		Outcome: Difficult tracheal intubation		
Test:		Yes	No	Total
Previous difficult tracheal intubation	Yes	170	528	698
	No	619	14 171	14 790
	Total	789	14 699	15 488

		95 % confidence intervals
Sensitivity	0.22	(0.19 - 0.25)
Specificity	0.96	(0.96 - 0.96)
Predictive value of positive test	0.24	(0.21 - 0.28)
Predictive value of negative test	0.95	(0.95 - 0.95)
Positive likelihood ratio	6.00	(5.12 - 7.02)
Negative likelihood ratio	0.81	(0.78 - 0.84)

The total number of patients differs because of missing values.

Previous studies have reported predictive values that exceed our findings markedly. An explanation may be that only the most severe episodes of a previous DTI may be reported to the patients and consequently only these severe episodes may be included in the previously reported assessments. However both patient-reported episodes of previous difficulties and our results concerning documented previous difficulties strongly suggest that the patients who previously underwent a tracheal intubation with difficulties or underwent a tracheal intubation which failed will be at considerable risk of encountering similar problems during a future tracheal intubation.

Study IV

'The prognostic value of the modified Mallampati-score to predict difficult tracheal intubation. A meta-analysis'

Introduction

Several studies have focused on the modified Mallampati-score as a risk factor for DTI. Shiga et al [85] and Lee et al [97] both performed meta-analyses to evaluate the accuracy of the original and the modified Mallampati tests to predict a difficult intubation or difficult laryngoscopy. The Danish Anaesthesia Database contains more than 92 000 records of patients undergoing tracheal intubation and evaluated by the modified Mallampati-score which substantially exceeds the number of patients included in previous meta-analyses. The aim of this study was to assess the performance of the modified Mallampati-score as a prognostic test of a DTI based on a meta-analysis including several recent studies published since the meta-analyses of Shiga and Lee et al including the large cohort from the Danish Anaesthesia Database.

Methods

In an electronic search covering the time since introduction of the modified Mallampati-score May 1987 until December 2009, The Cochrane Library, MEDLINE, Science Citation Index and EMBASE, we included studies of the modified Mallampati-score of adults undergoing direct laryngoscopy. The data of the studies were prospectively collected and the studies were reported in English. The absolute number of true positive, false negative, true negative and false negative were extracted from the articles, based on a DTI, or a difficult laryngoscopy in combination with the modified Mallampati-score.

If possible, the following additional data were extracted: the settings of the Mallampati-score by retrieving the position of the head and body and if the patients phonated during the evaluation. The number of anaesthesiologists performing the preoperative airway assessments and the number of anaesthesiologists handling the tracheal intubations were retrieved. It was noted, if the assessment of the modified Mallampati-score was blinded for the anaesthesiologists performing the airway management. The participant sampling, inclusion and exclusion criteria of patient population were retrieved as well as how the patients were recruited. The data were used to

explore possible causes of heterogeneity across the studies by performing meta-regression analyses. Further, the data were quality assessed based on the following four criteria: 1) blinding of the test; 2) settings of the test; 3) selection of the population; 4) recruitment of the population. Studies fulfilling all four criteria were classified as studies with low-risk of bias, if three criteria were fulfilled, they where categorized as medium-risk of bias studies. Otherwise they were classified as studies with high-risk of bias.

The modified Mallampati-score from the pooled estimates in the meta-analyses and from the Danish Anaesthesia Database were described by: sensitivity; specificity; positive likelihood ratio; and negative likelihood ratio. The 'random-effects model' by DerSimonian and Laird[120] was used incorporating a moment-based between study variance when calculating the pooled estimates. Because the sensitivity and specificity were associated across the studies, a summary receiver operator characteristics curve (sROC)[121] was conducted. The area under the sROC curve was used as a measure for the description of diagnostic accuracy of the Mallampati test. To ensure precise pooled estimates, the pooled sensitivity was derived from the sROC curve using corresponding pooled specificity[121;122]. Thus, the pooled sensitivity was calculated as

$$Sensitivity = \frac{1}{1 + \frac{1}{DOR * \left(\frac{1 - specificity}{specificity}\right)}}$$

DOR= diagnostic odds ratio.

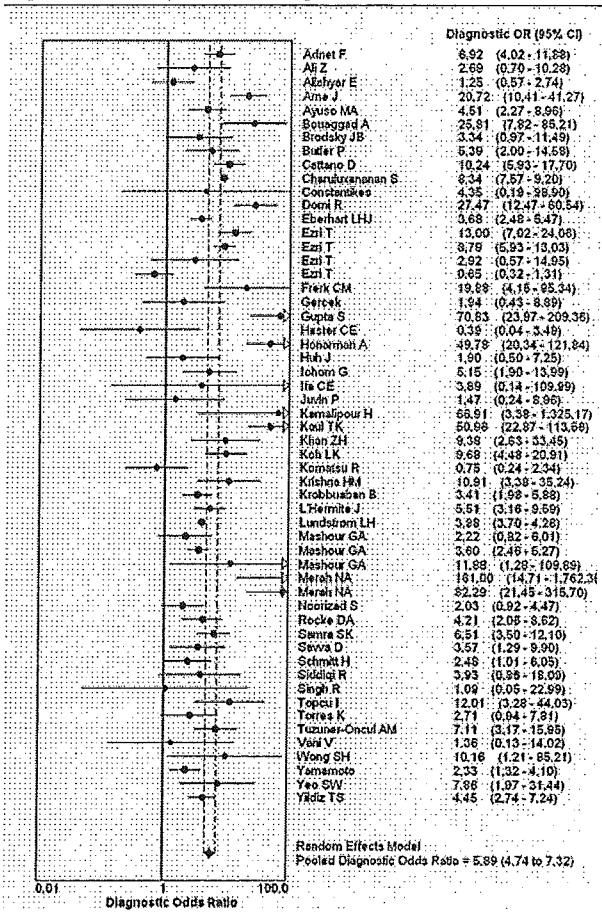
Degrees of heterogeneity displayed by the I^2 of all estimates were calculated[123]. Possible publication bias was assessed by the method described by Eggers[124].

Results

A total of 55 studies representing 177 088 patients met the inclusion criteria for the meta-analysis. The prognostic performance in the individual studies of the modified Mallampati-score varied considerably between the studies. This is exemplified by the forest plot of the diagnostic odds ratio of the individual studies shown below (Figure 5). There was a high degree of heterogeneity among the studies as I^2 in the meta-analyses of all the pooled estimates ranged ranging from 87.2 % to 99.4 %. The sensitivity and specificity were statistically significant (Spearman correlation coefficient: 0,362, p-value = 0.007). We composed a symmetric sROC curve (see below) with the

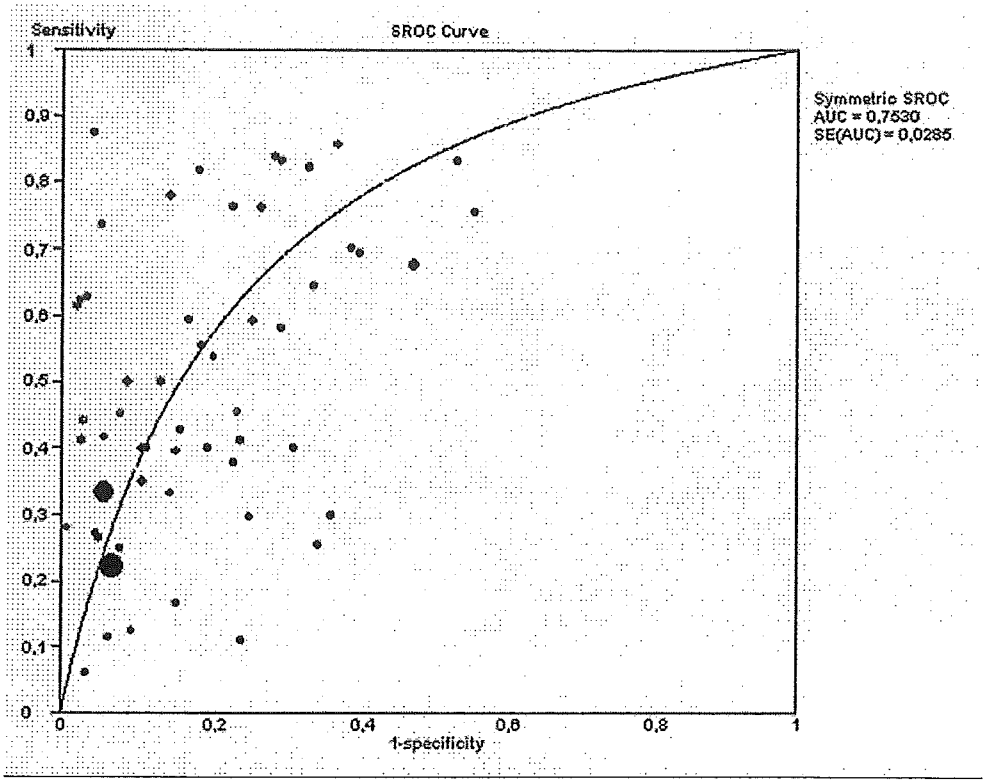
area under the curve calculated to 0.753 (SE = 0.03). The pooled diagnostic odds ratio was 5.89 (4.74 – 7.32, 95 % CI). The pooled estimate of the specificity was 0.91 (0.91 – 0.91, 95 % CI). Based on the sROC curve, the pooled specificity was used to derive a corresponding pooled sensitivity of 0.35 (0.34 – 0.36, 95 % CI). The pooled positive and negative likelihood ratios were derived from the pooled specificity and sensitivity, and calculated to 4.13 (3.60 - 4.66, 95 % CI) and 0.70 (0.65 – 0.75, 95 % CI), respectively.

Figure 5. Forest plot of the diagnostic odds ratio of the individual studies



The cohort from Danish Anaesthesia Database demonstrated a sensitivity of 0.22 (0.21 – 0.24, 95 % CI), a specificity of 0.93 (0.92 – 0.93, 95 % CI), a predictive value of a positive test of 0.15 (0.14 – 0.16, 95 % CI), a predictive value of a negative test of 0.96 (0.96 – 0.96, 95 % CI), a positive likelihood ratio of 3.31 (3.12 – 3.51, 95 % CI) and negative likelihood ratio of 0.83 (0.82 – 0.85, 95 % CI).

Figure 6. The summary receiver operator characteristics (sROC) curve of 55 studies evaluating the modified Mallampati score as a predictor for difficult tracheal intubation or difficult laryngoscopy. AUC = area under the curve; SE = standard error.



Conclusion and discussion

As a stand-alone test both the cohort study and the meta-analysis demonstrated that the modified Mallampati-score was an inadequate predictor of a difficult laryngoscopy or tracheal intubation. Our results differ from the results reported in previous meta-analyses, which may be caused by the increased number of studies and patients included in our updated assessment. Our meta-analyses had a high degree of statistical and clinical heterogeneity. But, meta-regression analyses did not identify any significant explanation of the heterogeneity. Because of the apparent high precision of some of the studies estimate of diagnostic accuracy[30;125] and these particular estimates discrepancy with the estimates from other studies, the statistical heterogeneity may be exaggerated[126]. The number of patients evaluated in each study varied a lot. In our assessment two studies[30;125] evaluated 84 % of all included patients, while the accumulated weight of the two studies in the random effect model evaluating the diagnostic odds ratio was only 6.3 %. The random-effects model used for pooling diagnostic studies may have important shortcomings when large cohort studies comprising more than 80 % of the included patients may be inappropriately down-weighted[127;128].

Despite of the limited value of the modified Mallampati-score as a prognostic stand alone test, it may still play a very important role as a part of a multivariate model for the prediction of a DTI.

A possible association between difficult tracheal intubation and death; an additional analysis

Introduction

Based upon the cohort of 103 812 patients retrieved from the Danish Anaesthesia Database we evaluated if a DTI or a failed tracheal intubation by direct laryngoscopy were statistical associated with death as an additional study.

Methods

The following covariates were retrieved: DTI; failed tracheal intubation by direct laryngoscopy; age; sex; the ASA classification physical status. We retrieved vital status of patients with a follow up timed until the 14th January 2008. The associations between death and the predefined covariates were assessed by Cox regression analysis, assuming proportional hazards. Initially, univariate regression analyses were performed. Subsequently, all significant ($p < 0.05$) covariates from the univariate analyses were included in a multivariate regression analysis. Backward stepwise regression was performed to identify a final Cox regression model.

Results

The associations between death and a DTI in a univariate Cox regression analysis was not statistically significant; hazard ratio = 1.08 (0.99 – 1.18, 95 % CI, p = 0.079).

The univariate analysis of a failed tracheal intubation by direct laryngoscopy demonstrated a hazard ratio for death of 1.40 (1.24–1.58, P < 0.0001). A subsequent multivariate analysis (table below) demonstrated a hazard ratio for death of 1.14 (1.01–1.30, P = 0.039).

Discussion

It is the first step in the validation of a putative surrogate to demonstrate an association between the surrogate and the clinical outcome. In our assessment, we did no demonstrate a significant association between death and DTI. However, a univariate p-value of 0.079 may indicate a

possible association. The lack of a significant association may be caused by a low prevalence of failed tracheal intubation by direct laryngoscopy, which may cause lack of

Table 5. Multivariate model for death of patients planned and attended tracheal intubation by direct laryngoscopy.

Covariates:	Hazard ratio	95 % CI.	P-value
Failed tracheal intubation by direct laryngoscopy			
= No	Reference		
= Yes	1.14	1.01 – 1.30	= 0.039
Age (year)			
Age < 40	Reference		
40 ≤ Age < 60	3.96	3.43 – 4.57	< 0.0001
60 ≤ Age < 80	6.89	5.98 – 7.94	< 0.0001
80 ≤ Age	14.18	12.28 – 16.38	< 0.0001
Gender			
Female	Reference		
Male	1.13	1.08 – 1.17	< 0.0001
ASA classification physical status			
ASA I	Reference		
ASA II	3.97	3.59 – 4.40	< 0.0001
ASA III	11.87	10.71 – 13.15	< 0.0001
ASA IV	34.99	31.22 – 39.20	< 0.0001
ASA V	56.22	45.92 – 68.83	< 0.0001

statistical power. However, by using the cut-off level of failed tracheal intubation by direct laryngoscopy (as in Study III)[103] for dichotomising the intubation score and hereby focusing on attempts of intubation where problems at least resulted in shift of intubation method or failure to intubate at all, we may have demonstrated both a univariate and a multivariate adjusted statistically significant association. Overall, our assessments do not contradict the assumption that a difficult or failed tracheal intubation by direct laryngoscopy is a surrogate marker for death but the risk of residual confounding being involved in this association is imminent.

Discussion and conclusion

Clinical implications

Based on a cohort of patients retrieved from the Danish Anaesthesia Database, we examined the roles of various clinical variables as risk factors for a DTI. *'Obesity'*, *'a previous difficult tracheal intubation'* and *'the modified Mallampati-score'*, all three risk factors, may help to convert a tracheal intubation from being 'unexpected difficult' to be 'expected difficult'. In doing so, you may have the opportunity to take precautions in order to reduce the risk of related complications. In our assessments, all three parameters had a statistically highly significant association with a DTI, but the clinical significance varied substantially between the evaluated variables.

Obesity measured by BMI, weight, or PI were clinical week predictors of a DTI assessed in multivariate regression models. Likewise, obesity was insufficient and weak as a dichotomous stand alone test for the prediction of a DTI. Overall, the impact of obesity alone, on the risk of DTI therefore may be weak.

The modified Mallampati-score was represented as a covariate in all the multivariate logistic analyses presented throughout this thesis. Here, it was demonstrated to be a clinically strong risk factor for a DTI. However, as a stand-alone test both the cohort study from Danish Anaesthesia Database and the meta-analysis of all studies so far demonstrated that the modified Mallampati-score was an inadequate predictor of a difficult laryngoscopy or tracheal intubation. However, the diagnostic performance of the modified Mallampati-score significantly exceeds the performance demonstrated by e.g. obesity.

Our multivariate analyses strongly suggest that patients who previously underwent a tracheal intubation with difficulties or underwent a tracheal intubation which failed will be at risk of encountering similar problems during a future tracheal intubation. As stand-alone tests, a previous DTI or a previous failed tracheal intubation by direct laryngoscopy are inadequate predictors of subsequent difficult or failed tracheal intubations by direct laryngoscopy respectively.

The fourth study in the current thesis differ substantial from the above-mentioned studies, as it considered the impact of an intervention rather than that of a patient-related factor on the risk of DTI. In this study, we investigated whether avoiding NMBA was associated with a DTI. The nature of this risk factor will not affect whether a DTI is expected or not, the assessment is about an intervention that changes the conditions so that a difficult intubation may be avoided. In our assessment, avoiding NMBA is a risk factor for difficult and abandoned tracheal intubation independent of other risk factors recorded in the Danish Anaesthesia Database. Among patients intubated using NMBA, a multivariate analysis identified that patients anaesthetised with non-depolarising NMBA to be more at risk for DTI than those anaesthetised with depolarizing NMBA.

Limitations

Overall, there are numerous limitations in our assessments. Confounding by indication is known to introduce bias when dealing with forecasts of DTI in any non-randomised study evaluating interventions[129]. As an example, the clinical choice of tracheal intubation with or without the use of NMBA depends on multiple factors related to the patient, to the surgery and to other aspects of the clinical situation. The choice of using or avoiding NMBA may be based on reasons not recorded in the Danish Anaesthesia Database. Confounding by indication may also introduce bias in cohort studies of patient-related risk factors. Unknown confounding variables may be important for the airway handling depending on the risk factor included in our assessments. As an example, a more experienced physician may be allocated the task; therefore, the patient with increased risk of a DTI may have been successfully intubated. Likewise, the airway management of an expected DTI is likely to differ from that of an unexpected DTI. It is a limitation of the present study that there was no record of the educational level or years of experience of the individuals performing or attempting the intubations. Those with least experience may have the highest number of difficult intubations. The number of risk factors that may be considered for difficult intubation used in our multivariate analyses was limited. An inclusion of other additional risk factors such as the thyromental distance, ability of mouth opening, range of neck movement, or jaw protrusion ability may change the impact of our included risk factors retrieved from the Danish Anaesthesia Database. Therefore, residual confounding may be present in our analyses.

Implications for future research

The three risk factors, *'obesity', 'a precious difficult tracheal intubation'* and *'the modified Mallampati-score'* were far from being sufficient as dichotomous stand-alone tests for the prediction of DTI. Therefore it seems rational to focus on the development, testing, and modification of multivariate models from and in large scale cohort studies, hereby making the prognostication operational in everyday clinical practice.

The aim of a multivariate model including an operational risk score is to reduce the prevalence of unexpected DTIs. However, while there are more estimates of the prevalence of a DTI by direct laryngoscope, the prevalence of an unexpected DTI remains unreported. In the current version 3.0 of the Danish Anaesthesia Database it should be declared, before performing a direct laryngoscopy, if the intubation is expected to be difficult or not using an overall clinical judgement. Hereby it may be possible to compare the expectation with what happens *de facto,* and the prevalence of the relevant outcome measure *unexpected* DTI may be described.

The 'true number' of deaths associated with failed airway management may be substantial. Because of the large number of consecutively recorded patients, it may be possible to discern a more precise prevalence of deaths caused by, or related to, DTI. However, in our large data set we identify a statistically significant association between a failed tracheal intubation by direct laryngoscopy and mortality. Further, our univariate assessment of a DTI indicates a possible association with death. Thus, at least our additional analyses do not contradict the assumption of a DTI as a surrogate for mortality.

Considering that the ultimate goal of a prognostic test is to guide clinicians in everyday practice, in clinical environments with possible diverse settings, the studies with very few evaluators adhering strictly to protocol procedures of both evaluation and settings for the intubation may exaggerate the prognostic value. Therefore, large database studies may convey a more realistic picture of the prognostic value achieved. Contrarily, the smaller studies adhering strictly to protocols of both evaluation and settings for the tracheal intubation procedure may describe what is ultimately possible if education and training are optimized.

By introducing a multivariate risk score for prediction of DTI as an obligatory record in a future version of the Danish Anaesthesia Database it may be possible to evaluate the impact of multivariate testing on the occurrence of an unanticipated DTI. Further, because of many participating departments and many records of patients, the set up of the Danish Anaesthesia Database may offer the opportunity to conduct a cluster (department) randomised trial testing the impact of different airway recommendations on the prevalence of unanticipated DTIs, complications, and possibly mortality. There may be an enormous potential of this method both for improving airway management of the patients and for the future development of the database. The Danish Anaesthesia Database already contains a high number of fields for registration and the demand for supplemental fields is high, highlighting the necessity that the database itself contains evidence based registrations. We need to take the old saying 'need to know and not nice to know' very seriously. Therefore, introducing new fields and/or removing old ones should be the results of 'tests' or trials demonstrating that these new database designs actually improve patient care, registration, and reports from the database.

Appendix I: Calculating estimates of diagnostic and prognostic test indices.

In our assessments of the accuracy of diagnostic and prognostic tests the calculations were based upon the definitions stated below in Table 6.

Table 6. The accuracy of a diagnostic test

			Outcome: Difficult tracheal intubation		
			Yes	No	
Test	Predicted difficult tracheal intubation	Yes	a = TP	b = FP	a+b
		No	c = FN	d = TN	c+d
			a+c	b+d	N

Sensitivity	=	a/(a+c)
Specificity	=	d/(b+d)
Predictive value of a positive test	=	a/(a+b)
Predictive value of a negative test	=	d/(c+d)
Positive likelihood ratio	=	sencitivity/(1-specificity)
Negative likelihood ratio	=	(1-sensitivity)/specificity

TP = true positive; FP = false positive; FN = false negative; TN = true negative

Interpretation of test estimates

- **Sensitivity** is the proportion of positives that are correctly identified by the test.
- **Specificity** is the proportion of negatives that are correctly identified by the test.
- **Predictive value of a positive test** is the proportion of patients with a positive test result who are correctly diagnosed.
- **Predictive value of a negative test** is the proportion of patients with a negative test result who are correctly diagnosed.
- **Likelihood ratio for a positive result** (LR+) tells you how much the odds of the disease increase when a test is positive.

- **Likelihood ratio for a negative result** (LR-) tells you how much the odds of the diseas decrease when a test is negative.

The likelihood ratio combines information about the sensitivity and specificity[130;131]. It tells yo how much a positive or negative result changes the likelihood that a patient would have a DT odds ratio in combination with the pre-test odds can be used to estimate the post-test odds:

$$Odds_{post\text{-}test} = Odds_{pre\text{-}test} * likelihood\ ratio$$

The post-test odds incorporates information about the disease prevalence, the patient pool, ar specific patient risk factors (pre-test odds) and information about the diagnostic test itself. However, it may difficult to interpret odds and therefore terms like 'probability' and 'risk' may l preferred. The example below is based upon the results from Study IV concerning the meta-analysis of the diagnostic performance of the modified Mallampati-score. Here the pooled prevalence of a DTI was 6.8 %, and the positive and negative likelihood ratios were 4.13 and 0.7 respectively. Thus, when the prevalence of a DTI represents the pre-test probability of a DTI, the if the test was positive:

$$Probability_{pre\text{-}test} = Prevalence = 0.068$$
$$Odds_{pre\text{-}test} = Prevalence\ /\ (1 - Prevalence) = 0.068\ /\ (1 - 0.068) = 0.073$$
$$Odds_{post\text{-}test} = Odds_{pre\text{-}test} * likelihood\ ratio = 0.073 * 4.13 = 0.301$$
$$Probability_{post\text{-}test} = Odds_{post\text{-}test}\ /\ (\ Odds_{post\text{-}test} + 1) = 0.301\ /\ (0.301 + 1) = 0.232$$

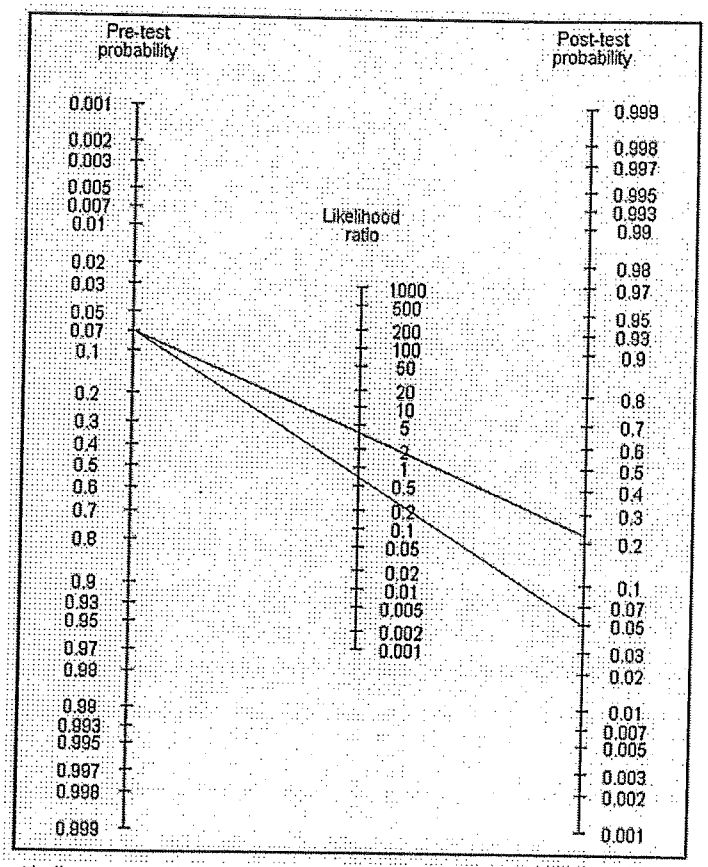
and likewise, if the Mallampati test was negative:

$$Probability_{pre\text{-}test} = Prevalence = 0.068$$
$$Odds_{pre\text{-}test} = Prevalence\ /\ (1 - Prevalence) = 0.068\ /\ (1 - 0.068) = 0.073$$
$$Odds_{post\text{-}test} = Odds_{pre\text{-}test} * likelihood\ ratio = 0.073 * 0.70 = 0.051$$
$$Probability_{post\text{-}test} = Odds_{post\text{-}test}\ /\ (\ Odds_{post\text{-}test} + 1) = 0.051/\ (0.051 + 1) = 0.049$$

Despite the simple maths it may still be a cumbersome task to convert odds into probabilities.

The Fagan nomogram[132] is a graphical tool for estimating how much the result of a diagnostic test changes the probability that a patient has a DTI.

Figure 7. Fagan's nomogram for calculating post-test probabilities



The lines represent the relations between the pre-test probability, the likelihood ratios of a positive and negative Mallampati test and the post-test probabilities.

You draw a line connecting the pre-test probability and the likelihood ratio and extend the line until it intersects with the post-test probability. The point of intersection is the new estimate of the probability that your patient is difficult to tracheal intubate.

Appendix II: Methods of multiple imputation.

As an alternative to sensitivity analysis, the "multiple imputation" method (MI) for handling missing data was performed. The goal is to reduce analytical bias and increase data quality of treatment. In multiple imputation, missing values for any variable are predicted using existing values from other variables. The predicted values, called "imputes", are substituted for the missi values, resulting in a full data set called an "imputed data set." This process is performed multipl times, producing multiple imputed data sets (hence the term "multiple imputation") avoiding the illusion created from single imputation that the imputed data come with the same certainty as th non-imputed data. Standard statistical analysis is carried out on each imputed data set, producing multiple analysis results. These analysis results are then combined to produce one overall analysis[104;105;133]. The process for "multiple imputation" is divided into three steps:

1. Construction of imputed data sets.

In order to generate imputations for the missing values, we imposed a probability model on the covariates recorded in the DAD (observed and missing values). In a random order (Markov Chain Monte Carlo simulation) the missing data were imputed from equally likely conditioned simulated distributions. Based on Rubin's formula for the calculation of the MI efficiency, where γ being

$$(1+\frac{\gamma}{m})^{-1}$$

the fraction of missingness and m the number of imputations, m=10 was calculated to reach 99 % efficiency[104;133].

2. Analysis of the imputed data sets. Ten complete datasets were analyzed as for the original dataset with list-wise deletion patients with missing data (a complete case analysis).

3. Pooling of analytical results. After completion the analysis of each imputed dataset, an aggregated estimate was calculated, based on an average of estimates from each imputed data set. There are well defined methods for weighting of estimates and for calculation of their corresponding confidence intervals[133].

From each analysis, one must first calculate the estimates and standard errors. If $\hat{Q}_j$ is an estimate of a scalar quantity of interest (e.g. a regression coefficient) obtained from data set *j* (*j*=1, 2,...,*m*) and U_j is the standard error associated with $\hat{Q}_j$. The overall estimate is the average of the individual estimates:

$$\overline{Q} = \frac{1}{m}\sum_{j=1}^{m}\hat{Q}_j$$

For the overall standard error, one must first calculate the within-imputation variance:

$$\overline{U} = \frac{1}{m}\sum_{j=1}^{m}U_j$$

and the between-imputation variance:

$$B = \frac{1}{m-1}\sum_{j=1}^{m}(\hat{Q}_j - \overline{Q})^2$$

The total variance is then given by:

$$T = \overline{U} + \left(1 + \frac{1}{m}\right)B$$

The overall standard error is the square root of *T*.

Appendix III: Establishing multivariate logistic regression models

In study I – III we performed logistic regression analyses to evaluate the associations between the predefined covariates and a DTI. The following data were obtained from the database: intubation score, age, sex, weight, height, BMI, classification of American Society of Anaesthesiologists physical status, the modified Mallampati-score, a history of previous difficult intubation, priority of surgery, time of surgery, and the use of NMBA. The stratification of the specific covariates may differ between the studies. Our assessments underwent following steps:

Univariate logistic regression was performed for all specified covariates. A p-value < 0.05 was considered as significant. Odds ratios were reported with 95 % confidence interval.

Multivariate logistic regression analysis was performed including all significant covariates from the univariate analyses. Backward stepwise regression was performed to identify a final model. A p-value < 0.05 was significant. Odds ratios were reported with their 95 % confidence interval.

Interactions of the first order between the primary covariate of the specific study and all the other covariates from the final multivariate model were explored. In a multivariate logistic regression it is assumed that the effect of a covariate is independent of the other covariates on the outcome measure. If two covariates have an effect upon one another on the outcome, the covariates interact.

Model control was performed with the Hosmer and Lemeshow goodness-of-fit test. In the model it is assumed that continuous covariates are linear associated to DTI. This assumption of linearity was tested for these covariates by testing whether replacing the specific covariate with square value of the covariate (e.g. Age replaced with Age * Age) resulted in any model improvement.

Appendix IV: Danish anaesthesia departments contributing patient records to DAD version 2

Department of Anaesthesia and Surgery, Abdominal Center, Copenhagen University Hospital, Rigshospitalet, Copenhagen.

Department of Anaesthesia and Surgery, Head and Orto Center, Copenhagen University Hospital, Rigshospitalet, Copenhagen.

Department of Anaesthesia and Surgery, Juliane Marie Center, Copenhagen University Hospital, Rigshospitalet, Copenhagen.

Department of Anaesthesia and Surgery, Neuro Center, Copenhagen University Hospital, Rigshospitalet, Copenhagen.

Department of Anaesthesia and Surgery, Bispebjerg Hospital, Copenhagen University Hospital, Copenhagen.

Department of Anaesthesiology, Hvidovre, Hospital, Copenhagen University Hospital, Hvidovre.

Department of Anaesthesia and Surgery, Amager Hospital, Copenhagen University Hospital, Copenhagen.

Department of Anaesthesia and Intensive Care, Frederiksberg Hospital, Copenhagen University Hospital, Frederiksberg.

Department of Anaesthesia and Surgery, Glostrup Hospital, Copenhagen University Hospital, Glostrup.

Department of Anaesthesia and Intensive Care, Herlev Hospital, Copenhagen University Hospital, Herlev.

Department of Anaesthesiology, Næstved Hospital, Næstved.

Department of Anaesthesiology, Nykøbing Falster Hospital, Nykøbing.

Department of Anaesthesiology, Bornholm's Hospital, Rønne.

Department of Anaesthesiology, Horsens Hospital, Horsens.

Department of Anaesthesiology, Vejle Hospital, Vejle.

Department of Anaesthesiology, Kolding Hospital, Kolding.

Department of Anaesthesiology, Brædstrup Hospital, Brædstrup.

Department of Anaesthesiology, Regionshospital Holstebro, Holstebro.

Department of Anaesthesiology, Regionshospital Herning, Herning.

Department of Anaesthesiology, Regionshospital Silkeborg, Silkeborg.

Department of Anaesthesiology, Århus Sygehus, Århus University Hospital, Århus.

Department of Anaesthesiology, Regionshospital Randers, Randers.

Department of Anaesthesiology, Odder of Århus Hospital, Odder.

Department of Anaesthesiology, Skejby Hospital, Århus University Hospital, Århus.

Department of Anaesthesiology, Thy-Mors Hospital, Thisted.

References

Reference List

1. Braz LG, Modolo NS, do NP, Jr., Bruschi BA, Castiglia YM, Ganem EM, de Carvalho LR, Braz JR: Perioperative cardiac arrest: a study of 53,718 anaesthetics over 9 yr from a Brazilian teaching hospital. Br.J.Anaesth. 2006; 96: 569-75

2. Braz LG, Braz DG, da Cruz DS, Fernandes LA, Modolo NS, Braz JR: Mortality in anesthesia: a systematic review. Clinics.(Sao Paulo) 2009; 64: 999-1006

3. Cheney FW, Posner KL, Lee LA, Caplan RA, Domino KB: Trends in anesthesia-related death and brain damage: A closed claims analysis. Anesthesiology 2006; 105: 1081-6

4. Cooper GM, McClure JH: Anaesthesia chapter from Saving mothers' lives; reviewing maternal deaths to make pregnancy safer. Br.J.Anaesth. 2008; 100: 17-22

5. Cooper JB, Gaba D: No myth: anaesthesia is a model for addressing patient safety. Anesthesiology 2002; 97: 1335-7

6. Gaba DM: Anaesthesiology as a model for patient safety in health care. BMJ 2000; 320: 785-8

7. Hove LD, Steinmetz J, Christoffersen JK, Moller A, Nielsen J, Schmidt H: Analysis of deaths related to anaesthesia in the period 1996-2004 from closed claims registered by the Danish Patient Insurance Association. Anesthesiology 2007; 106: 675-80

8. Kawashima Y, Takahashi S, Suzuki M, Morita K, Irita K, Iwao Y, Seo N, Tsuzaki K, Dohi S, Kobayashi T, Goto Y, Suzuki G, Fujii A, Suzuki H, Yokoyama K, Kugimiya T: Anesthesia-related mortality and morbidity over a 5-year period in 2,363,038 patients in Japan. Acta Anaesthesiol.Scand. 2003; 47: 809-17

9. Keenan RL, Boyan CP: Decreasing frequency of anesthetic cardiac arrests. J.Clin.Anesth. 1991; 3: 354-7

10. Lienhart A, Auroy Y, Pequignot F, Benhamou D, Warszawski J, Bovet M, Jougla E: Survey of anesthesia-related mortality in France. Anesthesiology 2006; 105: 1087-97

11. Morgan CA, Webb RK, Cockings J, Williamson JA: The Australian Incident Monitoring Study. Cardiac arrest--an analysis of 2000 incident reports. Anaesth.Intensive Care 1993; 21: 626-37

12. Rosenstock C, Moller J, Hauberg A: Complaints related to respiratory events in anaesthesia and intensive care medicine from 1994 to 1998 in Denmark. Acta Anaesthesiol.Scand. 2001; 45: 53-8

13. Tikkanen J, Hovi-Viander M: Death associated with anaesthesia and surgery in Finland in 1986 compared to 1975. Acta Anaesthesiol.Scand. 1995; 39: 262-7

14. Charuluxananan S, Chinachoti T, Pulnitiporn A, Klanarong S, Rodanant O, Tanudsintum S: The Thai Anaesthesia Incidents Study (THAI Study) of perioperative death: analysis of risk factors. J.Med.Assoc.Thai. 2005; 88 Suppl 7: S30-S40

15. Domino KB, Posner KL, Caplan RA, Cheney FW: Airway injury during anesthesia: a closed claims analysis. Anesthesiology 1999; 91: 1703-11

16. Peterson GN, Domino KB, Caplan RA, Posner KL, Lee LA, Cheney FW: Management of the difficult airway: a closed claims analysis. Anesthesiology 2005; 103: 33-9

17. Arbous MS, Grobbee DE, van Kleef JW, de Lange JJ, Spoormans HH, Touw P, Werner FM, Meursing AE: Mortality associated with anaesthesia : a qualitative analysis to identify risk factors. Anaesthesia 2001; 56: 1141-53

18. Tiret L, Desmonts JM, Hatton F, Vourc'h G: Complications associated with anaesthesia --a prospective survey in France. Can.Anaesth.Soc.J. 1986; 33: 336-44

19. Practice guidelines for management of the difficult airway: an updated report by the American Society of Anaesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology 2003; 98: 1269-77

20. Kheterpal S, Han R, Tremper KK, Shanks A, Tait AR, O'Reilly M, Ludwig TA: Incidence and predictors of difficult and impossible mask ventilation. Anesthesiology 2006; 105: 885-91

21. Kheterpal S, Martin L, Shanks AM, Tremper KK: Prediction and outcomes of impossible mask ventilation: a review of 50,000 anesthetics. Anesthesiology 2009; 110: 891-7

22. Langeron O, Masso E, Huraux C, Guggiari M, Bianchi A, Coriat P, Riou B: Prediction of difficult mask ventilation. Anesthesiology 2000; 92: 1229-36

23. Yildiz TS, Solak M, Toker K: The incidence and risk factors of difficult mask ventilation. J.Anesth. 2005; 19: 7-11

24. Han R, Tremper KK, Kheterpal S, O'Reilly M: Grading scale for mask ventilation. Anesthesiology 2004; 101: 267

25. Drolet P: Management of the anticipated difficult airway--a systematic approach: continuing Professional Development. Can.J.Anaesth. 2009; 56: 683-701

26. Wetterslev, J, Lundstrøm, L. H., Ørding, H, Hjortsøe, H, and Møller, A. M. Dansk Anæstesi Database Årsrapport 2006. 2007.

27. Ali Z, Bithal PK, Prabhakar H, Rath GP, Dash HH: An assessment of the predictors of difficult intubation in patients with acromegaly. J.Clin.Neurosci. 2009; 16: 1043-5

28. Allahyary E, Ghaemei SR, Azemati S: Comparison of Six Methods for Predicting Difficult Intubation in Obstetric Patients. Iranian Red Crescent Medical Journal 2008; 10: 194-201

29. Butler PJ, Dhara SS: Prediction of difficult laryngoscopy: an assessment of the thyromental distance and Mallampati predictive tests. Anaesth.Intensive Care 1992; 20: 139-42

30. Charuluxananan S, Suraseranivongse S, Punjasawadwong Y, Somboonviboon W, Nipitsukarn T, Sothikarnmanee T, Vasinanukorn M, Werawatganon T, Tanudsintum S, Lekprasert V, Hintong T: The Thai Anaesthesia Incidents Study (THAI Study) of anesthetic outcomes: I description of methods and populations. Journal of the Medical Association of Thailand.88(SUPPL.7) 2005; S1-S13

31. Constantikes J: Predicting difficult tracheal intubation using a modified Mallampati sign: a pilot study report. CRNA. 1993; 4: 16-20

32. Domi R: A comparison of Wilson sum score and combination Mallampati, tiromental and sternomental distances for predicting difficult intubation. Macedonian Journal of Medical Sciences. 2009; 141-4

33. Eberhart LH, Arndt C, Cierpka T, Schwanekamp J, Wulf H, Putzke C: The reliability and validity of the upper lip bite test compared with the Mallampati classification to predict difficult laryngoscopy: an external prospective evaluation. Anesth.Analg. 2005; 101: 284-9

34. Ezri T, Warters RD, Szmuk P, Saad-Eddin H, Geva D, Katz J, Hagberg C: The incidence of class "zero" airway and the impact of Mallampati-score, age, sex, and body mass index on prediction of laryngoscopy grade. Anesth.Analg. 2001; 93: 1073-5

35. Ezri T, Weisenberg M, Khazin V, Zabeeda D, Sasson L, Shachner A, Medalion B: Difficult laryngoscopy: incidence and predictors in patients undergoing coronary artery bypass surgery versus general surgery patients. J.Cardiothorac.Vasc.Anesth. 2003; 17: 321-4

36. Ezri T, Medalion B, Weisenberg M, Szmuk P, Warters RD, Charuzi I: Increased body mass index per se is not a predictor of difficult laryngoscopy. Can.J.Anaesth. 2003; 50: 179-83

37. Ezri T, Gewurtz G, Sessler DI, Medalion B, Szmuk P, Hagberg C, Susmallian S: Prediction of difficult laryngoscopy in obese patients by ultrasound quantification of anterior neck soft tissue. Anaesthesia 2003; 58: 1111-4

38. Frerk CM: Predicting difficult intubation. Anaesthesia 1991; 46: 1005-8

39. Hester CE, Dietrich SA, White SW, Secrest JA, Lindgren KR, Smith T: A comparison of preoperative airway assessment techniques: the modified Mallampati and the upper lip bite test. AANA J. 2007; 75: 177-82

40. Honarmand A, Safavi MR: Prediction of difficult laryngoscopy in obstetric patients scheduled for Caesarean delivery. Eur.J.Anaesthesiol. 2008; 25: 714-20

41. Huh J, Shin HY, Kim SH, Yoon TK, Kim DK: Diagnostic predictor of difficult laryngoscopy: the hyomental distance ratio. Anesth.Analg. 2009; 108: 544-8

42. Iohom G, Ronayne M, Cunningham AJ: Prediction of difficult tracheal intubation. Eur.J.Anaesthesiol. 2003; 20: 31-6

43. Ita CE, Eshiet AI, Akpan SG: Recognition of the difficult airway in normal Nigerian adults (a prospective study). West Afr.J.Med. 1994; 13: 102-4

44. Kamalipour H, Bagheri M, Kamali K, Taleie A, Yarmohammadi H: Lateral neck radiography for prediction of difficult orotracheal intubation. Eur.J.Anaesthesiol. 2005; 22: 689-93

45. Kaul TK, Deepika, Singh A, Bansal M: Prediction of difficult intubation - Analysis in 500 adult patients. Journal of Anaesthesiology Clinical Pharmacology.14(4) 1998; 323-8

46. Khan ZH, Kashfi A, Ebrahimkhani E: A comparison of the upper lip bite test (a simple new technique) with modified Mallampati classification in predicting difficulty in endotracheal intubation: a prospective blinded study. Anaesthesia and Analgesia 2003; 96: 595-9

47. Komatsu R, Sengupta P, Wadhwa A, Akca O, Sessler DI, Ezri T, Lenhardt R: Ultrasound quantification of anterior soft tissue thickness fails to predict difficult laryngoscopy in obese patients. Anaesth.Intensive Care 2007; 35: 32-7

48. Krishna HM, Agarwal M, Dali JS, Rampal P, Dua CK: Prediction of difficult laryngoscopy in indian population: Role of ratio of patient's height to thyromental distance. Journal of Anaesthesiology Clinical Pharmacology.21; 2005; 257-60

49. Krobbuaban B, Diregpoke S, Kumkeaw S, Tanomsat M: The predictive value of the height ratio and thyromental distance: four predictive tests for difficult laryngoscopy. Anesth.Analg. 2005; 101: 1542-5

50. Mashour GA, Sandberg WS: Craniocervical extension improves the specificity and predictive value of the Mallampati airway evaluation. Anesth.Analg. 2006; 103: 1256-9

51. Mashour GA, Kheterpal S, Vanaharam V, Shanks A, Wang LY, Sandberg WS, Tremper KK: The extended Mallampati-score and a diagnosis of diabetes mellitus are predictors of difficult laryngoscopy in the morbidly obese. Anesth.Analg. 2008; 107: 1919-23

52. Merah NA, Foulkes-Crabbe DJ, Kushimo OT, Ajayi PA: Prediction of difficult laryngoscopy in a population of Nigerian obstetric patients. West Afr.J.Med. 2004; 23: 38-41

53. Merah NA, Wong DT, Ffoulkes-Crabbe DJ, Kushimo OT, Bode CO: Modified Mallampati test, thyromental distance and inter-incisor gap are the best predictors of difficult laryngoscopy in West Africans. Can.J.Anaesth. 2005; 52: 291-6

54. Noorizad S, Mahdian M: Mallampati and thyromental tests to predict difficult intubation. Journal of Medical Sciences. 2006; 6: 169-72

55. Samra SK, Schork MA, Guinto FC, Jr.: A study of radiologic imaging techniques and airway grading to predict a difficult endotracheal intubation. J.Clin.Anesth. 1995; 7: 373-9

56. Schmitt H, Buchfelder M, Radespiel-Troger M, Fahlbusch R: Difficult intubation in acromegalic patients: incidence and predictability. Anesthesiology 2000; 93: 110-4

57. Siddiqi R, Kazi WA: Predicting difficult intubation--a comparison between Mallampati classification and Wilson risk-sum. J.Coll.Physicians Surg.Pak. 2005; 15: 253-6

58. Singh R, Jain A, Mishra S, Kohli P: Clinical evaluation for predicting difficult laryngoscopy in obstetric patients. Journal of Anaesthesiology Clinical Pharmacology. 2009; 25: 38-42

59. Vani V, Kamath SK, Naik LD: The palm print as a sensitive predictor of difficult laryngoscopy in diabetics: a comparison with other airway evaluation indices. J.Postgrad.Med. 2000; 46: 75-9

60. Wong SH, Hung CT: Prevalence and prediction of difficult intubation in Chinese women. Anaesth.Intensive Care 1999; 27: 49-52

61. Yamamoto K, Tsubokawa T, Shibata K, Ohmura S, Nitta S, Kobayashi T: Predicting difficult intubation with indirect laryngoscopy. Anesthesiology.1997; 86: 316-21

62. Yeo SW, Chong JL, Thomas E: Difficult intubation: a prospective study. Singapore Med.J. 1992; 33: 362-4

63. Samsoon GL, Young JR: Difficult tracheal intubation: a retrospective study. Anaesthesia 1987; 42: 487-90

64. Yentis SM, Lee DJ: Evaluation of an improved scoring system for the grading of direct laryngoscopy. Anaesthesia 1998; 53: 1041-4

65. Adnet F, Racine SX, Borron SW, Clemessy JL, Fournier JL, Lapostolle F, Cupa M: A survey of tracheal intubation difficulty in the operating room: a prospective observational study. Acta Anaesthesiol.Scand. 2001; 45: 327-32

66. Arne J, Descoins P, Fusciardi J, Ingrand P, Ferrier B, Boudigues D, Aries J: Preoperative assessment for difficult intubation in general and ENT surgery: predictive value of a clinical multivariate risk index. Br.J.Anaesth. 1998; 80: 140-6

67. Ayuso MA, Sala X, Luis M, Carbo JM: Predicting difficult orotracheal intubation in pharyngo-laryngeal diseas preliminary results of a composite index. Can.J.Anaesth. 2003; 50: 81-5

68. Bouaggad A, Nejmi SE, Bouderka MA, Abbassi O: Prediction of difficult tracheal intubation in thyroid surgery Anesth.Analg. 2004; 99: 603-6

69. Brodsky JB, Lemmens HJ, Brock-Utne JG, Vierra M, Saidman LJ: Morbid obesity and tracheal intubation. Anesth.Analg. 2002; 94: 732-6

70. Cattano D, Panicucci E, Paolicchi A, Forfori F, Giunta F, Hagberg C: Risk factors assessment of the difficult airway: An Italian survey of 1956 patients. Anaesthesia and Analgesia.99(6)()(pp 1774-1779), 2004.Date of Publication: Dec 2004. 2004; 1774-9

71. Gercek A, Lim S, Isler FB, Eti Z, Gogus FY: The prediction of difficult intubation with bedside scoring systems. Marmara Medical Journal. 2003; 16: 16-9

72. Gupta S, Pareek S, Dulara SC: Comparison of two methods for predicting difficult intubation in obstetric patients. Middle East J.Anesthesiol. 2003; 17: 275-85

73. Juvin P, Lavaut E, Dupont H, Lefevre P, Demetriou M, Dumoulin JL, Desmonts JM: Difficult tracheal intubation is more common in obese than in lean patients. Anesth.Analg. 2003; 97: 595-600

74. L'hermite J, Nouvellon E, Cuvillon P, Fabbro-Peray P, Langeron O, Ripart J: The Simplified Predictive Intubation Difficulty Score: a new weighted score for difficult airway assessment. Eur.J.Anaesthesiol. 2009; 26: 1003-9

75. Mashour GA, Stallmer ML, Kheterpal S, Shanks A: Predictors of difficult intubation in patients with cervical spine limitations. J.Neurosurg.Anesthesiol. 2008; 20: 110-5

76. Rocke DA, Murray WB, Rout CC, Gouws E: Relative risk analysis of factors associated with difficult intubation in obstetric anesthesia. Anesthesiology 1992; 77: 67-73

77. Savva D: Prediction of difficult tracheal intubation. Br.J.Anaesth. 1994; 73: 149-53

78. Topcu I, Ovali GY, Yentur EA, Kefi A, Tuncyurek O, Pabuscu Y: Clinical and radiologic evaluations for predicting difficult tracheal intubation. [Italian, English]. Acta Anaesthesiologica Italica / Anaesthesia and Intensive Care in Italy. 2006; 57: 285-300

79. Torres K, Patel AA, Stylinski K, Blonski M, Torres A, Staskiewicz G, Maciejewski R, Wojtaszek M: The body constitution of patients and intubation scales as predictors of difficult intubation considered in relation to the experience of the intubator. Folia Morphol.(Warsz.) 2008; 67: 171-4

80. Tuzuner-Oncul AM, Kucukyavuz Z: Prevalence and prediction of difficult intubation in maxillofacial surgery patients. J.Oral Maxillofac.Surg. 2008; 66: 1652-8

81. Yildiz TS, Korkmaz F, Solak M, Toker K, Erciyes N, Bayrak F, Ganidagli S, Tekin M, Kizilkaya M, Karsli B, Turan A, Ozcan U: Prediction of difficult tracheal intubation in Turkish patients: a multi-center methodological study. Eur.J.Anaesthesiol. 2007; 24: 1034-40

82. Viby-Mogensen J, Engbaek J, Eriksson LI, Gramstad L, Jensen E, Jensen FS, Koscielniak-Nielsen Z, Skovgaard LT, Ostergaard D: Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents. Acta Anaesthesiol.Scand. 1996; 40: 59-74

83. Practice guidelines for management of the difficult airway. A report by the American Society of Anaesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology 1993; 78: 597-602

84. Adnet F, Borron SW, Racine SX, Clemessy JL, Fournier JL, Plaisance P, Lapandry C: The intubation difficulty scale (IDS): proposal and evaluation of a new score characterizing the complexity of endotracheal intubation. Anesthesiology 1997; 87: 1290-7

85. Shiga T, Wajima Z, Inoue T, Sakamoto A: Predicting difficult intubation in apparently normal patients: a meta-analysis of bedside screening test performance. Anesthesiology 2005; 103: 429-37

86. Gluud C, Brok J, Gong Y, Koretz RL: Hepatology may have problems with putative surrogate outcome measures. J.Hepatol. 2007; 46: 734-42

87. Petrini F, Accorsi A, Adrario E, Agro F, Amicucci G, Antonelli M, Azzeri F, Baroncini S, Bettelli G, Cafaggi C, Cattano D, Chinelli E, Corbanese U, Corso R, Della PA, Di FA, Facco E, Favaro R, Favero R, Frova G, Giunta F, Giurati G, Giusti F, Guarino A, Iannuzzi E, Ivani G, Mazzon D, Menarini M, Merli G, Mondello E, Muttini S, Nardi G, Pigna A, Pittoni G, Ripamonti D, Rosa G, Rosi R, Salvo I, Sarti A, Serafini G, Servadio G, Sgandurra A, Sorbello M, Tana F, Tufano R, Vesconi S, Villani A, Zauli M: Recommendations for airway control and difficult airway management. Minerva Anestesiol. 2005; 71: 617-57

88. Crosby ET, Cooper RM, Douglas MJ, Doyle DJ, Hung OR, Labrecque P, Muir H, Murphy MF, Preston RP, Rose DK, Roy L: The unanticipated difficult airway with recommendations for management. Can.J.Anaesth. 1998; 45: 757-76

89. Boisson-Bertrand D, Bourgain JL, Camboulives J, Crinquette V, Cros AM, Dubreuil M, Eurin B, Haberer JP, Pottecher T, Thorin D, Ravussin P, Riou B: [Difficult intubation. French Society of Anaesthesia and Intensive Care. A collective expertise]. Ann.Fr.Anesth.Reanim. 1996; 15: 207-14

90. Henderson JJ, Popat MT, Latto IP, Pearce AC: Difficult Airway Society guidelines for management of the unanticipated difficult intubation. Anaesthesia 2004; 59: 675-94

91. Rosenstock C, Ostergaard D, Kristensen MS, Lippert A, Ruhnau B, Rasmussen LS: Residents lack knowledge and practical skills in handling the difficult airway. Acta Anaesthesiol.Scand. 2004; 48: 1014-8

92. Rosenstock C, Hansen EG, Kristensen MS, Rasmussen LS, Skak C, Ostergaard D: Qualitative analysis of unanticipated difficult airway management. Acta Anaesthesiol.Scand. 2006; 50: 290-7

93. el-Ganzouri AR, McCarthy RJ, Tuman KJ, Tanck EN, Ivankovich AD: Preoperative airway assessment: predictive value of a multivariate risk index. Anesth.Analg. 1996; 82: 1197-204

94. Naguib M, Malabarey T, AlSatli RA, Al DS, Samarkandi AH: Predictive models for difficult laryngoscopy and intubation. A clinical, radiologic and three-dimensional computer imaging study. Can.J.Anaesth. 1999; 46: 748-59

95. Tse JC, Rimm EB, Hussain A: Predicting difficult endotracheal intubation in surgical patients scheduled for general anesthesia: a prospective blind study. Anesth.Analg. 1995; 81: 254-8

96. Wilson ME, Spiegelhalter D, Robertson JA, Lesser P: Predicting difficult intubation. Br.J.Anaesth. 1988; 61: 211-6

97. Lee A, Fan LT, Gin T, Karmakar MK, Ngan Kee WD: A systematic review (meta-analysis) of the accuracy of the Mallampati tests to predict the difficult airway. Anesth.Analg. 2006; 102: 1867-78

98. Adnet F, Baillard C, Borron SW, Denantes C, Lefebvre L, Galinski M, Martinez C, Cupa M, Lapostolle F: Randomized study comparing the "sniffing position" with simple head extension for laryngoscopic view in elective surgery patients. Anesthesiology 2001; 95: 836-41

99. Collins JS, Lemmens HJ, Brodsky JB, Brock-Utne JG, Levitan RM: Laryngoscopy and morbid obesity: a comparison of the "sniff" and "ramped" positions. Obes.Surg. 2004; 14: 1171-5

100. Combes X, Andriamifidy L, Dufresne E, Suen P, Sauvat S, Scherrer E, Feiss P, Marty J, Duvaldestin P: Comparison of two induction regimens using or not using muscle relaxant: impact on postoperative upp airway discomfort. Br.J.Anaesth. 2007; 99: 276-81

101. Perry JJ, Lee JS, Sillberg VA, Wells GA: Rocuronium versus succinylcholine for rapid sequence induction intubation. Cochrane.Database.Syst.Rev. 2008; CD002788

102. Karkouti K, Rose DK, Ferris LE, Wigglesworth DF, Meisami-Fard T, Lee H: Inter-observer reliability of ten t used for predicting difficult tracheal intubation. Can.J.Anaesth. 1996; 43: 554-9

103. Lundstrom LH, Moller AM, Rosenstock C, Astrup G, Gatke MR, Wetterslev J: A documented previous diffi tracheal intubation as a prognostic test for a subsequent difficult tracheal intubation in adults. Anaesthes 2009; 64: 1081-8

104. Schafer JL: Multiple imputation: a primer. Stat.Methods Med.Res. 1999; 8: 3-15

105. Schafer JL, Graham JW: Missing data: our view of the state of the art. Psychol.Methods 2002; 7: 147-77

106. Berthoud MC, Peacock JE, Reilly CS: Effectiveness of preoxygenation in morbidly obese patients. Br.J.Anae 1991; 67: 464-6

107. Bagust A, Walley T: An alternative to body mass index for standardizing body weight for stature. QJM. 200(93: 589-96

108. Riess ML, Connolly LA, Woehlck HJ: Body mass index: an illogical correlate of obesity. Anesthesiology 2009; 111: 920-1

109. Lundstrøm LH, Møller AM, Wetterslev J: Body mass index: an illogical correlate of obesity, reply. Anesthesiology 2009; 111: 921

110. Alcock R, Peachey T, Lynch M, McEwan T: Comparison of alfentanil with suxamethonium in facilitating nasotracheal intubation in day-case anaesthesia. Br.J.Anaesth. 1993; 70: 34-7

111. Alexander R, Olufolabi AJ, Booth J, El-Moalem HE, Glass PS: Dosing study of remifentanil and propofol for tracheal intubation without the use of muscle relaxants. Anaesthesia 1999; 54: 1037-40

112. Bouvet L, Stoian A, Jacquot-Laperriere S, Allaouchiche B, Chassard D, Boselli E: Laryngeal injuries and intubating conditions with or without muscular relaxation: an equivalence study. Can.J.Anaesth. 2008; 55: 674-84

113. Harsten A, Gillberg L: Intubating conditions provided by propofol and alfentanil--acceptable, but not ideal. Acta Anaesthesiol.Scand. 1997; 41: 985-7

114. Lieutaud T, Billard V, Khalaf H, Debaene B: Muscle relaxation and increasing doses of propofol improve intubating conditions. Can.J.Anaesth. 2003; 50: 121-6

115. McNeil IA, Culbert B, Russell I: Comparison of intubating conditions following propofol and succinylcholine with propofol and remifentanil 2 micrograms kg-1 or 4 micrograms kg-1. Br.J.Anaesth. 2000; 85: 623-5

116. Mencke T, Echternach M, Kleinschmidt S, Lux P, Barth V, Plinkert PK, Fuchs-Buder T: Laryngeal morbidity and quality of tracheal intubation: a randomized controlled trial. Anesthesiology 2003; 98: 1049-56

117. Naguib M, Samarkandi AH, El-Din ME, Abdullah K, Khaled M, Alharby SW: The dose of succinylcholine required for excellent endotracheal intubating conditions. Anesth.Analg. 2006; 102: 151-5

118. Scheller MS, Zornow MH, Saidman LJ: Tracheal intubation without the use of muscle relaxants: a technique using propofol and varying doses of alfentanil. Anesth.Analg. 1992; 75: 788-93

119. Stevens JB, Vescovo MV, Harris KC, Walker SC, Hickey R: Tracheal intubation using alfentanil and no muscle relaxant: is the choice of hypnotic important? Anesth.Analg. 1997; 84: 1222-6

120. DerSimonian R, Laird N: Meta-analysis in clinical trials. Control Clin.Trials 1986; 7: 177-88

121. Moses LE, Shapiro D, Littenberg B: Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. Stat.Med. 1993; 12: 1293-316

122. Jaeschke R, Guyatt GH, Sackett DL: Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. JAMA 1994; 271: 703-7

123. Higgins JP, Thompson SG, Deeks JJ, Altman DG: Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-60

124. Egger M, Davey SG, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-34

125. Lundstrom LH, Moller AM, Rosenstock C, Astrup G, Gatke MR, Wetterslev J: Avoidance of neuromuscular blocking agents may increase the risk of difficult tracheal intubation: a cohort study of 103,812 consecutive adult patients recorded in the Danish Anaesthesia Database. Br.J.Anaesth. 2009; 103: 283-90

126. Rucker G, Schwarzer G, Carpenter JR, Schumacher M: Undue reliance on I(2) in assessing heterogeneity may mislead. BMC.Med.Res.Methodol. 2008; 8: 79

127. Higgins JP, Spiegelhalter DJ: Being sceptical about meta-analyses: a Bayesian perspective on magnesium trials in myocardial infarction. Int.J.Epidemiol. 2002; 31: 96-104

128. Li J, Zhang Q, Zhang M, Egger M: Intravenous magnesium for acute myocardial infarction. Cochrane.Database.Syst.Rev. 2007; CD002755

129. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, Petticrew M, Altman DG: Evaluating non-randomised intervention studies. Health Technol.Assess. 2003; 7: iii-173

130. Halkin A, Reichman J, Schwaber M, Paltiel O, Brezis M: Likelihood ratios: getting diagnostic testing into perspective. QJM. 1998; 91: 247-58

131. Deeks JJ, Altman DG: Diagnostic tests 4: likelihood ratios. BMJ 2004; 329: 168-9

132. Fagan TJ: Letter: Nomogram for Bayes theorem. N.Engl.J.Med. 1975; 293: 257

Anesthesiology 2009; 110:266–74

High Body Mass Index Is a Weak Predictor for Difficult and Failed Tracheal Intubation

A Cohort Study of 91,332 Consecutive Patients Scheduled for Direct Laryngoscopy Registered in the Danish Anesthesia Database

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Background: Previous studies have failed to detect high body mass index (BMI) as a risk factor for difficult tracheal intubation (DTI). BMI was investigated as a risk factor for DTI in patients planned for direct laryngoscopy.

Methods: A cohort of 91,332 consecutive patients planned for intubation by direct laryngoscopy was retrieved from the Danish Anesthesia Database. A four-point scale to grade the tracheal intubation was used. Age, sex, American Society of Anesthesiologists physical status classification, priority of surgery, history of previous DTI, modified Mallampati-score, use of neuromuscular blocker, and BMI were retrived. Logistic regression to assess whether BMI was associated with DTI was performed.

Results: The frequency of DTI was 5.2% (95% confidence interval [CI] 5.0–5.3). In multivariate analyses adjusted for other significant covariates, BMI of 35 or more was a risk for DTI with an odds ratio of 1.34 (95% CI 1.19–1.51, $P < 0.0001$). As a stand alone test, BMI of 35 or more predicted DTI with a sensitivity of 7.5% (95% CI 7.3–7.7%) and with a predictive value of a positive test of 6.4% (95% CI 6.3–6.6%). BMI as a continuous covariate was a risk for failed intubation with an odds ratio of 1.031 (95% CI 1.002–1.061, $P < 0.04$).

Conclusions: High BMI is a weak but statistically significant predictor of difficult and failed intubation and may be more appropriate than weight in multivariate models of prediction of DTI.

DIFFICULT tracheal intubation (DTI) is feared among anesthesiologists due to the increased risk of perioperative morbidity and mortality.[1–4] The ability to predict a DTI allows anesthesiologists to take precautions to reduce the risk.[5] Several studies have investigated the possible association between obesity and DTI, but their results are ambiguous. Some studies did not demonstrate obesity as an independent risk of DTI,[6–8] but others seemed to show that obese patients are at risk of DTI[9,13]. These studies may have failed to detect or reject obesity as a risk factor for DTI due to small patient numbers and subsequent lack of power. Obesity is a worldwide, constantly growing problem. It is therefore appropriate to evaluate whether obesity confers a risk of DTI and failed tracheal intubation (FTI).

There is a lack of consensus about how to measure obesity as a risk factor for DTI. Two studies used weight (kg),[9,13] and others used body mass index (BMI; $kg \cdot m^{-2}$).[7,8,10,12] The clinical cut-off value defining obesity by BMI has been applied from that used for other medical events and may not be appropriate for DTI. One study did not demonstrate that morbidly obese patients were more at risk of DTI than those with moderate obesity.[12] In contrast other studies have suggested that the risk of DTI increases with weight.[9,13] The aim of this study is to assess whether obesity measured by BMI is associated with DTI, independent of other risk factors registered in the Danish Anesthesia Database (DAD). We also wish to assess whether the risk of DTI is greater in patients with high BMI. We will evaluate the different levels of BMI used to categorize obesity. We will compare BMI and weight to decide if there are differences in their association with a DTI or FTI. We will evaluate the accuracy of obesity as a stand-alone clinical test to predict a DTI.

Materials and Methods

Fourteen Danish anesthesia departments in 2005 and 25 in 2006–07 prospectively and consecutively recorded patients undergoing surgery and anesthesia in the DAD. The DAD contains specific quantitative anesthetic and surgical indicators describing the perioperative period. This information is registered immediately after each anesthesia by the anesthesiologist. The departments (appendix I) were connected *via* the Internet to a central server.

The Danish Data Protection Agency, Copenhagen, Denmark (journal-number 750.16–5) approved the registration in the DAD. The Ethics Committees for Biomedical Research, Glostrup, Denmark (reference KA-06751),

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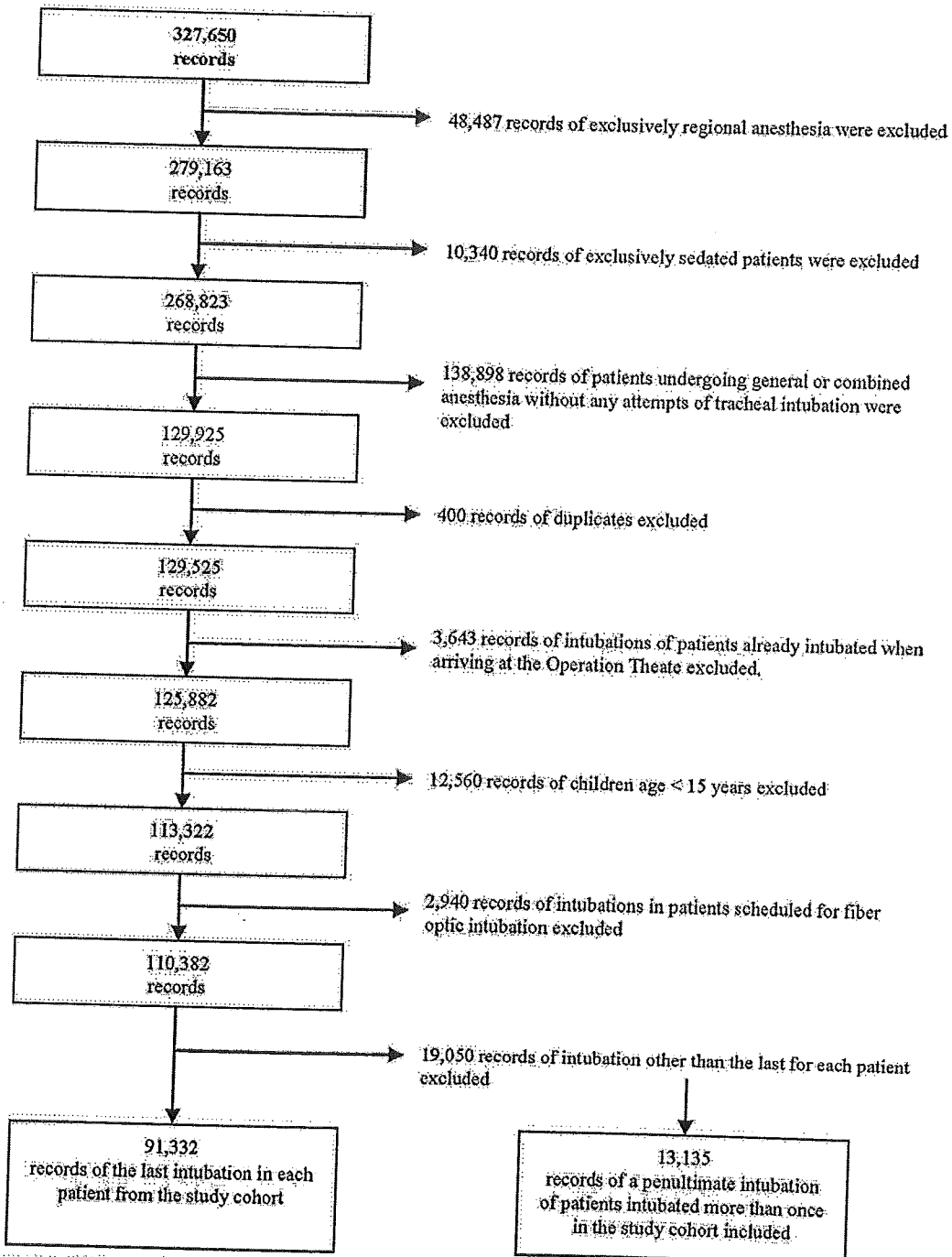

Fig. 1. A total of 327,650 records of patients undergoing anesthesia were identified in Danish Anesthesia Database. Excluding records of anesthesia other than patients undergoing general or combined anesthesia and primarily scheduled for tracheal intubation, the cohort included 129,925 records. Registered intubations were excluded as explained. The subgroup of 13,135 records representing the penultimate intubations of patients intubated more than once were merged to the corresponding last intubation for the specific patient, and hereby confirmed information according to the covariate previous difficult intubation was created. Thus, 78,162 patients were only intubated once, and 13,135 patients were intubated two or more times; information was missing for 35 patients.

and the Steering Committee of the DAD approved this study and provided access to the data.

We retrieved 129,925 records of tracheal intubations of patients undergoing general or combined anesthesia from January 1, 2005, to September 30, 2007, (fig. 1). We excluded patients aged less than 15 yr and those primarily scheduled for fiberoptic intubation. There were no records of the reason for these patients to be

Table 1. Danish Anesthesia Database Tracheal Intubation Score

All patients primarily attempted for tracheal intubation by direct laryngoscopy were scored as defined
1 Intubated by direct laryngoscope by the first anesthetist and in two attempts maximally
2 Intubated by direct laryngoscope by the first anesthetist but with more than two attempts or secondarily intubated by a supervising anesthetist
3 Intubated by another method than direct laryngoscopy
4 Intubation failed after multiple attempts; no tracheal tube was inserted

Difficult intubation was defined as an intubation score > 1.

allocated for fiberoptic intubation. Thus, these patients may be allocated for other reason than anticipated difficult tracheal intubation. We included 91,332 patients tracheally intubated 110,382 times. Only the last record of 13,135 patients scheduled for intubation by direct laryngoscopy more than once was included. The final cohort includes 91,332 patients, each represented by only one session of attempted tracheal intubation by direct laryngoscopy. Except for cardiothoracic surgery, all types of surgery are represented in the DAD.

There is no Danish recommendation for the evaluation and handling of the airway in patients undergoing tracheal intubation. The anesthesia departments may differ in their recommendations for the evaluation and handling of the airway.

There is no international consensus defining a difficult intubation. Difficult laryngoscopy is often used as a surrogate outcome for difficult intubation,[14] but others suggest a specific definition of DTI.[5,15] We registered an intubation score (DTI score, table 1) for all patients primarily attempted for tracheal intubated by direct laryngoscopy.

The DTI score, age, sex, priority of surgery, weight, height, American Society of Anesthesiologists physical status classification, modified Mallampati score,[16] use of neuromuscular blocking agents (NMBA), and history of previous difficult intubation (PDI) were used as covariates in the assessments.

Every patient is registered with a unique identifying number from the centralized civil register. This unique identifier contains information regarding the patient's sex and date of birth. This identifies each patient during the statistical analysis, allowing exclusion of duplicates and patients anesthetized and registered more than once during the observation period. A total of 13,135 patients were anesthetized more than once (fig. 1). For these patients, PDI was categorized as Yes or No on the basis of DTI score of the penultimate intubation. Patients anesthetized and registered only once, with absence of information of a possible PDI, were categorized as Unknown (lack of clinical information in contrary to statistical missing value). Priority of surgery was defined as nonscheduled if a patient was anesthetized without being planned for surgery the previous day. Height and weight were registered on the basis of preoperative measures at the surgical wards or as reported by the patients. If records of height or weight were omitted, they were categorized as a missing value. BMI was calculated as weight · height^{-2} (kg · m^{-2}). An automatic validation of weight and height is incorporated in the DAD. A warning appeared during registration if the calculated BMI exceeded 35 or was below 17, to emphasize that the weight and height entries should be reconsidered. We manually performed an additional validation before the statistical analysis, in which only height of 125–230 cm and height of 30–250 kg were accepted; otherwise, the registration was categorized as missing. If the Mallampati class was registered as unknown, the registration was categorized as a missing value. For the analyses, the Mallampati score was dichotomized by combining classes I with II and classes III with IV. The use of NMBA was categorized as no relaxation or relaxation. If relaxation was used, it was not possible to distinguish between relaxation used for intubation, during anesthesia or both. The DAD did not record the type of equipment used for intubation.

Statistical Analysis

We attempted a power and sample size calculation in the protocol.[17] With a type I error risk set to $\alpha = 0.05$, the type II error risk of $\beta = 0.10$, a relative risk increase of obesity of 0.30, a frequency of DTI of 0.058,[18] and a multivariate correlation coefficient, $R^2 = 0.917$, the number of patients needed was 25,618. R^2 was unknown and estimated from a linear regression of BMI dependent on height and weight. This assumption is restrictive as height and weight are closely associated; therefore, the true number of patients needed for investigation may be lower.

We performed univariate regression analyses to evaluate the associations between the covariates and DTI. In the primary analysis, weight and height were replaced by BMI. A subsequent multivariate logistic regression analysis was performed including all significant covariates from the univariate analyses. Backward stepwise regression was performed to identify a final model. Only interactions of the first order between BMI and all the other covariates were explored. Hereafter, BMI was categorized into six intervals, and a univariate logistic regression analysis was performed to determine if the risk of DTI increased with BMI. We also explored the combination of some of the intervals and the changing of their borders. After a final fitting of the categorized BMI, it was included in a new multivariate logistic regression analysis. A model control was performed. The receiver operating characteristic curve tested the final fitted model, and the area under the curve was estimated.

On the basis of the final model, we evaluated dichotomized BMI intervals as a stand-alone predictor of DTI.

Table 2. Characteristics of the Patients

	Difficult Intubation			
	Yes	No	Total	Missing of Total
All patients	4,704	86,593	91,297	35 (0.0%)
Covariates				
Sex				35 (0.0%)
Male	2,379 (50.6%)	36,611 (42.3%)	38,990	
Female	2,325 (49.4%)	49,982 (57.7%)	52,307	
Surgery priority				41 (0.0%)
Scheduled	3,582 (76.1%)	60,434 (69.8%)	64,016	
Nonscheduled	1,122 (23.9%)	26,153 (30.2%)	27,275	
Classification				1,516 (1.7%)
ASA 1	1,517 (32.6%)	34,612 (40.6%)	36,129	
ASA 2	2,167 (46.6%)	34,623 (40.7%)	36,790	
ASA 3	817 (17.6%)	13,848 (16.3%)	14,665	
ASA 4	128 (2.8%)	1,870 (2.2%)	1,998	
ASA 5	15 (0.3%)	161 (0.2%)	176	
ASA 6	3 (0.1%)	55 (0.1%)	58	
Mallampati score				9,932 (10.9%)
I	1,655 (39.9%)	48,541 (62.8%)	50,196	
II	1,559 (37.6%)	23,475 (30.4%)	25,034	
III	729 (17.6%)	4,609 (6.0%)	5,338	
IV	207 (5.0%)	625 (0.8%)	832	
Previous difficult intubation				35 (0.0%)
Yes	148 (3.1%)	437 (0.5%)	585	
Unknown	4,032 (85.7%)	74,130 (85.6%)	78,162	
No	524 (11.1%)	12,026 (13.9%)	12,550	
Neuromuscular blocking				36 (0.0%)
No relaxation	1,640 (34.9%)	22,428 (25.9%)	24,068	
Relaxation	3,064 (65.1%)	64,164 (74.1%)	67,228	
Age, mean	56.4	52.7		35 (0.0%)
Weight, mean	77.9	75.4		752 (0.8%)
Height, mean	171.7	171.0		1,489 (1.6%)
Body mass index, mean	26.3	25.6		1,561 (1.7%)

ASA = American Society of Anesthesiologists physical status classification.

The accuracy of the predictor was described by sensitivity, specificity, predictive value of a positive test, predictive value of a negative test, positive likelihood ratio, and negative likelihood ratio.

The prevalence and pattern of missing values among all covariates were described. Afterwards, multiple imputations for missing values were performed.[19] SPSS v. 15.0 and AMOS v. 7.0 (SPSS Inc., Chicago, IL) and NORM v 2.03 by Joseph L. Schafer, M.Sc., Ph.D. (Associate Professor, Department of Statistics and The Methodology Center, The Pennsylvania State University, University Park, Pennsylvania), were used for the analyses. The number of imputations ($m = 10$) was calculated to reach 99% efficiency.[20] Ten complete datasets were analyzed as described above, and the estimates were pooled for overall estimates.[20] A similar analysis was performed for the original dataset with listwise deletion patients with missing data—a complete case analysis. The pooled estimates and their corresponding complete case analysis estimates, including 95% confidence intervals (CI), were compared. If there were any noticeable differences between complete case analysis and analysis of the pooled estimates of the multiple imputations, both results are presented. Otherwise, only the pooled estimates of the multiple imputations are presented. $P < 0.05$ was regarded as statistically significant. This study has been presented according to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[21]

Results

The overall proportion of patients with DTI was 5.2% (95% CI 5.0–5.3). The proportion of patients with DTI in 2005, 2006, and 2007 were 5.8%, 4.9% and 5.1%, respectively. FTI occurred in 141 patients with a frequency of 0.15% (95% CI 0.13–0.18). The characteristics of the patients are displayed in table 2. In univariate analyses, the covariates American Society of Anesthesiologists physical status classification, BMI, age, sex, priority of surgery, Mallampati score, use of NMBA, and PDI were all associated with DTI with statistical significance ($P < 0.0001$).

The results of the univariate analysis of BMI stratified in six categories are listed in table 3. The odds ratio (OR) for DTI increased with BMI. Based on level of significance and the OR, it seemed reasonable to combine the

Table 3. The Univariate Association between BMI Stratified into Six Classes and DTI

	OR	95.0 % CI	*P*
BMI < 18.5 Underweight	0.91	0.78–1.06	0.22
18.5 ≤ BMI < 25 Normal weight	Reference		
25 ≤ BMI < 30 Overweight	1.24	1.16–1.33	< 0.0001
30 ≤ BMI < 35 Obese	1.25	1.13–1.37	< 0.0001
35 ≤ BMI < 40 Severely obese	1.40	1.22–1.61	< 0.0001
40 ≤ BMI Morbidly obese	1.47	1.22–1.78	< 0.0001

BMI = body mass index; CI = confidence interval; DTI = difficult tracheal intubation; OR = odds ratio.

six intervals into three: less than 25; 25–34; 35 or more. A univariate analysis with BMI less than 25 used as reference demonstrated OR for DTI of 1.42 (95% CI 1.26–1.59, $P < 0.0001$) for BMI of 35 or more and OR of 1.24 (95% CI 1.17–1.32, $P < 0.0001$) for BMI 25–34. Further analysis did not demonstrate other reasonable alternative intervals for the categorization of BMI. A multivariate analysis, including all significant covariates from the univariate analyses, identified all covariates except the American Society of Anesthesiologists physical status classification to be independent risk factors of DTI. Adjusted for all other significant covariates, BMI of 35 or more and BMI 25–34 remained statistically significant risk factors of DTI with an OR of 1.34 (95% CI 1.19–1.51, $P < 0.0001$) and 1.11 (95% CI 1.04–1.18, $P < 0.0016$), respectively (table 4).

Controlling the multivariate model with the Hosmer and Lemeshow goodness-of-fit test ($P < 0.3$) indicated that the statistical model was reasonable fitted. Adding age^2 as an extra covariate did not improve the model. In a receiver operating characteristic curve analysis of the final model, the area under the curve was 0.65 (95% CI 0.64–0.66, $P < 0.0001$).

Table 4. Multivariate Model for the Prediction of Difficult Intubation

	OR	95 % CI	*P*
35 ≤ BMI	1.34	1.19–1.51	< 0.0001
25 ≤ BMI < 35	1.11	1.04–1.18	< 0.0016
Mallampati III and IV	3.70	3.41–4.00	< 0.0001
Male	1.35	1.27–1.44	< 0.0001
Age, year	1.01	1.01–1.01	< 0.0001
Surgical Priority = Scheduled	1.34	1.24–1.44	< 0.0001
Previous difficult intubation = Yes	6.32	5.11–7.84	< 0.0001
Previous difficult intubation = Unknown	1.26	1.15–1.39	< 0.0001
NMBA = No relaxation	1.59	1.49–1.70	< 0.0001

BMI = body mass index; CI = confidence interval; NMBA = neuromuscular blocking agent; OR = odds ratio.

Reference: Previous difficult intubation = No; Surgical priority = Nonscheduled; Sex = Female; Mallampati = I and II; BMI < 25; NMBA = Relaxed. Age is expressed as continuous covariate. The OR = 1.01 represents the increased risk of difficult tracheal intubation being 1 year older.

Table 5. Agreement between Stratified BMI and Weight

	Weight (w) Intervals			
	w < 90 kg	90 kg ≤ w < 110 kg	110 kg ≤ w	Total
BMI < 25	46,249	428	0	46,677
25 ≤ BMI < 35	25,379	11,246	1212	37,837
35 ≤ BMI	221	2158	2906	5,285
Total	71,849	13,832	4118	89,799

Illustrates complete cases only. A total of 1533 (1.7 %) patients were missing information about BMI.

BMI = body mass index; w = weight.

Both weight and height were statistically significant in a univariate analysis associated with DTI. Performing another multivariate analysis including the same statistically significant covariates from the univariate analyses included previously, but replacing BMI with weight and height, demonstrated only weight as an independent risk factor of DTI with OR of 1.004 (95% CI 1.002–1.006, $P < 0.0001$). A goodness-of-fit test ($P < 0.01$) indicated that this model was poorly fitted. We used the same stratified weight as El-Ganzouri *et al.*[9] A multivariate analysis with weight less than 90 kg as reference demonstrated OR for DTI of 1.28 (95% CI 1.12–1.46, $P < 0.0002$) for weight of 110 kg or more and OR of 1.10 (95% CI 1.02–1.20, $P < 0.02$) for 90–110 kg.

Table 5 illustrates the agreement of the two categorical covariates, BMI and weight, with a weighted kappa value of 0.44 (95% CI 0.43–0.44, $P < 0.0001$). The distribution of the patients in this table is asymmetric; more patients are located below than above the diagonal of the table. This indicates that patients categorized with a low or a moderate risk of DTI according to their weight may be categorized with a moderate or a high risk of DTI according to their BMI. On the other hand, patients categorized with low BMI had no or much lower probability of being categorized with moderate or high risk of DTI according to their weight. Thus, despite weight being included in the calculation of BMI, the risk profile for DTI for a specific patient might differ considerably when the two categorical risk factors are compared.

We performed a multivariate logistic regression analysis to determine if it was possible to include both BMI and weight. In the first step of the analysis, we included BMI, weight, height, and all other covariates that were statistically significant in univariate analyses. According to nonsignificant and high *P* values as well as nonsignificant changes of deviances, we excluded first weight and subsequently height from the model, leaving BMI as the only independent significant risk factor for DTI. Repeating the analysis with both the categorical BMI and weight confirmed the result. Therefore, height and weight may be confounders for BMI in the prediction of DTI.

Table 6. Accuracy of the Prediction of DTI with Dichotomous Stand-alone Tests of BMI and Weight (kg)

	TP	FP	TN	FN	OR	Sens.	Spec.	PPV	NPV	PosLR	NegLR
BMI ≥ 25	2526	41,368	45,249	2179	1.27	0.54	0.52	0.06	0.95	1.12	0.89
BMI ≥ 35	352	5136	81,481	4352	1.28	0.07	0.94	0.06	0.95	1.26	0.98
Weight ≥ 90	1121	17,159	69,458	3583	1.27	0.24	0.80	0.06	0.95	1.20	0.95
Weight ≥ 110	284	3942	82,675	4421	1.35	0.06	0.95	0.07	0.95	1.33	0.98

TP, FP, TN, and FN calculations were based on the pooled estimates from multiple imputations Chi-square; $P < 0.0001$ for all tests.

BMI = body mass index; DTI = difficult tracheal intuabtion; FN = false negative; FP = false positive; NegLR = negative likelihood ratio; NPV = predictive value of negative test; OR = odds ratio; PosLR = positive likelihood ratio; PPV = predictive value of positive test; Sens = sensitivity; Spec = specificity; TN = true negative; TP = true positive.

Based on the cut-off values defining the three intervals of BMI and weight, the following dichotomous stand-alone tests were assessed (table 6). BMI of 35 or more as the only predictor had a sensitivity of 7% and a specificity of 94%. The predictive value of positive test was 6%. Using weight of 110 kg or more gave a predictive value of positive test of 7%, a sensitivity of 6%, and a specificity of 95%.

In both univariate and multivariate analyses, age, sex, Mallampati score, PDI, NMBA, weight, and BMI were significantly associated with FTI. In a multivariate analysis, BMI as a continuous covariate remained an independent risk factor of FTI (OR 1.031, 95% CI 1.002–1.061, $P < 0.04$); as a categorical covariate, BMI was not significantly associated with FTI. If BMI was replaced with weight, similar multivariate analyses demonstrated weight as an independent continuous covariate (OR 1.012, 95% CI 1.003–1.021, $P < 0.01$). As categorical covariate, only weight of 90–109 kg was significantly associated with FTI (OR 2.44, 95% CI 1.67–3.56, $P < 0.0001$), whereas weight of 110 kg or more was not ($P < 0.119$).

With the same methodological approach used for DTI, we performed *post hoc* analyses of the association between BMI of 35 or more and planned fiberoptic intubation. A new study cohort including patients primarily scheduled for fiberoptic intubation was retrieved. We performed logistic regression with Yes and No values for the dependent dichotomous covariate primarily scheduled fiberoptic intubation. In the univariate analysis, the OR was 1.31 (95% CI 1.12–1.53, $P < 0.001$); in the multivariate analysis (table 7), the OR was 1.17 (95% CI 0.99–1.39, $P = 0.0588$) for a patient with a BMI of 35 or more being scheduled to fiberoptic intubation.

Discussion

We found that 5.2% of the patients had DTI, confirming the estimate in a previous meta-analysis.[18] In this large DAD cohort, obesity was associated with an OR of 1.42 for DTI with BMI of 35 or more and an OR of 1.24 with BMI of 25–35. This is much less than the estimates found by Shiga *et al.*, where obese patients had a three times higher risk of DTI than lean patients.[18] We also found that Mallampati score of III and IV and a history of PDI were predictors of DTI, with ORs of 3.7 and 6.3, respectively. Furthermore, male sex, scheduled surgery, and absence of NMBA were identified as risk factors of DTI with ORs of 1.35, 1.34, and 1.59, respectively. These OR were similar to that of obesity. The impact of obesity, in itself, on the risk of DTI therefore may seem weak.

The risk of DTI increased with degree of obesity, which concurs with earlier studies.[9,13] However, in our study the most reasonable cut-off values stratifying BMI differed from previous studies.[7–10,12,22] Our data suggest that a BMI of 35 is the cut-off value that relevantly divides overweight and obese patients into two groups with different risks of DTI. BMI of 35 or more may be a better clinical cut-off than BMI of 30 or more or BMI of 40 or more, as previously suggested.

We found that weight was also an independent risk factor for DTI. Compared to El-Ganzouri *et al.*[9] our

Table 7. Multivariate Model for Scheduled Fiberoptic Intubation

	OR	95 % CI	*P*
BMI ≥ 35	1.17	0.99–1.39	< 0.0588
Mallampati III and IV	3.70	3.41–4.00	< 0.0001
Male	1.35	1.27–1.44	< 0.0001
Age, yr	1.00	1.00–1.01	< 0.0041
Surgical priority = Scheduled	1.75	1.57–1.95	< 0.0001
Previous difficult intubation = Yes	6.48	4.89–8.58	< 0.0001
Previous scheduled fiberoptic intubation = Yes	49.71	38.87–63.59	< 0.0001
Previous scheduled fiberoptic intubation = Unknown	1.41	1.21–1.63	< 0.0001

BMI = body mass index; CI = confidence interval; OR = odds ratio.

Reference: Previous difficult intubation = No and Unknown; Surgical priority = Nonscheduled; Sex = Female; Mallampati = I and II; BMI < 35; Previous scheduled fiberoptic intubation = No. Age is expressed as continuous covariate. OR = 1.01 represents the increased risk of difficult tracheal intubation being 1 year older.

estimates of the OR were considerably lower, although we used the same stratification of weight. This difference may be explained by their use of Cormack and Lehanes classification of the glottic view as a surrogate parameter for DTI. In our final multivariate analysis, where BMI was compared with weight, only BMI qualified as a statistically significant risk factor. This indicates that BMI rather than weight may be the measure of choice for describing obesity as a risk for DTI.

As sole predictors of DTI, the accuracy of both BMI and weight assessed as dichotomous tests performed poorly. Previous studies have also suggested that the value of screening tests for DTI is limited when a single test is used.[18,23] Therefore, combining different predictors may improve diagnostic accuracy, and a multivariate test including numerous known risk factors for DTI may allow the use of BMI as a measure of obesity.

In our results, the low ORs of BMI and weight may indicate a limited importance of obesity as a risk of DTI. However, obesity has been identified as a risk of difficult mask ventilation.[22,24,25] Kheterpal *et al.* investigated 22,660 attempts of mask ventilation where BMI of 30 or more was identified as an independent risk factor for the combination of difficult mask ventilation and difficult intubation. Mask ventilation is an important rescue technique in a situation with DTI or FTI; therefore, the knowledge of obesity being a risk factor for DTI simultaneously with difficult mask ventilation is important. The airway management of obese patients may also be associated with accelerated oxygenic desaturation[26] and difficult emergency tracheotomy.[27]

Our analyses indicated that both age and male sex were risk factors of DTI. This may be due to sex being a confounder of parameters not observed, and the status of age is in agreement with Kheterpal *et al.*, who identified age of 57 yr or more as a risk of difficult mask ventilation.[22]

The present study is based on a large cohort of prospectively and consecutively collected data representing everyday experience from Danish clinical practice. Presently, half of Danish anesthesia departments register in the DAD. The number of registered patients is approximately half of all the patients in Denmark undergoing anesthesia. The DAD requires all registered indicators to be subjected to relevant rules of validation. This minimizes subsequent problems of missing and invalid data, which is supported by the fact that there was no noticeable difference between the estimates from the complete case analyses and the pooled estimates from the multiple imputations. The interface of DAD to register the airway evaluation, plan, and management was the same for all the registrations as well as the validation and user manual for the DAD. This confers a high external validity to our results. Our study included more than 91,000 registered intubations, thereby exceeding the total number of intubations included in the latest meta-analyses dealing with prediction of DTI.[18,23] This large number of patients enabled us to detect or reject even weak associations with great power and strengthened the precision of the estimates by narrowing their confidence intervals. However, we cannot ensure that controlled and uniform conditions were met and applied in all the patient encounters due to a heterogeneous population of patients and reporters and a lack of a national recommendation for airway management. This may reduce the internal validity of our data.

Obesity may create anatomical difficulties for the intubation caused by the decreased mobility and enlargement of structures in the throat and around the neck. Therefore, it seems rational to hypothesize that obesity in terms of BMI may be independently associated with DTI. However, the number of risk factors that may be considered for difficult intubation used in our study was limited. Including more predictors of DTI in our investigation may have changed the result, revealing BMI as a confounder for other and more closely related risk factors for DTI. This is suggested by the receiver operating characteristic curve analysis in our final model revealing an area under the curve of 0.65, indicating ample room for model improvement. That gender was independently associated with DTI may exemplify a likelihood that unknown confounding variables were missing in our analyses. The neck circumference may be a better and more relevant predictor than BMI, but again the current literature does not provide an adequate answer to this question.[7,28–30] Including other additional risk factors for DTI as the thyromental distance, ability of mouth opening, range of neck movement, or ability to prognath in a future analysis may remove obesity as an independent risk factor for DTI. Although these covariates are considered well-known risk factors for DTI, they have not succeeded as a stand-alone test or in combination to predict DTI with sufficient accuracy.[9,18,31] In our analysis, however, high BMI was identified as a risk factor for DTI. At the obese patient's preanesthetic visit, the anesthetist should therefore take the precaution of including a very careful airway examination.

The importance of relaxation is supported by our results, as the lack of NMBA use for intubation was identified as a risk of DTI and FTI. It is a limitation of the study that there was no record of the educational level or years of experience of the persons performing the intubations. Those with least experience may have the most episodes of difficult intubations. No information regarding different height of the pillow and the position of head and neck of the obese patients during intubation was registered. An elevated compared with a sniffing position may improve the conditions for intubation of obese patients.[32] This information might have changed the results of our study if we had been able to include it in our analyses.

Confounding by indication is known to introduce bias when dealing with forecasts of DTI in any nonrandom-

ized study involving interventions.[33] The airway management of anticipated DTI is likely to differ from that of unanticipated DTI. Our results could be biased by numerous variables not recorded in DAD. These unknown confounding variables may be important for the airway handling depending on the BMI. As an example, a more experienced physician may be allocated for the task; therefore, the obese patient may have been successfully tracheally intubated. It may be another confounder that a patient may be scheduled for a fiberoptic intubation because of obesity, leaving this particular patient ineligible for the analysis. This finding may be supported in part by our *post hoc* analyses, where the risk of being scheduled for fiberoptic intubation for patients with BMI of 35 or more was evaluated. Thus, the association was significant in our univariate assessment; whereas the association was marginally nonsignificant in our multivariate model. These results are encumbered with uncertainty because we cannot identify if a patient was initially allocated for fiberoptic intubation because of an anticipated difficult intubation or for other reasons. It is likely that an experienced anesthetist with the best airway management skills will be allocated for a patient judged to be of high priority. In our study, nonscheduled surgery may be associated with high-priority surgery, which may explain why it was associated with a decreased risk of DTI when compared with scheduled surgery.

This study adds to the numerous studies dealing with the prediction of DTI. It adds to the description of the total risk profile of patients with DTI. In our large cohort, increasing obesity was demonstrated as a risk factor for DTI independent of other risk factors registered in DAD. The impact of BMI of 35 or more on DTI was limited compared to other known risk factors such as PDI and the modified Mallampati score. BMI appears to be a better measure than weight to describe obesity as a risk for DTI. Obesity measured by BMI cannot in itself identify patients at risk of DTI. A multifactorial test including previously validated risk factors as well as obesity in terms of BMI of 35 or more may improve prediction of DTI.

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References

1. Hove LD, Steinmetz J, Christoffersen JK, Moller A, Nielsen J, Schmidt H: Analysis of deaths related to anesthesia in the period 1996-2004 from closed claims registered by the Danish Patient Insurance Association. Anesthesiology 2007; 106:675–80

2. Rosenstock C, Moller J, Hauberg A: Complaints related to respiratory events in anaesthesia and intensive care medicine from 1994 to 1998 in Denmark. Acta Anaesthesiol.Scand 2001; 45:53–8

3. Peterson GN, Domino KB, Caplan RA, Posner KL, Lee LA, Cheney FW: Management of the difficult airway: A closed claims analysis. Anesthesiology 2005; 103:33–9

4. Cooper GM, McClure JH: Anaesthesia chapter from Saving mothers' lives: Reviewing maternal deaths to make pregnancy safer. Br J Anaesth 2008; 100: 17–22

5. Practice guidelines for management of the difficult airway: An updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology 2003;98: 1269–77

6. Bond A: Obesity and difficult intubation. Anaesth Intensive Care 1993; 21:828–30

7. Brodsky JB, Lemmens HJ, Brock-Utne JG, Vierra M, Saidman LJ: Morbid obesity and tracheal intubation. Anesth.Analg 2002; 94:732–6

8. Ezri T, Medalion B, Weisenberg M, Szmuk P, Warters RD, Charuzi I: Increased body mass index *per se* is not a predictor of difficult laryngoscopy. Can J Anaesth 2003; 50:179–83

9. el-Ganzouri AR, McCarthy RJ, Tuman KJ, Tanck EN, Ivankovich AD: Preoperative airway assessment: Predictive value of a multivariate risk index. Anesth Analg 1996; 82:1197–204

10. Juvin P, Lavaut E, Dupont H, Lefevre P, Demetriou M, Dumoulin JL, Desmonts JM: Difficult tracheal intubation is more common in obese than in lean patients. Anesth Analg 2003; 97:595–600

11. Rose DK, Cohen MM: The airway: Problems and predictions in 18,500 patients. Can J Anaesth 1994; 41:372–83

12. Voyagis GS, Kyriakis KP, Dimitriou V, Vrettou I: Value of oropharyngeal Mallampati classification in predicting difficult laryngoscopy among obese patients. Eur J Anaesthesiol 1998; 15:330–4

13. Wilson ME, Spiegelhalter D, Robertson JA, Lesser P: Predicting difficult intubation. Br J Anaesth 1988; 61:211–6

14. Cormack RS, Lehane J: Difficult tracheal intubation in obstetrics. Anaesthesia 1984; 39:1105–11

15. Adnet F, Borron SW, Racine SX, Clemessy JL, Fournier JL, Plaisance P, Lapandry C: The intubation difficulty scale (IDS): Proposal and evaluation of a new score characterizing the complexity of endotracheal intubation. Anesthesiology 1997; 87:1290–7

16. Samsoon GL, Young JR: Difficult tracheal intubation: A retrospective study. Anaesthesia 1987; 42:487–90

17. Hsieh FY, Bloch DA, Larsen MD: A simple method of sample size calculation for linear and logistic regression. Stat Med 1998; 17:1623–34

18. Shiga T, Wajima Z, Inoue T, Sakamoto A: Predicting difficult intubation in apparently normal patients: a meta-analysis of bedside screening test performance. Anesthesiology 2005; 103:429–37

19. Schafer JL, Graham JW: Missing data: Our view of the state of the art. Psychol Methods 2002; 7:147–77

20. Schafer JL: Multiple imputation: A primer. Stat Methods Med.Res 1999; 8:3–15

21. von EE, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP: The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. J Clin Epidemiol 2008; 61:344–9

22. Kheterpal S, Han R, Tremper KK, Shanks A, Tait AR, O'Reilly M, Ludwig TA: Incidence and predictors of difficult and impossible mask ventilation. Anesthesiology 2006; 105:885–91

23. Lee A, Fan LT, Gin T, Karmakar MK, Ngan Kee WD: A systematic review (meta-analysis) of the accuracy of the Mallampati tests to predict the difficult airway. Anesth.Analg 2006; 102:1867–78

24. Langeron O, Masso E, Huraux C, Guggiari M, Bianchi A, Coriat P, Riou B: Prediction of difficult mask ventilation. Anesthesiology 2000; 92:1229–36

25. Yildiz TS, Solak M, Toker K: The incidence and risk factors of difficult mask ventilation. J Anesth 2005; 19:7–11

26. Berthoud MC, Peacock JE, Reilly CS: Effectiveness of preoxygenation in morbidly obese patients. Br J Anaesth 1991; 67:464–6

27. Henderson JJ, Popat MT, Latto IP, Pearce AC: Difficult Airway Society guidelines for management of the unanticipated difficult intubation. Anaesthesia 2004; 59:675–94

28. Hekiert AM, Mick R, Mirza N: Prediction of difficult laryngoscopy: Does obesity play a role? Ann Otol Rhinol Laryngol 2007; 116:799–804

29. Naguib M, Malabarey T, AlSatli RA, Al DS, Samarkandi AH: Predictive models for difficult laryngoscopy and intubation. A clinical, radiologic and three-dimensional computer imaging study. Can J Anaesth 1999; 46:748–59

30. Komatsu R, Sengupta P, Wadhwa A, Akca O, Sessler DI, Ezri T, Lenhardt R: Ultrasound quantification of anterior soft tissue thickness fails to predict difficult laryngoscopy in obese patients. Anaesth Intensive Care 2007; 35:32–7

31. Arne J, Descoins P, Fusciardi J, Ingrand P, Ferrier B, Boudigues D, Aries J: Preoperative assessment for difficult intubation in general and ENT surgery: Predictive value of a clinical multivariate risk index. Br J Anaesth 1998; 80:140–6

32. Collins JS, Lemmens HJ, Brodsky JB, Brock-Utne JG, Levitan RM: Laryngoscopy and morbid obesity: A comparison of the "sniff" and "ramped" positions. Obes Surg 2004; 14:1171–5

33. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, Petticrew M, Altman DG: Evaluating non-randomised intervention studies. Health Technol Assess 2003; 7: iii–173

Appendix

Appendix 1. Contributing Departments.

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RESPIRATION AND THE AIRWAY

Avoidance of neuromuscular blocking agents may increase the risk of difficult tracheal intubation: a cohort study of 103 812 consecutive adult patients recorded in the Danish Anaesthesia Database

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Background. Previous studies indicate that avoiding neuromuscular blocking agents (NMBAs) may be a risk factor for difficult tracheal intubation (DTI). We investigated whether avoiding NMBA was associated with DTI.

Methods. A cohort of 103 812 consecutive patients planned for tracheal intubation by direct laryngoscopy was retrieved from the Danish Anaesthesia Database. We used an intubation score based upon the number of attempts, change from direct laryngoscopy to a more advanced technique, or intubation by a different operator. We retrieved data on age, sex, ASA physical status classification, priority of surgery, time of surgery, previous DTI, modified Mallampati score, BMI, and the use of NMBA. Using logistic regression, we assessed whether avoiding NMBA was associated with DTI.

Results. The frequency of DTI was 5.1 [95% confidence interval (CI): 5.0–5.3]%. In a univariate analysis, avoiding NMBA was associated with DTI, odds ratio (OR) 1.52 (95% CI: 1.43–1.61)%, $P<0.0001$. Using multivariate analysis, avoiding NMBA was associated with DTI, OR 1.48 (95% CI: 1.39–1.58), $P<0.0001$. Among patients intubated using NMBA, a multivariate analysis identified patients anaesthetized with only non-depolarizing NMBA to be more at risk for DTI than those anaesthetized with depolarizing NMBA alone.

Conclusions. Avoiding NMBA may increase the risk of DTI. However, confounding by indication may be a problem in this observational study and systematic reviews with meta-analysis or more randomized clinical trials are needed.

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Difficult airway management including difficult tracheal intubation (DTI) may be a major cause of severe perioperative morbidity and mortality related to anaesthesia.[1–4] Predicting DTI enables the anaesthesiologist to take precautions to reduce the risks associated with tracheal intubation.[5] Several studies have focused on one or more factors related to the patient which may identify those at risk of difficult intubation.[6,7] In addition to patient factors, successful airway management is determined by the anaesthetist's technical skills, non-technical skills, the facilities available, and the local environment.[8,9] The results of previous randomized trials, although small and with surrogate outcome measures, indicate that avoiding neuromuscular blocking agents (NMBAs) may be associated with

increased risk of difficult intubation and more postoperative discomfort to the patients.[10–18]

An evaluation of the use of neuromuscular blocking drugs during anaesthesia of patients recorded in the Danish Anaesthesia Database from January 2005 to December 2007 demonstrated a decrease in the use of these drugs for general anaesthesia including intubation. In light of this change of practice, the aim of this study was to evaluate whether avoiding the use of neuromuscular blocking drugs for general anaesthesia including intubation by direct laryngoscopy is a risk factor for difficult intubation and failed tracheal intubation (FTI). Also, the use of non-depolarizing drugs was compared with depolarizing drugs as a risk factor for difficult intubation.

Methods

Fourteen Danish anaesthesia departments in 2005 and 25 in 2006–7 prospectively and consecutively reported data on patients undergoing anaesthesia and surgery to the Danish Anaesthesia Database version 2. The Danish Anaesthesia Database contains specific quantitative anaesthetic and surgical indicators describing the perioperative period. This information is recorded immediately after each operation by the anaesthesiologist. The departments (Appendix I) are connected online, via the Internet, to a central server.

The Danish National Board of Health and The Danish Data Protection Agency approved the registration in the Danish Anaesthesia Database of all patients undergoing anaesthesia. The steering committee of the Danish Anaesthesia Database approved this study and provided access to the data.

We retrieved 148 546 records of patients undergoing general or combined anaesthesia with tracheal intubation from January 1, 2005, to December 31, 2007 (Fig. 1). We excluded patients aged <15 yr, those already intubated, and those primarily undergoing rigid and flexible fibreoptic intubation. We included 103 812 patients, who were intubated 126 433 times in this study. About 15 512 patients were anaesthetized and undergoing intubation by direct laryngoscopy on more than one occasion, for these patients only the last record was included. Thus, the final cohort includes 103 812 patients each represented by only one session of attempted tracheal intubation by direct laryngoscopy. Of these patients, 84 had missing records of an intubation score (Table 1). About 12 850 patients had missing records for one or more covariates, whereas 90 962 patients had complete records without any missing data. All types of surgery are represented in the Danish Anaesthesia Database except for cardiothoracic surgery.

There is no national recommendation for the evaluation and handling of the airway in patients undergoing tracheal intubation in Denmark. Therefore, participating anaesthetic departments may differ in their recommendations for airway management.

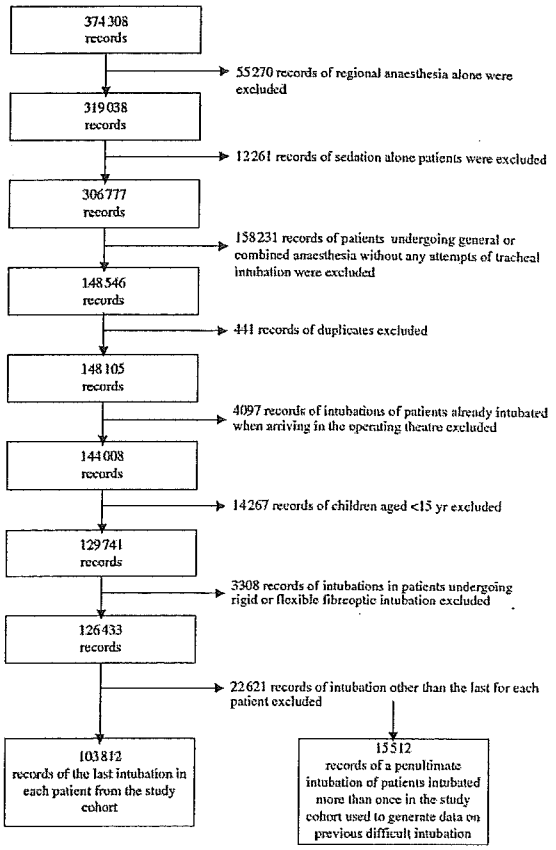

Fig 1 Selection of the study cohort. About 374 308 records of patients undergoing anaesthesia were identified in the Danish Anaesthesia Database. Excluding records of anaesthesia other than patients undergoing general or combined anaesthesia who were primarily undergoing tracheal intubation, the cohort included 148 546 records. Recorded intubations were excluded as explained in the figure. The subgroup of 15 512 records representing the penultimate intubations of patients intubated more than once was merged to the corresponding last intubation for the specific patient, and thereby information for the covariate PDI was created. Thus, 88 265 patients were only tracheal intubated once, 15 512 patients were intubated two or more times, while information was missing for 35.

Intubation score and covariates recorded in the Danish Anaesthesia Database

International consensus defining a DTI does not exist. Often, difficult laryngoscopy is used as a surrogate for difficult intubation,[19] whereas others suggest a specific definition of DTI.[5 20] We devised an intubation score based on fields in the Danish Anaesthesia Database (DTI score, Table 1) and recorded this score for all patients in whom tracheal intubation by direct laryngoscopy was attempted

Table 1 The Danish Anaesthesia Database tracheal intubation score. DTI was defined as an intubation score >1. Consequently, the definition of DTI includes FTI

All patients in whom the primary airway management plan was tracheal intubation by direct laryngoscopy were scored as follows	
Score=1	Intubated by direct laryngoscopy by the first anaesthetist and in two attempts maximally
Score=2	Intubated by direct laryngoscopy by the first anaesthetist but with more than two attempts or intubated by a supervising anaesthetist after one or more failed attempts at intubation
Score=3	Intubated by a method other than direct laryngoscopy
Score=4	Intubation failed after multiple attempts, no tracheal tube was inserted

and was the primary strategy planned for airway management.

The following data were obtained from the database: DTI score, age, sex, BMI, classification of ASA physical status, modified Mallampati score,[21] history of previous difficult intubation (PDI), priority of surgery, time of surgery, and the use of NMBA.

Each patient in the Danish Anaesthesia Database is recorded with a unique identifying number from the centralized civil register. This unique identifier contains information regarding the patient's sex and date of birth and enables exclusion of duplicate anaesthesia reports and identification of patients anaesthetized and recorded more than once during the period of observation. Patients anaesthetized more than once and with a previous record of at least one DTI in Danish Anaesthesia Database based on the intubation score (Table 1) were categorized as 'PDI'. The remaining patients were categorized as 'No or unknown PDI'.

Priority of surgery was defined as non-scheduled, if a patient was anaesthetized without being planned for surgery the previous day. Otherwise, surgery was categorized as scheduled. Time of surgery was categorized as 'Daytime' if start of surgery was between 08:00 and 16:00 or as 'Shift' if start of surgery was between 16:00 and 08:00. Height and weight were recorded in the Danish Anaesthesia Database based on preoperative measurements at the surgical wards or as reported by the patients. If records of height or weight were omitted, they were categorized as missing values. Height and weight ranges of 125–230 cm and 30–250 kg, respectively, were accepted as valid entries for the purpose of this analysis. BMI was calculated as weight/height^2 (kg m^{-2}). A warning appears during registration, if the calculated BMI exceeds 35 or is below 17, to emphasize that the weight and height entries should be reconsidered. If the Mallampati score was recorded as unknown, it was categorized as a missing value. For the analyses, the Mallampati score was dichotomized by combining class I with II and class III with IV. The use of NMBA was classified as 'depolarizing drugs with or without non-depolarizing drugs', 'non-depolarizing drugs only', or 'none'. If NMBA were used, it was not possible to distinguish between NMBA used exclusively for intubation, to facilitate surgery, or both. We also conducted analyses using a covariate combining the two classes describing the use of NMBA into one common class. The use of NMBA was dichotomized as the 'use of NMBA' and 'avoidance of NMBA'. For our assessments, we therefore used variables describing the use of NMBA in either two or three categories. There are no records of actual anaesthetic drugs used for the anaesthesia. It is not recorded in the Danish Anaesthesia Database whether neuromuscular monitoring is used for quantifying the degree of NMBA. It is not possible to acquire detailed information of airway management from the Danish Anaesthesia Database such as the type of laryngoscope blade or other types of equipment used for intubation.

Statistical analysis

We performed univariate regression analyses to evaluate the possible associations between DTI and the predefined covariates. A subsequent multivariate logistic regression analysis was performed including all significant covariates from the univariate analyses. Backward stepwise regression was performed to identify a final model. In logistic regression, it is assumed that the effect of a covariate is independent of the other covariates on the outcome measure. We tested if there were any first-order interactions between the use of NMBA and all the other covariates on the occurrence of DTI.

All regression analyses are presented with the significant covariates listed with their odds ratios (ORs) and corresponding 95% confidence interval (CI). A model control was performed with the Hosmer and Lemeshow goodness-of-fit test. In the model, it is assumed that continuous covariates have a linear association with DTI. This assumption of linearity was tested for age by testing whether replacing Age with (Age×Age) resulted in any model improvement.

We evaluated whether the 'avoidance of NMBA' increased the risk of FTI. Uni- and multivariate analyses were performed based upon the cohort selected as previously described. The Danish Anaesthesia Database does not offer a description of the type of NMBA used in patients with failed intubation, if a planned general anaesthetic is changed into a regional anaesthetic or monitored anaesthesia care (sedation).

The prevalence and pattern of missing data among all covariates were examined. We used the statistical method of multiple imputations for handling missing data. We imputed 10 data sets and pooled the estimates as described by Rubin[22] and Schafer and colleagues.[23 24] If there were any noticeable differences between the pooled estimates of

Table 2 The use of neuromuscular blocking agents over the 3 yr of the study for patients undergoing tracheal intubation. Each figure is: number of patients (percentage of column total). NMBA, neuromuscular blocking agent. The table illustrates complete cases. Data were missing in 84 patients

Year	2005	2006	2007	Total
No use of NMBA	3115 (17.5)	9159 (25.8)	15 917 (31.6)	28 191 (27.2)
Non-depolarizing NMBA	9266 (52.0)	15 769 (44.4)	18 342 (36.4)	43 377 (41.8)
Depolarizing ± non-depolarizing NMBA	5453 (30.6)	10 551 (29.7)	16 156 (32.0)	32 160 (31.0)
Total	17 834	35 479	50 443	103 728

the multiple imputation and the original estimates, both results are presented. In all analyses, $P<0.05$ was regarded as statistically significant. SPSS v15.0 and AMOS v7.0 were used for the analyses. NORM v2.03 by Schafer was used for pooling of estimates from the statistical analyses of each imputed data set.

This study has been presented according to the STROBE statement on the reporting of an observational cohort study.[25]

Results

The frequency of patients undergoing tracheal intubation without the use of NMBA increased over the 3 yr of observation from 17.5% in 2005 to 25.8% in 2006 and to 31.6% in 2007 (Table 2). The incidence of 'no use of NMBA' may have been influenced by the large increase of patients from different hospitals included over the years of observation. The incidence of 'no use of NMBA' in the original 14 hospitals over the 3 yr increased from 17.5% in 2005 to 24.8% in 2007. The overall frequency (95% CI) of DTI was 5.1 (5.0–5.3)%. The frequencies of DTI in 2005, 2006, and 2007 were 5.8%, 4.9% and 5.1%, respectively. Failed intubation occurred in 277 patients with an overall frequency of 0.27 (0.24–0.30)%. The characteristics of all patients are displayed in Table 3.

The univariate analysis of the dichotomized covariate of the use/avoidance of NMBA demonstrated an OR for DTI of 1.52 (1.43–1.61, $P<0.0001$) with 'avoidance of NMBA'. In the univariate analyses, the covariates: sex, priority of surgery, time of surgery, ASA classification, BMI, Mallampati score, PDI, and age were all statistically significantly associated with difficult intubation ($P<0.0001$). These covariates were included in the subsequent multivariate analyses.

A multivariate analysis of the 90 962 patients without any missing data, including all the statistically significant covariates from the univariate analyses, identified all covariates except the ASA classification and time for surgery to be independent risk factors of DTI (Table 4). The multivariate analysis of the dichotomized covariate of the avoidance of NMBA/use demonstrated an OR for DTI 1.48 (1.39–1.58, $P<0.0001$) with 'avoidance of NMBA'.

Exploring the model for interactions identified a statistically significant interaction of NMBA with surgical priority ($P<0.0001$). This means that the association between DTI and the use of NMBA is dependent on surgical priority and vice versa. Therefore, we introduced a new covariate combining the use/avoidance of NMBA and levels of surgical priority and repeated the multivariate analysis with this covariate having four levels. Among the patients undergoing non-scheduled surgery, the OR of difficult intubation was 3.10 (2.69–3.57, $P<0.0001$) for those anaesthetized without the use of NMBA. In those undergoing scheduled surgery, the OR of difficult intubation was 1.26 (1.18–1.35, $P<0.0001$) for those anaesthetized without the use of NMBA. These analyses show that regardless of surgical priority, the risk of DTI was highest in patients anesthetized and intubated without using NMBA, and the impact of avoiding the use of NMBA on the risk of DTI was highest for non-scheduled patients.

The dichotomized covariate avoidance of NMBA (as opposed to the use of NMBA) was statistically significantly associated with FTI. In a multivariate analysis, the OR of FTI was 1.72 (1.21–2.43, $P<0.0001$) for 'avoidance of NMBA'. The model in this case included adjustments for BMI as a continuous covariate; Mallampati score; sex male; PDI; and age were also significantly associated with FTI in this multivariate analysis.

We repeated our analysis with the use of NMBA stratified into three classes as 'depolarizing drugs with or without non-depolarizing drugs', 'non-depolarizing drugs only', or 'none'. Univariate analysis with 'depolarizing drug with or without non-depolarizing drug' as the reference group demonstrated an OR for DTI of 1.80 (1.68–1.94, $P<0.0001$) for the avoidance of NMBA and of 1.33 (1.24–1.43, $P<0.0001$) for 'non-depolarizing drug only'. Multivariate analysis demonstrated an OR for DTI of 1.74 (1.59–1.90, $P<0.0001$) with avoidance of NMBA and of 1.26 (1.16–1.37, $P<0.0001$) for 'non-depolarizing drug only'.

Performing multiple imputations for handling missing values did not exhibit noticeable differences between our original estimates and the pooled imputed estimates. As an example, because of missing data concerning the use of NMBA, the original assessment did not include 109 patients for whom a general anaesthesia was converted into a regional anaesthesia or sedation because of an FTI. We included these patients in a new assessment by using multiple imputations. The OR for FTI for 'avoidance of NMBA' was 1.85 (1.37–2.51) after multiple imputations and 1.72 (1.21–2.43) in our complete case analysis, respectively.

Table 3 Characteristics of the patients. The table shows the number of patients. The figures in parentheses are the column percentage within each categorical covariate. For continuous covariates, the figures in parentheses show the range. NMBA, neuromuscular blocking agent; ASA, American Society of Anesthesiologists physical status classification

	Use of NMBA			Total	Missing of total
	No NMBA	Non-depolarizing	Depolarizing ± non-depolarizing		
All patients	28 201	43 394	32 189		84 (0.1%)
Categorical covariates					
Difficult intubation					84 (0.1%)
Yes	1899 (6.7)	2192 (5.1)	1239 (3.9)	5330	
No	26 292 (93.3)	41 185 (94.9)	30 921 (96.1)	98 398	
Sex					84 (0.1%)
Male	12 388 (43.9)	18 676 (43.1)	13 429 (41.8)	44 493	
Female	15 803 (56.1)	24 701 (56.9)	18 731 (58.2)	59 235	
Priority of surgery					88 (0.1%)
Scheduled	23 897 (84.8)	37 089 (85.5)	12 048 (37.5)	73 034	
Non-scheduled	4292 (15.2)	6286 (14.5)	20 112 (62.5)	30 690	
Time of surgery					106 (0.1%)
Daytime	26 110 (92.7)	40 369 (93.1)	19 653 (61.1)	86 132	
Shift	2064 (7.3)	3004 (6.9)	12 506 (38.9)	17 574	
ASA classification					1770 (1.7%)
I	14 879 (53.9)	15 357 (35.8)	10 582 (33.5)	40 818	
II	9883 (35.8)	19 075 (44.5)	12 931 (40.9)	41 889	
III	2570 (9.3)	7537 (17.6)	6772 (21.4)	16 879	
IV	232 (0.8)	809 (1.9)	1222 (3.9)	2263	
V	25 (0.1)	71 (0.2)	97 (0.3)	193	
BMI					1747 (1.7%)
<35	26 818 (96.3)	41 106 (96.0)	28.146 (89.7)	96 070	
≥35	1043 (3.7)	1735 (4.0)	3224 (10.3)	6007	
Mallampati score					11 741 (11.3%)
I and II	22 635 (93.0)	37 083 (93.7)	25 433 (90.2)	85 151	
III and IV	1696 (7.0)	2495 (6.3)	2749 (9.8)	6940	
Previous difficult intubation					84 (0.1%)
Yes	243 (0.9)	351 (0.8)	312 (1.0)	906	
Unknown	24 690 (87.6)	37 265 (85.9)	26 279 (81.7)	88 234	
No	3258 (11.6)	5761 (13.3)	5569 (17.3)	14 588	
Continuous covariates					
	Means				
Age (yr)	48 (15–104)	56 (15–104)	53 (15–106)	0 (0%)	
Weight (kg)	75 (30–213)	74 (30–195)	77 (30–225)	857 (0.8)	
Height (cm)	172 (125–218)	171 (130–211)	171 (125–218)	1640 (1.6)	

Table 4 Multivariate model for DTI. References comparators were: 'Use of NMBA'; Surgical priority: non-scheduled; 'no or unknown PDI'; Sex: female; Mallampati class I or II; BMI <35

Covariates	Odds ratio	95% CI	*P*-value
Avoidance of NMBA	1.48	1.39–1.58	<0.0001
Surgical priority: scheduled	1.46	1.36–1.57	<0.0001
Sex: male	1.34	1.26–1.42	<0.0001
BMI ≥35	1.31	1.16–1.46	<0.0001
Mallampati class III and IV	3.72	3.44–4.01	<0.0001
PDI	3.94	3.27–4.75	<0.0001
Age (yr)	1.01	1.01–1.01	<0.0001

Discussion

We found a frequency of 5.1% of DTI confirming the estimate in a previous meta-analysis.[7] The frequency of patients intubated without the use of NMBA increased considerably over the 3 yr of observation whereas the frequency of DTI was relatively constant during the same period. In both our univariate and multivariate analyses of this large Danish Anaesthesia Database cohort, avoiding NMBA was associated with DTI with an OR of 1.5. We identified a statistical interaction between the covariates such that the impact of avoiding NMBA on DTI differed with surgical priority. Regardless of surgical priority, the risk of DTI was highest in patients anaesthetized and intubated without the use of NMBA. Among patients intubated using NMBA, a multivariate analysis identified that patients anaesthetized with only non-depolarizing NMBA to be more at risk for DTI than those anaesthetized with depolarizing NMBA alone. Meta-analyses indicate that succinylcholine offers better conditions for tracheal intubation than rocuronium when evaluating both excellent and clinically acceptable conditions of tracheal intubation.[26 27] Our results may support the position that the use of a depolarizing neuromuscular blocking drug is associated with fewer difficult intubations than that of a non-depolarizing NMBA. However, the

Danish Anaesthesia Database does not contain data on whether patients were intubated using a rapid sequence induction or not. Including more covariates, especially records of rapid sequence induction, in our investigation may have changed the result, and ultimately remove 'non-depolarizing NMBA' as an independent risk factor for difficult intubation. Finally, avoiding NMBA was identified as a significant risk factor for failed intubation with an OR of 1.7.

In our multivariate analysis, we found that a Mallampati score III and IV was associated with DTI with an OR of 3.7, which is slightly lower than reported by Shiga and colleagues.[7] PDI was associated with difficult intubation with an OR of 3.9. Both male sex and a BMI of $\geq$35 were identified as risk factors of DTI with an OR of 1.3 in each case.[28]

Confounding by indication[29] is recognized to introduce bias in non-randomized studies evaluating interventions.[30] In this case, the clinical choice of tracheal intubation with or without the use of NMBA depends on multiple factors related to the patient, to the surgery, and to other aspects of the clinical situation. The choice to use or avoiding neuromuscular blocking drugs may be based on reasons not recorded in the Danish Anaesthesia Database. Therefore, patients in whom NMBA are avoided, tracheal intubation may be fundamentally different from those in whom such drugs are used. This may be the reason for the patients anaesthetized without the use of these drugs were more likely to be difficult to intubate. The airway management of a patient with an anticipated difficult intubation is likely to differ from that of a patient with unanticipated difficult intubation. If a difficult intubation is anticipated, this may influence the decision to use or avoid NMBAs. Likewise, a more experienced physician may be allocated for the task, or the patient may be undergoing a fibreoptic intubation, with a rigid or flexible scope, making the patient ineligible for our analysis. Thus, despite the fact that our study clearly exhibits a robust statistical association between avoiding NMBA and DTI, it does not prove unequivocally that avoiding NMBAs is a cause of difficult intubation.

Several studies indicate[13 16 31–33] numerous possible disadvantages associated with avoiding neuromuscular blocking drugs. However, our results illustrate a dramatic change in clinical behaviour among Danish anaesthesiologists with the avoidance of NMBAs during anaesthesia having almost doubled between 2005 and 2008.

The Danish Anaesthesia Database does not contain any information on the actual anaesthetic drugs. However, based on our experiences, we believe that total i.v. anaesthesia with propofol and remifentanil makes up the majority of the anaesthesia without any use of neuromuscular blockers. Several studies have evaluated the optimal doses of drugs used for different regimens for tracheal intubation without the use of relaxants.[14 34–36] As there are no records of anaesthetic drugs and dosing, it is impossible to assess the influence of these drugs on intubating conditions. Hence, we cannot exclude that a suboptimal administration of the adjuvant hypnotics and analgesics contributes to our result.

Despite the evidence that avoiding neuromuscular blocking drugs is associated with difficult intubation, the overall frequency of difficult intubation did not increase over the study period, whereas avoidance of neuromuscular blockers increased considerably. There may be more explanations for this, as time-related factors, observed and unobserved, may have changed over the years of observation. First, the overall characteristics of the populations recorded in the Danish Anaesthesia Database may have changed within each of the participating departments. Secondly, the overall characteristics of the populations recorded in the Danish Anaesthesia Database may have changed after 2005 due to substantial differences in the populations of the 11 new participating departments. Finally, during this period, the anaesthesiologists and the departments may have learned to manage tracheal intubation without using neuromuscular blockers, so reducing the incidence of difficult or failed intubation.

There is no international consensus definition of a 'difficult intubation'. An intubation score simply based upon the number of attempts shows that multiple attempts at tracheal intubation may be associated with morbidity.[37] The intubation difficulty scale[20] in contrast gives a detailed description of the circumstances of the tracheal intubation. An intubation score, which includes all possible factors of importance for a successful intubation, may not be feasible. Therefore, most intubation scores are compromises. The intubation score in the Danish Anaesthesia Database is based upon: the number of attempts, intubation by a different operator, or change from direct laryngoscopy to a more advanced technique.

The present study is based upon a large cohort of prospectively and consecutively collected data representing everyday experience from clinical practice. The interface to register the airway-evaluation, -plan, and -management was the same for all the registration sites as was the validation and the online user manual for the Danish Anaesthesia Database. This confers a high external validity. The large number of patients enabled us to detect or reject weak associations with adequate statistical power and strengthened the precision of the estimates. However, we cannot ensure that controlled and uniform conditions were met and applied in all the patient encounters due to a heterogeneous population of patients and reporters and a lack of national recommendations for airway management. This may reduce the internal validity of this study.

It is a limitation of our study that there were no records of the degree of relaxation measured by nerve stimulation during intubation and there were no records of actual anaesthetic drugs used for the anaesthesia. It is also a limitation of the study that when NMBAs were used, it was impossible to distinguish whether this was for intubation or to facilitate surgery. This is of greater concern for the records dealing with the sole use of non-depolarizing agents. It seems reasonable that when a depolarizing agent was used, this was exclusively for intubation. Difficult

intubation in patients who received a non-depolarizing NMBA to facilitate surgery may explain why the use of non-depolarizing agents was associated with more at risk of difficult intubation than the use of a depolarizing with or without additional non-depolarizing agents.

There were numerous missing records of the use of neuromuscular blocking drugs in the patients recorded as failed intubation. Therefore, the validity of our results regarding failed intubation may be limited. It is a limitation of the study that records of the educational level or years of experience of the anaesthetists performing the intubations are not available. Those with the least experience may have more episodes of difficult intubation. Finally, the number of risk factors for difficult intubation examined in our study is limited. Additional risk factors for difficult intubation may change the importance of neuromuscular blocking drugs as an independent risk factor for difficult intubation.

The present study adds to previous studies dealing with the risk of difficult intubation and offers a description of the risk of difficult intubation in daily anaesthetic practice. In our large Danish cohort, avoiding neuromuscular blocking drugs was demonstrated to be a risk factor for difficult and failed intubation independent of other risk factors recorded in the Danish Anaesthesia Database. Confounding by indication is a major problem in observational studies to describe the effect of interventions. Randomized clinical trials comparing the avoidance and use of neuromuscular blocking drugs for intubation and examining patient-centred outcomes would be of value.

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Appendix I: Contributing departments

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Department of Anaesthesia and Surgery, Head and Orto Center, Copenhagen University Hospital, Rigshospitalet, Copenhagen.

Department of Anaesthesia and Surgery, Juliane Marie Center, Copenhagen University Hospital, Rigshospitalet, Copenhagen.

Department of Anaesthesia and Surgery, Neuro Center, Copenhagen University Hospital, Rigshospitalet, Copenhagen.

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Department of Anaesthesia and Surgery, Glostrup Hospital, Copenhagen University Hospital, Glostrup.

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Department of Anaesthesiology, Næstved Hospital, Næstved.

Department of Anaesthesiology, Nykøbing Falster Hospital, Nykøbing.

Department of Anaesthesiology, Bornholm's Hospital, Rønne.

Department of Anaesthesiology, Horsens Hospital, Horsens.

Department of Anaesthesiology, Vejle Hospital, Vejle.

Department of Anaesthesiology, Kolding Hospital, Kolding.

Department of Anaesthesiology, Brædstrup Hospital, Brædstrup.

Department of Anaesthesiology, Regionshospital Holstebro, Holstebro.

Department of Anaesthesiology, Regionshospital Herning, Herning.

Department of Anaesthesiology, Regionshospital Silkeborg, Silkeborg.

Department of Anaesthesiology, Århus Sygehus, Århus University Hospital, Århus.

Department of Anaesthesiology, Regionshospital Randers, Randers.

Department of Anaesthesiology, Odder of Århus Hospital, Odder.

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Department of Anaesthesiology, Thy-Mors Hospital, Thisted.

References

1 Hove LD, Steinmetz J, Christoffersen JK, Moller A, Nielsen J, Schmidt H. Analysis of deaths related to anesthesia in the period 1996–2004 from closed claims registered by the Danish Patient Insurance Association. *Anesthesiology* 2007; **106**: 675–80

2 Rosenstock C, Moller J, Hauberg A. Complaints related to respiratory events in anaesthesia and intensive care medicine from 1994 to 1998 in Denmark. *Acta Anaesthesiol Scand* 2001; **45**: 53–8

3 Peterson GN, Domino KB, Caplan RA, Posner KL, Lee LA, Cheney FW. Management of the difficult airway: a closed claims analysis. *Anesthesiology* 2005; **103**: 33–9

4 Cooper GM, McClure JH. Anaesthesia chapter from Saving mothers' lives; reviewing maternal deaths to make pregnancy safer. *Br J Anaesth* 2008; **100**: 17–22

5 Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology* 2003; **98**: 1269–77

6 Lee A, Fan LT, Gin T, Karmakar MK, Ngan Kee WD. A systematic review (meta-analysis) of the accuracy of the Mallampati tests to predict the difficult airway. *Anesth Analg* 2006; **102**: 1867–78

7 Shiga T, Wajima Z, Inoue T, Sakamoto A. Predicting difficult intubation in apparently normal patients: a meta-analysis of bedside screening test performance. *Anesthesiology* 2005; **103**: 429–37

8 Rosenstock C, Ostergaard D, Kristensen MS, Lippert A, Ruhnau B, Rasmussen LS. Residents lack knowledge and practical skills in handling the difficult airway. *Acta Anaesthesiol Scand* 2004; **48**: 1014–8

9 Rosenstock C, Hansen EG, Kristensen MS, Rasmussen LS, Skak C, Ostergaard D. Qualitative analysis of unanticipated difficult airway management. *Acta Anaesthesiol Scand* 2006; **50**: 290–7

10 Alcock R, Peachey T, Lynch M, McEwan T. Comparison of alfentanil with suxamethonium in facilitating nasotracheal intubation in day-case anaesthesia. *Br J Anaesth* 1993; **70**: 34–7

11 Alexander R, Booth J, Olufolabi AJ, El-Moalem HE, Glass PS. Comparison of remifentanil with alfentanil or suxamethonium following propofol anaesthesia for tracheal intubation. *Anaesthesia* 1999; **54**: 1032–6

12 Harsten A, Gillberg L. Intubating conditions provided by propofol and alfentanil—acceptable, but not ideal. *Acta Anaesthesiol Scand* 1997; **41**: 985–7

13 McNeil IA, Culbert B, Russell I. Comparison of intubating conditions following propofol and succinylcholine with propofol and remifentanil 2 $\mu g\ kg^{-1}$ or 4 $\mu g\ kg^{-1}$. *Br J Anaesth* 2000; **85**: 623–5

14 Scheller MS, Zornow MH, Saidman LJ. Tracheal intubation without the use of muscle relaxants: a technique using propofol and varying doses of alfentanil. *Anesth Analg* 1992; **75**: 788–93

15 Woods AW, Allam S. Tracheal intubation without the use of neuromuscular blocking agents. *Br J Anaesth* 2005; **94**: 150–8

16 Combes X, Andriamifidy L, Dufresne E, *et al.* Comparison of two induction regimens using or not using muscle relaxant: impact on postoperative upper airway discomfort. *Br J Anaesth* 2007; **99**: 276–81

17 Lieutaud T, Billard V, Khalaf H, Debaene B. Muscle relaxation and increasing doses of propofol improve intubating conditions. *Can J Anaesth* 2003; **50**: 121–6

18 Stevens JB, Vescovo MV, Harris KC, Walker SC, Hickey R. Tracheal intubation using alfentanil and no muscle relaxant: is the choice of hypnotic important? *Anesth Analg* 1997; **84**: 1222–6

19 Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984; **39**: 1105–11

20 Adnet F, Borron SW, Racine SX, *et al.* The intubation difficulty scale (IDS): proposal and evaluation of a new score characterizing the complexity of endotracheal intubation. *Anesthesiology* 1997; **87**: 1290–7

21 Samsoon GL, Young JR. Difficult tracheal intubation: a retrospective study. *Anaesthesia* 1987; **42**: 487–90

22 Rubin DB. *Multiple Imputations for Nonresponse in Surveys.* New York: J. Wiley & Sons, 1987

23 Schafer JL. Multiple imputation: a primer. *Stat Methods Med Res* 1999; **8**: 3–15

24 Schafer JL, Graham JW. Missing data: our view of the state of the art. *Psychol Methods* 2002; **7**: 147–77

25 von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008; **61**: 344–9

26 Perry JJ, Lee JS, Sillberg VA, Wells GA. Rocuronium versus succinylcholine for rapid sequence induction intubation. *Cochrane Database Syst Rev* 2008; CD002788

27 Karcioglu O, Arnold J, Topacoglu H, Ozucelik DN, Kiran S, Sonmez N. Succinylcholine or rocuronium? A meta-analysis of the effects on intubation conditions. *Int J Clin Pract* 2006; **60**: 1638–46

28 Lundstrøm LH, Møller AM, Rosenstock C, Astrup G, Wetterslev J, Danish Anesthesia Database. High body mass index is a weak predictor for difficult and failed tracheal intubation. A cohort study of 91,332 consecutive patients scheduled for direct laryngoscopy registered in the Danish Anesthesia Database. *Anesthesiology* 2009; **110**: 266–74

29 Signorello LB, McLaughlin JK, Lipworth L, Friis S, Sorensen HT, Blot WJ. Confounding by indication in epidemiologic studies of commonly used analgesics. *Am J Ther* 2002; **9**: 199–205

30 Deeks JJ, Dinnes J, D'Amico R, *et al.* Evaluating non-randomised intervention studies. *Health Technol Assess* 2003; **7**: 1–173

31 Alexander R, Olufolabi AJ, Booth J, El-Moalem HE, Glass PS. Dosing study of remifentanil and propofol for tracheal intubation without the use of muscle relaxants. *Anaesthesia* 1999; **54**: 1037–40

32 Coghlan SF, McDonald PF, Csepregi G. Use of alfentanil with propofol for nasotracheal intubation without neuromuscular block. *Br J Anaesth* 1993; **70**: 89–91

33 Klemola UM, Mennander S, Saarnivaara L. Tracheal intubation without the use of muscle relaxants: remifentanil or alfentanil in combination with propofol. *Acta Anaesthesiol Scand* 2000; **44**: 465–9

34 Grant S, Noble S, Woods A, Murdoch J, Davidson A. Assessment of intubating conditions in adults after induction with propofol and varying doses of remifentanil. *Br J Anaesth* 1998; **81**: 540–3

35 Stevens JB, Wheatley L. Tracheal intubation in ambulatory surgery patients: using remifentanil and propofol without muscle relaxants. *Anesth Analg* 1998; **86**: 45–9

36 Woods AW, Grant S, Harten J, Noble JS, Davidson JA. Tracheal intubating conditions after induction with propofol, remifentanil and lignocaine. *Eur J Anaesthesiol* 1998; **15**: 714–8

37 Mort TC. Emergency tracheal intubation: complications associated with repeated laryngoscopic attempts. *Anesth Analg* 2004; **99**: 607–13, table

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A documented previous difficult tracheal intubation as a prognostic test for a subsequent difficult tracheal intubation in adults

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Summary

We investigated the diagnostic accuracy of a documented previous difficult tracheal intubation as a stand-alone test for predicting a subsequent difficult intubation. Our assessment included patients from the Danish Anaesthesia Database who were scheduled for tracheal intubation by direct laryngoscopy. We used a four-point scale to grade the tracheal intubation. A previous difficult intubation was defined according to the presence of a record documenting a difficult penultimate tracheal intubation-score for the 15 499 patients anaesthetised more than once. Our assessment demonstrates that a documented history of previous difficult or failed intubation using direct laryngoscopy are strong predictors of a subsequent difficult or failed intubation and may identify 30% of these patients. Although previous investigators have reported predictive values that exceed our findings markedly, a documented previous difficult or failed tracheal intubation appears in everyday anaesthetic practice to be a strong predictor of a subsequent difficult tracheal intubation.

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Difficult airway management including difficult tracheal intubation may be a major cause of severe perioperative morbidity and mortality related to anaesthesia [1–4]. Predicting difficult tracheal intubation enables the anaesthesiologist to take precautions to reduce the associated risks [5]. Several studies have focused on one or more patient factors which may identify those at risk of undergoing difficult tracheal intubation [6, 7]. Among these, a previous difficult tracheal intubation has been identified as a risk factor for a future difficult tracheal intubation [8, 9]. In these studies, however, the information of a previous difficult tracheal intubation was partly or totally reported by the patient, and therefore documented information may have only been partly retrieved for their assessments.

The Danish Anaesthesia Database contains information of 15 499 patients in whom anaesthesia and tracheal intubation was performed more than once. A recorded intubation score contains documented information about the association between a previous intubation score and a future difficult tracheal intubation. The primary aim of this study was to evaluate the diagnostic accuracy of a documented previous difficult tracheal intubation and a previous failed tracheal intubation by direct laryngoscopy as stand-alone tests for the prediction of a subsequent difficult tracheal intubation and a failed tracheal intubation by direct laryngoscopy, respectively. Furthermore, in a multivariate regression model we evaluated a documented previous failed intubation by direct laryngoscopy as a

risk factor of a subsequent failed tracheal intubation by direct laryngoscopy.

Material and method

The Danish National Board of Health, The Danish Data Protection Agency and The Danish Ethics Committees for Biomedical Research approved the registration of data in the Danish Anaesthesia Database. The steering committee of the Danish Anaesthesia Database approved this study and provided access to the data for the analysis presented here.

Fourteen Danish departments of anaesthesia in 2005, and 25 departments in 2006–07, prospectively and consecutively reported data to the Danish Anaesthesia Database version 2 (the database) concerning all patients undergoing anaesthesia for surgery. The database contains specific quantitative anaesthetic and surgical indicators describing the perioperative period. All types of surgery are represented in the database. The departments are connected via the Internet to a central server hosted by The Unit for Clinical Quality, in the Capital Region, Denmark. The information is recorded immediately after each anaesthetic and surgical procedure. The interface of the database is interactive and changes depending on the type of anaesthesia and surgery that is registered. All registered parameters are predefined and the interface to register the airway-evaluation, plan, and management was the same for all the registration sites as well as the rules of validation and the on-line user manual.

Each patient entered into the database is registered with a unique identifying number from the centralised civil register. This unique identifier contains information regarding the patient's gender and date of birth, enables registration of each patient during the statistical analysis and prevents duplicates of anaesthetic reports. Furthermore, the identifier made it possible to retrieve information of patients anaesthetised and registered more than once during the period of observation.

From the database we retrieved 374 308 records of patients undergoing anaesthesia from January 2005 to December 2007 (Fig. 1). We excluded records of patients exclusively undergoing regional anaesthesia or sedation. Records of patients undergoing general or combined anaesthesia without any attempts of tracheal intubation were also excluded. We identified a total number of 148 546 records of patients undergoing general or combined anaesthesia who were primarily scheduled to undergo tracheal intubation. We excluded patients who had already undergone tracheal intubation before arriving in the operating room, patients aged < 15 years and those primarily scheduled to undergo flexible or rigid fiberoptic tracheal intubation. There were no records of the reason

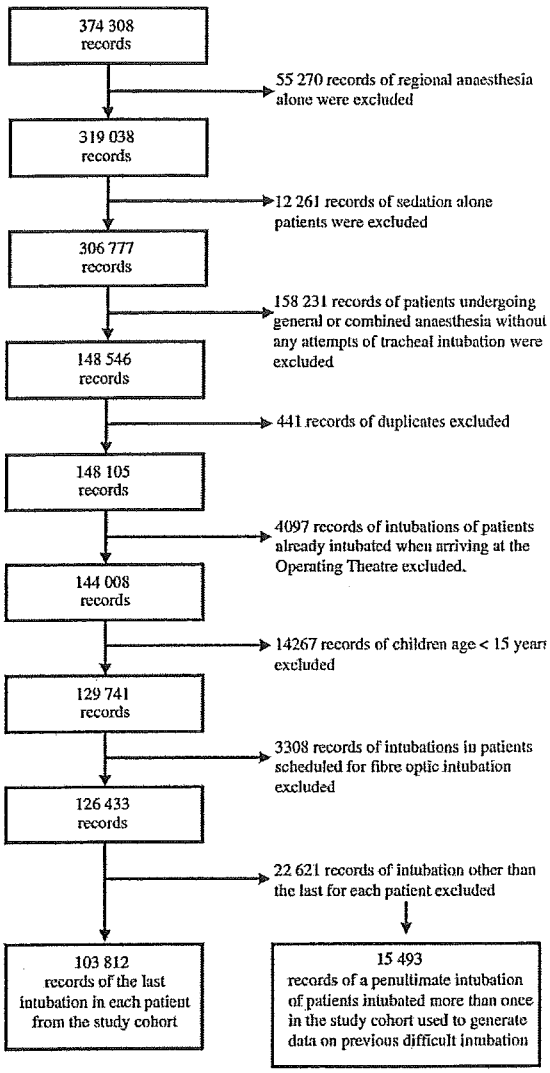

Figure 1 Selection of the study cohort. The final cohort includes 103 812 patients each represented by only one record of planned tracheal intubation by direct laryngoscopy. Of these patients, 88 313 underwent tracheal intubation only once, while 15 499 patients underwent tracheal intubation on more occasions, and therefore they had two or more records of tracheal intubation. For these last patients the penultimate record of a tracheal intubation was retrieved from the 22 621 records of tracheal intubation other than the last. Based on the penultimate record, information of a documented previous tracheal intubation was generated. Of these 15 499 patients information of a previous intubation score was missing for 6 patients.

for these patients to be allocated to undergo fiberoptic tracheal intubation; some may have been allocated to undergo this procedure due to educational purposes rather than anticipated difficult tracheal intubation.

Table 1 The Danish Anaesthesia Database tracheal intubation score.

All patients in whom the primary airway management was planned and attempted for tracheal intubation by direct laryngoscopy were scored as follows:	
Score = 1	Intubated by direct laryngoscopy by the first anaesthetist within a maximum of two attempts.
Score = 2	Intubated by direct laryngoscopy by the first anaesthetist but with more than two attempts or intubated by a supervising anaesthetist after one or more failed attempts at intubation.
Score = 3	Intubated by a method other than direct laryngoscopy.
Score = 4	Intubation abandoned after multiple attempts, no tracheal tube was inserted.
The predefined difficult tracheal intubation was defined as an intubation score > 1. Failed tracheal intubation by direct laryngoscopy was defined as an intubation score > 2.	

Tracheal intubation was performed or attempted in 103 812 eligible patients. However, records of 126 433 intubations exist as some patients underwent tracheal intubation by direct laryngoscopy for anaesthesia on more than one occasion. Of these patients, 88 313 underwent tracheal intubation only once (patients without documented information of a previous tracheal intubation), while 15 499 patients had been anaesthetised on more than one occasion, and therefore had two or more records of tracheal intubation by direct laryngoscopy. For these 15 499 patients both the last and the penultimate record of tracheal intubation were retrieved for the assessment.

We registered a tracheal intubation score (Table 1) for all patients in whom tracheal intubation by direct laryngoscopy was planned or primarily attempted. We defined difficult tracheal intubation as an intubation score > 1. Furthermore, for our assessments, we defined a 'failed tracheal intubation by direct laryngoscopy' as an intubation score > 2. This includes a change from direct laryngoscopy to a more advanced technique and any situation where tracheal intubation was abandoned. Both of these outcomes may be more significant clinical outcomes than the predefined definition of a difficult tracheal intubation. Based on the penultimate tracheal intubation of the patients who were anaesthetised more than once, the same intubation score and cut off values were used to identify a previous difficult tracheal intubation and a previous failed tracheal intubation by direct laryngoscopy.

A previous difficult tracheal intubation was categorised as 'yes' for patients who have a documented record of a previously difficult tracheal intubation (penultimate intubation score > 1). Otherwise the patients were categorised as 'no'. Consequently, the last group includes both patients who previously underwent a tracheal intubation without problems (penultimate intubation score of 1) and patients without documented information of a previous tracheal intubation. Likewise, based on a penultimate intubation score > 2, a previous failed tracheal intubation by direct laryngoscopy was categorised as 'yes' or 'no'.

In addition, we performed a multivariate regression analysis of a previous failed intubation by direct laryngoscopy as a risk factor for a subsequent failed intubation by direct laryngoscopy. The following other covariates were used: age; gender; body mass index (BMI) [10]; classification of American Society of Anesthesiologist physical status; modified Mallampati score [11]; use of a neuromuscular blocking agent [12]; priority of surgery and time of surgery.

Priority of surgery was defined as non-scheduled if there was no plan for anaesthesia and surgery the day before the actual procedure was performed. Otherwise surgery was categorised as scheduled. Time of surgery was categorised as daytime if surgery began between 08:00 and 16:00 or as shift if it began between 16:00 and 08:00. Body Mass Index was calculated as weight.height^{-2} (kg.m^{-2}) and was categorised as BMI ≥ 35 or BMI < 35. If the Mallampati class was registered in the database as unknown, the registration was categorised as a missing value. For the analyses, the four classes of the modified Mallampati score were categorised into three classes by combining class I with II. The use of a neuromuscular blocking agent was categorised as 'yes' or 'no' though it is impossible to determine from the database whether the neuromuscular blocking agent was used solely for tracheal intubation. At present it is not possible to acquire detailed information of airway management from the database records such as the type of laryngoscope blade or other types of equipment used for intubation.

There is no national or uniform recommendation for the evaluation and management of the airway in patients undergoing tracheal intubation in Denmark. Therefore, departments of anaesthesia reporting to the database may differ in their recommendations for the evaluation and handling of the airway.

Statistical analysis

We evaluated a previous difficult tracheal intubation as the sole predictor of a subsequent difficult tracheal intubation and a previous failed tracheal intubation by direct laryngoscopy as the sole predictor of a failed tracheal intubation by direct laryngoscopy. The accuracy of the predictors was described by: sensitivity; specificity; predictive value of a positive test; predictive value of a negative test; positive likelihood ratio; and negative likelihood ratio with 95% confidence intervals [13].

Table 2 The characteristics of the patients. Of all patients 84 had a missing intubation score. Because of missing values, the total number of patients within the cross tabulation of the covariates and difficult Intubation differs from the Total column. The (%) refers to the column percent within each covariate.

	Difficult tracheal Intubation		Total	
	Yes (%)	No (%)	(%)	Missing from total
All patients	5330	98398	103728	
Categorical covariates				
Previous difficult tracheal intubation				6 (0.0)
Yes	170 (3.2)	528 (0.5)	698 (0.7)	
No	5159 (96.8)	97865 (99.5)	103108 (99.3)	
Sex				0 (0.0)
Male	2707 (50.8)	41786 (42.5)	44525 (42.9)	
Female	2623 (49.2)	56612 (57.5)	59287 (57.1)	
Age				0 (0.0)
Age < 40 years	880 (16.5)	27855 (28.3)	28761 (27.7)	
40 ≤ Age < 60	1934 (36.3)	30995 (31.5)	32959 (31.7)	
60 ≤ Age < 80	2139 (40.1)	31083 (31.6)	33247 (32.0)	
80 ≤ Age	377 (7.1)	8465 (8.6)	8845 (8.5)	
Priority of surgery				21 (0.0)
Scheduled	4072 (76.4)	68962 (70.1)	73096 (70.4)	
Non-scheduled	1258 (23.6)	29432 (29.9)	30695 (29.6)	
Time of surgery				81 (0.1)
Daytime	4654 (87.3)	81478 (82.8)	86153 (83.0)	
Shift	676 (12.7)	16898 (17.2)	17578 (16.9)	
ASA classification				1729 (1.7)
ASA 1	1690 (32.1)	39128 (40.4)	40841 (39.3)	
ASA 2	2459 (46.7)	39430 (40.7)	41903 (40.4)	
ASA 3	953 (18.1)	15926 (16.5)	16883 (16.3)	
ASA 4	147 (2.8)	2116 (2.2)	2263 (2.2)	
ASA 5	15 (0.3)	178 (0.2)	193 (0.2)	
Mallampati score				11697 (11.3)
I	1855 (39.8)	54991 (62.9)	56862 (54.8)	
II	1765 (37.9)	26540 (30.4)	28313 (27.3)	
III	812 (17.4)	5181 (5.9)	5993 (5.8)	
IV	230 (4.9)	717 (0.8)	947 (0.9)	
Body mass index				1705 (1.6)
< 35	4858 (92.6)	91212 (94.2)	96104 (92.6)	
≥ 35	388 (7.4)	5614 (5.8)	6003 (5.8)	
Use of neuromuscular blocking agents				84 (0.1)
No	1899 (35.6)	26292 (26.7)	28191 (27.2)	
Yes	3431 (64.4)	72106 (73.3)	75537 (72.8)	
Continuous covariates		Means (range)		
Age; years	56.6 [15–100]	52.7 [15–106]	52.9 [15–106]	0 (0.0)
Weight; kg	78.2 [30–183]	75.5 [30–225]	75.6 [30–225]	854 (0.8)
Height; cm	171.7 [125–211]	171.1 [125–218]	171.1 [125–218]	1633 (1.6)

We performed univariate regression analyses to evaluate the possible associations between a failed tracheal intubation by direct laryngoscopy and the predefined covariates. A subsequent multivariate logistic regression analysis was performed including all significant covariates from the univariate analyses. Backward stepwise regression was performed to identify a final model.

The prevalence and pattern of missing data among all covariates were described. We used multiple imputations as a statistical method for handling missing data. [14–16]. SPSS version 15.0 and AMOS version 7.0 (SPSS Inc., Chicago, IL, USA) and NORM v 2.03 (J. L. Schafer, Department of Statistics and The Methodology Center, The Pennsylvania State University) were used for the analyses.

This study has been presented according to the recommendation of the STROBE-statement of the reporting of an observational cohort study [17].

Results

The overall proportion of patients who underwent a difficult tracheal intubation was 5.1% (5.0–5.3, 95% confidence interval (CI)). The proportion of a difficult

Table 3 The accuracy of previous difficult tracheal intubation as a dichotomous stand-alone test for the prediction of a subsequent difficult tracheal intubation.

	Outcome: difficult tracheal intubation	
	Yes	No
Test: previous difficult tracheal intubation		
Yes	170	528
No	5163	97865
Total	5329	98393
		95% confidence intervals
Sensitivity	0.03	(0.03–0.04)
Specificity	0.99	(0.99–1.00)
Predictive value of positive test	0.24	(0.21–0.28)
Predictive value of negative test	0.95	(0.95–0.95)
Positive likelihood ratio	5.94	(5.01–7.05)
Negative likelihood ratio	0.97	(0.97–0.98)

Table 4 The accuracy of a previous failed tracheal intubation by direct laryngoscopy as a dichotomous stand-alone test for the prediction of a subsequent failed tracheal intubation by direct laryngoscopy.

	Outcome: failed tracheal intubation by direct laryngoscopy	
	Yes	No
Test: previous failed tracheal intubation by direct laryngoscopy		
Yes	75	174
No	1908	101565
Total	1983	101739
		95% confidence intervals
Sensitivity	0.04	(0.03–0.05)
Specificity	1.00	(1.00–1.00)
Predictive value of positive test	0.30	(0.24–0.36)
Predictive value of negative test	0.98	(0.98–0.98)
Positive likelihood ratio	22.09	(16.92–28.86)
Negative likelihood ratio	0.96	(0.96–0.97)

tracheal intubation in 2005, 2006 and 2007 were 5.8%, 4.9% and 5.1%, respectively. The proportion of a failed tracheal intubation by direct laryngoscopy was 1.9% (1.82–1.98% CI). The characteristics of the patients are displayed in Table 2. The results are presented in Tables 3 and 4.

A proportion of 24% (21–28%) of the patients, who previously underwent tracheal intubation with difficulties, subsequently experienced a difficult tracheal intubation. Among the patients who previously underwent a tracheal intubation without difficulties, 95% (95–95%) subsequently went through tracheal intubation without problems.

The proportion of patients registered with a previous failed tracheal intubation by direct laryngoscopy and who subsequently underwent a failed tracheal intubation by direct laryngoscopy was 30% (24–36%). Among the patients who had no record of a previously failed tracheal intubation by direct laryngoscopy 98% (98–98%) did not subsequently experience a failed tracheal intubation by direct laryngoscopy.

A univariate regression analysis demonstrated a previous failed tracheal intubation by direct laryngoscopy to be a risk factor for subsequent failed tracheal intubation by direct laryngoscopy, with an odds ratio (OR) of 22.9 (17.4 – 30.2, 95% CI, $p < 0.0001$). In the univariate analyses the covariates: gender; time of surgery; American Society of Anesthesiologists classification; Mallampati score; use of neuromuscular blocking agents; and age were all statistically significantly associated with difficult intubation ($p < 0.0001$). In a subsequent multivariate regression model (Table 5) adjusted for all other significant covariates, a previous failed tracheal intubation by direct laryngoscopy remained a statistically significant risk factor of a subsequent failed tracheal intubation by direct

Table 5 Multivariate model for a failed tracheal intubation by direct laryngoscopy.

Covariates	Odds ratio	95% confidence interval	p value
Previous failed tracheal intubation by direct laryngoscopy			
No	Reference		
Yes	16.59	11.86–23.20	< 0.0001
Mallampati score			
Mallampati = I or II	Reference		
Mallampati = III	2.85	2.49–3.28	< 0.0001
Mallampati = IV	7.70	6.21–9.56	< 0.0001
Age; year			
Age < 40	Reference		
40 ≤ Age < 60	1.43	1.25–1.63	< 0.0001
60 ≤ Age < 80	1.60	1.40–1.84	< 0.0001
80 ≤ Age	1.15	0.92–1.44	0.24
Gender			
Female	Reference		
Male	1.27	1.15–1.40	< 0.0001
Use of neuromuscular blocking agent			
Yes	Reference		
No	3.19	2.89–3.53	< 0.0001

laryngoscopy with an OR of 16.6 (11.9–23.2, 95% CI, $p < 0.0001$).

Performing multiple imputations for handling missing values did not exhibit noticeable differences between our original estimates and the pooled imputed estimates.

Discussion

We found the frequency of difficult tracheal intubation to be 5.1%; similar to the estimate in a previous meta-analysis [7]. Use of a previous difficult tracheal intubation as a dichotomous test enables us to predict 24% of the patients who will subsequently undergo a difficult tracheal intubation. Further, a previous failed tracheal intubation by direct laryngoscopy was able to predict 30% of the patients with a subsequent failure. In our multivariate analysis a previous failed tracheal intubation by direct laryngoscopy was associated with a subsequent failure with an odds ratio of 16.6.

As stand-alone tests, a previous difficult tracheal intubation or a previous failed tracheal intubation by direct laryngoscopy are inadequate predictors of subsequent difficult or failed tracheal intubations by direct laryngoscopy respectively. However, our results indicate that the anaesthesiologist must take serious precautions if a patient who previously underwent a difficult or even a failed tracheal intubation by direct laryngoscopy is scheduled to undergo another tracheal intubation. For these patients, meticulous airway evaluation followed by careful planning of airway handling is mandatory.

As a consequence of our findings, the Danish Anaesthesia Database has implemented software, which will provide a pre-operative warning if the patient has a record of a previous difficult intubation. Furthermore, based on the Intubation Difficulty Scale [18] a detailed description of the circumstances and the method used for the tracheal intubation is now recorded in the database if a patient is registered with a difficult tracheal intubation. The clinical implications of these new capacities may help to identify those patients who had a previous difficult tracheal intubation and help the anaesthesiologist to make the necessary precautions before the patient undergoes tracheal intubation again.

A failed tracheal intubation by direct laryngoscopy may seem like a more clinically significant outcome than the predefined definition of a difficult tracheal intubation in the database. A previous study shows that multiple attempts at tracheal intubation may be associated with morbidity [19]. In a clinical context, it therefore seems reasonable that the Danish Anaesthesia Database intubation score includes the number of attempts to graduate difficulties.

Our estimates differ from previous reported results. A positive predictive value between 69% [9] and 78% [8] and an OR of 9.5 reported by El-Ganzouri et al. [9] are significantly greater than our findings. There may be several reasons for these differences. Arne et al. [8] demonstrated that only 44% of the patients with Cormack and Lehane [20] score of III or IV in fact underwent difficult tracheal intubations. El-Ganzouri et al. used the Cormack and Lehane score for graduating tracheal intubation difficulties, which may explain their higher estimates compared with our findings when using the Danish Anaesthesia Database intubation score. Arne et al. [8] used an intubation score, but only a few patients were registered with previous knowledge of difficult intubation and hence the statistical confidence interval of their findings is wide. In addition to patient factors successful airway management is determined by the anaesthetists technical skills, non-technical skills, as well as the facilities available, and the local environment [21, 22]. These determining factors may vary over time. As an example many more anaesthetists performing or attempting tracheal intubation participated in this study of everyday practice on Danish anaesthesia departments, which possibly adds to the variation and lack of agreement between the evaluations of a previous and a present difficult intubation. Finally, only the most severe episodes of a previous difficult tracheal intubation may be reported to the patients and consequently only these severe episodes may be included in the previously reported assessments. This may explain their higher positive predictive values of a previous difficult tracheal intubation as a risk factor and predictor for a subsequent difficult tracheal intubation.

The present study is based upon a large cohort of prospectively and consecutively collected data representing everyday experience from clinical anaesthesia practice in Denmark. The Danish Anaesthesia Database requires all recorded indicators to be subjected to relevant rules of validation. This minimises subsequent problems of missing and invalid data. This confers a high external validity to our results. The large number of patients enabled us to detect or reject even weak associations with great power and to strengthen the precision of the estimates to very narrow confidence intervals.

Limitations of the study

Confounding by indication is well-known to introduce bias in the results in any non-randomised study involving interventions [23]. The airway management of anticipated difficult tracheal intubation is likely to differ from that of an unanticipated difficult tracheal intubation. Our results could be biased by numerous variables that are not recorded in the Danish Anaesthesia Database. These unknown confounding variables may be important for the airway handling depending on the previous difficult

tracheal intubation. As an example a more experienced physician may be allocated for the task thereby resulting in a successful tracheal intubation. As another possible confounding factor, a patient may be scheduled for a fiberoptic intubation because of a record of a previous difficult tracheal intubation, thereby leaving this particular patient ineligible for the analysis performed in this study. The number of risk factors that may be considered for difficult intubation used in our multivariate analysis was limited. In future analysis, the inclusion of other additional risk factors for a failed tracheal intubation by direct laryngoscopy (such as the thyromental distance, ability of mouth opening, range of neck movement, or jaw protrusion ability) may change the impact of a previous failed tracheal intubation by direct laryngoscopy as a risk factor for subsequent failure. It is a limitation of the present study that there was no record of the educational level or years of experience of the individuals performing or attempting the intubations. Those with least experience may have the most episodes of difficult intubations. This information might have changed the results of our multivariate analysis. We cannot ensure that controlled and uniform conditions were met and applied in all the patient encounters due to a heterogeneous population of patients and reporters and a lack of a national recommendation for airway management. This may reduce the internal validity of this study.

Our assessment indicates that neither a documented previous difficult tracheal intubation nor a previous failed tracheal intubation by direct laryngoscopy are sufficient as sole predictors for a subsequent difficult tracheal intubation or failed tracheal intubation by direct laryngoscopy. However our results strongly suggest that the patients who previously underwent a tracheal intubation with difficulties or underwent a tracheal intubation which failed will be at risk of undergoing identical problems during a future tracheal intubation. For these patients, a careful airway evaluation including other significant predictors of a difficult tracheal intubation may be of vital importance to ensure adequate and safe handling of the airway.

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References

1 Hove LD, Steinmetz J, Christoffersen JK, Moller A, Nielsen J, Schmidt H. Analysis of deaths related to anesthesia in the period 1996–2004 from closed claims registered by the Danish Patient Insurance Association. *Anesthesiology* 2007; **106**: 675–80.

2 Rosenstock C, Moller J, Hauberg A. Complaints related to respiratory events in anaesthesia and intensive care medicine from 1994 to 1998 in Denmark. *Acta Anaesthesiologica Scandinavica* 2001; **45**: 53–8.

3 Peterson GN, Domino KB, Caplan RA, Posner KL, Lee LA, Cheney FW. Management of the difficult airway: a closed claims analysis. *Anesthesiology* 2005; **103**: 33–9.

4 Cooper GM, McClure JH. Anaesthesia chapter from Saving mothers lives; reviewing maternal deaths to make pregnancy safer. *British Journal of Anaesthesia* 2008; **100**: 17–22.

5 Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology* 2003; **98**: 1269–77.

6 Lee A, Fan LT, Gin T, Karmakar MK, Ngan Kee WD. A systematic review (meta-analysis) of the accuracy of the Mallampati tests to predict the difficult airway. *Anesthesia and Analgesia* 2006; **102**: 1867–78.

7 Shiga T, Wajima Z, Inoue T, Sakamoto A. Predicting difficult intubation in apparently normal patients: a meta-analysis of bedside screening test performance. *Anesthesiology* 2005; **103**: 429–37.

8 Arne J, Descoins P, Fusciardi J, et al. Preoperative assessment for difficult intubation in general and ENT surgery: predictive value of a clinical multivariate risk index. *British Journal of Anaesthesia* 1998; **80**: 140–6.

9 el-Ganzouri AR, McCarthy RJ, Tuman KJ, Tanck EN, Ivankovich AD. Preoperative airway assessment: predictive value of a multivariate risk index. *Anesthesia and Analgesia* 1996; **82**: 1197–204.

10 Lundstrøm LH, Møller AM, Rosenstock C, Astrup G, Wetterslev J, Danish Anesthesia Database. High body mass index is a weak predictor for difficult and failed tracheal intubation. A cohort study of 91,332 consecutive patients scheduled for direct laryngoscopy registered in the Danish Anesthesia Database. *Anesthesiology* 2009; **110**: 266–74.

11 Samsoon GL, Young JR. Difficult tracheal intubation: a retrospective study. *Anaesthesia* 1987; **42**: 487–90.

12 Lundstrom LH, Moller AM, Rosenstock C, Astrup G, Gatke MR, Wetterslev J. Avoidance of neuromuscular blocking agents may increase the risk of difficult tracheal intubation: a cohort study of 103 812 consecutive adult patients recorded in the Danish Anaesthesia Database. *British Journal of Anaesthesia* 2009; **103**: 283–90.

13 Altman DG. *Practical Statistics for Medical Research*, 1st edn. London: Chapman & Hall, 1991.

14 Rubin DB. *Multiple Imputations for Nonresponse in Surveys*. New York: J. Wiley & Sons, 1987.

15 Schafer JL. Multiple imputation: a primer. *Statistical Methods in Medical Research* 1999; **8**: 3–15.

16 Schafer JL, Graham JW. Missing data: our view of the state of the art. *Psychological Methods* 2002; 7: 147–77.
17 von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Journal of Clinical Epidemiology* 2008; 61: 344–9.
18 Adnet F, Borron SW, Racine SX, et al. The intubation difficulty scale (IDS): proposal and evaluation of a new score characterizing the complexity of endotracheal intubation. *Anesthesiology* 1997; 87: 1290–7.
19 Mort TC. Emergency tracheal intubation: complications associated with repeated laryngoscopic attempts. *Anesthesia and Analgesia* 2004; 99: 607–13.
20 Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984; 39: 1105–11.
21 Rosenstock C, Ostergaard D, Kristensen MS, Lippert A, Ruhnau B, Rasmussen LS. Residents lack knowledge and practical skills in handling the difficult airway. *Acta Anaesthesiologica Scandinavica* 2004; 48: 1014–18.
22 Rosenstock C, Hansen EG, Kristensen MS, Rasmussen LS, Skak C, Ostergaard D. Qualitative analysis of unanticipated difficult airway management. *Acta Anaesthesiologica Scandinavica* 2006; 50: 290–7.
23 Deeks JJ, Dinnes J, DAmico R, et al. Evaluating non-randomised intervention studies. *Health Technology Assessment* 2003; 7: 1–173.

Submitted version

The prognostic value of the modified Mallampati score to predict difficult tracheal intubation. A meta-analysis of studies including 177 088 patients.

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Abbreviated Title: Meta-analyses of the modified Mallampati score.

Summery statement: Meta-analyses of 55 studies representing 177 088 patients support that the modified Mallampati Score is inadequate as a prognostic stand alone test for the prediction of a difficult tracheal intubation.

Abstract

Background: The aim of this study was to assess the performance of the modified Mallampati score as prognostic test of a difficult tracheal intubation based on meta-analyses including a large cohort from the Danish Anesthesia Database and several other studies.

Methods: A total of 55 studies representing 177 088 patients were included after electronic and manual searches. A single cohort from The Danish Anesthesia Database contributed by itself with 92 092 patients. The pooled estimates from the meta-analyses were calculated based on a random-effects model and a summary receiver operating curve. Meta-regression analyses were performed to explore sources of possible heterogeneity between the studies.

Results: The summary receiver operating curve demonstrated an area under the curve of 0.75. The pooled odds ratio was 5.89 (95 % Confidence interval (CI), 4.74 – 7.32). The pooled estimates of the specificity and sensitivity were 0.91 (CI, 0.91 – 0.91) and 0.35 (CI, 0.34 – 0.36) respectively. The pooled positive and negative likelihood ratios were 4.13 (CI, 3.60 - 4.66) and 0.70 (CI, 0.65 – 0.75), respectively. The meta-analyses had a high degree of statistical and clinical heterogeneity (I^2 ranging from 87.2 % to 99.4 %). Meta-regression analyses did not identify any significant explanation of the heterogeneity.

Conclusions: The modified Mallampati Score is inadequate as a prognostic stand alone test for the prediction of a difficult tracheal intubation. However, it may still play a very important roll as a part of a multivariate model for the prediction of a difficult tracheal intubation.

Introduction:

Difficult tracheal intubation may be a major cause of severe perioperative morbidity and mortality related to anesthesia [1-4]. Several studies have focused on one or more patient related factors which may identify those at risk of undergoing difficult tracheal intubation. Among these, the Mallampati score [5] and the modified Mallampati score [6] have been evaluated as risk factors for difficult tracheal intubation. Shiga et al [7] and Lee et al [8] both performed meta-analyses to evaluate the accuracy of the original and the modified Mallampati tests to predict a difficult intubation or difficult laryngoscopy. However, only Lee et al specifically evaluated the modified Mallampati score. The Danish Anesthesia Database contains more than 92 000 records of patients undergoing tracheal intubation and evaluated by the modified Mallampati score. The number of patients in this single cohort substantial exceeds the 17 900 patients included by Lee et al in their meta-analysis. The aim of this study was to assess the performance of the modified Mallampati score as prognostic test of a difficult tracheal intubation based on a meta-analysis including several recent studies published since the meta-analyses of Shiga and Lee et al and the large cohort from the Danish Anesthesia Database.

Material and Methods:

The Meta-analysis

Search strategy. In an electronic search covering the time since introduction of the modified Mallampati score [6], May 1987 until December 2009, The Cochrane Library, MEDLINE, Science Citation Index and EMBASE were used as sources for the identification of studies: The search was conducted with the following search string [9]: *(Sensitivity OR specificity OR screening OR false positive OR false negative OR predictive value of tests OR reference values OR roc analyses OR roc area OR roc characteristics OR roc curve) AND (intubation OR endotracheal intubation OR intratracheal intubation OR laryngoscopy OR difficult laryngoscopy OR difficult intubation OR Cormack lehane) AND Mallampati.* To determine the studies to be assessed further, two authors (LHL, JW) independently scanned the abstract, title or both sections of every record retrieved. All potentially relevant articles were investigated as full text. In addition, we checked the references from included studies. Any relevant missing information on the study was sought from the original author(s) of the article, if required. The inclusion criteria were: I) The modified Mallampati score was used. II) Studies including prospectively collected data. III) The study included adult patients. IV) Direct laryngoscopy with a standard laryngoscope was performed. V) The absolute number of true positive, false negative, true negative and false negative could be extracted from the article, from previous meta-analyses [7;8] or extracted by contacting the author(s). VI) The study was reported in English.

Data extraction. For studies that fulfilled the inclusion criteria, two authors (LHL, MVA) independently abstracted relevant information and characteristics using standard data extraction templates. When differences in opinion existed, they were resolved by a third party (JW). The following information was extracted:

1. The outcome measure, as a difficult tracheal intubation, or a difficult laryngoscopy defined by Cormack and Lehane score of III and IV [10] or a modified Cormack and Lehane score of IIb, III and IV [11]. As there is no international consensus of defining an intubation score, the definitions of a difficult tracheal intubation presented in the individual articles were accepted. However, if the authors defined a difficult laryngoscopy by Cormack and Lehane as a difficult intubation, we included and reported the Cormack and Lehane score as an

outcome measure in our assessment. A difficult laryngoscopy is a surrogate outcome measure for a difficult tracheal intubation. Therefore, if a study both reported an intubation score and the Cormack and Lehane score based on the same population in the same assessment, only the intubation score was extracted for our assessment.

2. A modified Mallampati score of III or IV was considered a risk factor for difficult laryngoscopy /intubation. When a single study has evaluated various versions of the modified Mallampati score, the results of the score performed similar to the one reported by Samsoon and Young [6] were extracted for the meta-analyses.

If possible, the following other data were extracted:

3. The settings of the Mallampati score by retrieving the position of the head and body, and if the patients phonated during the evaluating.
4. The number of anesthesiologists performing the preoperative airway assessments and the number of anesthesiologists handling the tracheal intubations were retrieved.
5. It was noted, if the modified Mallampati score was blinded for the anesthesiologists performing the airway management.
6. The participant sampling, inclusion and exclusion criteria of patient population were retrieved.
7. How the patients were recruited.

Quality assessment and risk of bias. We applied QUADAS, a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews [12] as an inspiration for the quality assessment of the included studies. The quality assessment was based on the following criteria:

1. Was the modified Mallampati score blinded for the anesthesiologist performing the airway management?
2. Was the setting of how the modified Mallampati test was performed clearly described?
3. Selection of study population: Was the inclusion and exclusion criteria described?
4. Recruitment of study population described (e.g. consecutive, randomly, case-control)?

Studies fulfilling all four criteria were classified as studies with low-risk of bias, if three criteria were fulfilled, they where categorized as medium risk of bias studies. Otherwise they were classified as studies with high-risk of bias.

Our meta-analysis included studies reporting difficult laryngoscopy or difficult tracheal intuba Further, subgroup meta-analyses of difficult laryngoscopy and difficult tracheal intubation we presented separately. Finally, a subgroup meta-analysis of studies with low and medium-risk bias was presented.

The Cohort Study from Danish Anesthesia Database

The Danish National Board of Health, The Danish Data Protection Agency and The Danish Ethi Committees for Biomedical Research approved the registration of data in the Danish Anesthe Database (database). The steering committee of the database approved this study and provid access to the data for the analysis presented here. As elsewhere reported [13;14] we retrieved a cohort of 103 812 eligible patients from the database. Of these 92 092 had complete records without any missing data of the Mallampati score and intubation score. The modified Mallam score was registered as defined by Samsoon and Young [6]. The view was graded as follows: cla soft palate, fauces, uvula, and pillars visible; class II = soft palate, fauces, and uvula visible; cla = soft palate and base of the uvula visible; class IV = soft palate not visible at all. The patients placed in a sitting position with the head in a neutral potion and the assessment was perform without phonation. Both the preoperative airway evaluation and airway management were performed by multiple anesthesiologists, and there was no blinding of the modified Mallampa score for the anesthesiologist performing the airway management. We registered a tracheal intubation score (Table 1) for all patients in whom tracheal intubation by direct laryngoscopy v planned and primarily attempted.

Statistical Analysis

The modified Mallampati score from the pooled estimates in the meta-analyses and from the Danish Anesthesia Database were described as: sensitivity; specificity; positive likelihood ratio; and negative likelihood ratio. The pooled estimates were presented with 95 % confidence inter If a study was reported with a 0 value in any outcome, 0.5 was added as a continuity correctior all values in the study before performing the meta-analysis. Before conducting a meta-analysis the degrees of heterogeneity displayed by the I^2 of all estimates were calculated [15]. Because of

expected clinical diversity and high I^2 values, the 'random-effects model' by DerSimonian Laird [16] was used incorporating a moment-based between study variance when calculating the pooled estimates. The calculation of the Spearman correlation coefficient of logit (True Positive Rates) vs. logit (False Positive Rates) demonstrated that the sensitivity and specificity were associated across the studies. Therefore a summary receiver operator characteristics (sROC) curve as described by Moses et al [17] was conducted. The area under the sROC curve was used as a measure for the description of diagnostic accuracy of the Mallampati test. To ensure precise pooled estimates, the pooled sensitivity was derived from the sROC curve using corresponding pooled specificity [17;18]. Subsequently, the pooled sensitivity and specificity were used to calculate the positive and negative likelihood ratios. To explore sources of heterogeneity in the studies, meta-regression analyses using the Moses-Shapiro-Littenberg method [17] was performed. All covariates associated with a p-value < 0.10 in the univariate analyses were included in a subsequent multivariate meta-regression analysis. In the multivariate analysis a p-value < 0.05 was considered significant. Possible bias was assessed by the method described by Eggers [19]. SPSS v. 17.0 (SPSS Inc., Wacker Drive, Chicago, IL 60606-6307, US), Comprehensive Meta Analysis version 2.2.048 (Borenstein M, Hedges L, Higgins J, Rothstein H. Biostat, Englewood NJ, US) and MetaDiSc version 1.4 (Zamora J, Muriels A, Abraira V, Madrid, Spain) were used for the analyses.

Results:

A total of 55 studies representing 177 088 patients [13;20-73] meet the inclusion criteria for the m analysis. In three of the included studies the necessary data was extract by contacting the autl [29;53;67]. Table 2 displays characteristics of the individual studies. A difficult tracheal intubation v applied as outcome measure in 20 studies [13;20;23-26;28;37-39;43;45;53;55;60;62;66-68;73], difficult laryngos defined as Cormack and Lehane [10] score of III and IV was used in 34 studies [21;22;27;29-36;40-42;44;46 52;54;56-59;61;63-65;69-72], while one study [49] applied a modified definition of the Cormack and Lehan The definitions of a difficult tracheal intubation varied across studies. As examples, some studi defined a difficult tracheal intubation as a Cormack and Lehane score of III and IV or if a gum elastic bougie was used [37;43] while other studies [20;25;45;53] used the more detailed and complex 'Intubation Difficulty Scale' [74]. The test results of the Mallampati score was blinded in 21 studie [21;22;24;31;32;38-43;46;48;51;52;60;62;68;70;71;73]. The inclusion and exclusion criteria, and hereby the select of the study populations were described in 48 studies [13;20-36;38;40-55;57;58;61-66;69-73]. A total of 34 studies [13;20-26;28;29;32-34;36;41;42;45;46;48;49;51-55;57;58;62;63;66;67;70-72] described the recruitment of the patients. Of these, the patients were recruited consecutively in 27 studies [13;20-26;28;29;32;33;41;42;48;49;51-54;57;58;62;63;66;71;72]. There were adequate description of the use of or absen of use of phonation [13;20;22;25;26;29;30;32;33;37;41;43;45;47;48;52-54;56;57;60;62;63;65;68-70;73], the head position [13;20;22;26;28-30;33;37;39;40;47;53;54;56;57;59;60;62;63;68;69;71;72] and the body position [13;22;25;27;29;30;32;33;37;39-43;47;48;52-54;56;57;59-64;68-72] in 29, 24 and 32 studies, respectively. Of these, 16 studies [13;22;29;30;33;37;47;53;54;56;57;60;62;63;68;69] contained information on all three conditions, and hereby cle described the setting of how the modified Mallampati test was performed. Thus, the numbers studies with a low, a medium and a high-risk of bias were 2, 18 and 35, respectively. To ensure uniform conditions when performing the assessments, several studies used a single or few pers to perform the preoperative airway evaluation and/or the subsequent handling of the tracheal intubation. Thus, the number of studies using limited number of persons performing the airwa evaluation [20;22;23;27;30;32-36;38;40-44;46;48;50-52;57;58;61-63;65;66;68;70;73] and limited number of persons performing the tracheal intubation [20;22;23;27;32;34-36;40-42;44-46;50;52;57;63;65;67;68;73] were 31 and 22, respectively. The type of patients differed between the studies, as both general and selected patient populations were evaluated. The modified Mallampati test was used evaluating the following specific patient populations: Obstetric [22;39;41;57;60;65] and obstetric vs. non-obstetrics [70

Obese [26;35;50;54] and obese vs. non-obese [34;45]; acromegali [21;63]; cervical spine limit [55]; laryngeal disease [24]; Thyroid surgery [25]; maxillofacial surgery [68]; diabetes [69] and coronary artery bypass grafting surgery vs. control [36].

The prognostic performance in the individual studies of the modified Mallampati score are displayed in Table 3. The prevalence of difficult intubation or difficult laryngoscopy varied between 0.7 and 31.3 %. The sensitivity and specificity ranged from 0.0 to 1.00 and 0.44 to 1.00, respectively. The positive and negative likelihood ratio varied from 0.46 to 48.38 and from 0.13 to 1.18, respectively. The diagnostic odds ratio ranged from 0.38 to 161.00. There was a high degree of heterogeneity among the studies as I^2 in the meta-analyses of all the pooled estimates ranged ranging from 87.2 % to 99.4 %. As there was a statistically significant association between logit (True Positive Rate) and logit (False Positive Rate) (Spearman correlation coefficient: 0,362, p-value = 0.007) we composed a symmetric sROC curve (Figure 1), with the area under the curve calculated to 0.753 (SE = 0.03). The threshold effect of the pooled diagnostic odds ratio was 5.89 (4.74 – 7.32, 95 % CI). The pooled estimate of the specificity was 0.91 (0.91 – 0.91, 95 % CI). Based on the sROC curve, the pooled specificity was used to derive a corresponding pooled sensitivity of 0.35 (0.34 – 0.36, 95 % CI). The pooled positive and negative likelihood ratios were derived from the pooled specificity and sensitivity, and calculated to 4.13 (3.60 - 4.66, 95 % CI) and 0.70 (0.65 – 0.75, 95 % CI), respectively. Using the same methodological approach we performed the subgroup analyses presented in table 4.

To explore possible causes of heterogeneity across the studies, we performed univariate meta-regression analyses. For the dichotomous covariates and outcome, the classification = "No" was used as reference value. We did not identify any significant multivariate associations, thus the relative diagnostic odds ratios (rDOR) of the covariates were: Difficult tracheal intubation (rDOR = 1.11 (0.57 - 2.13, 95 % CI)); Blinding (rDOR = 0.94; (0.49-1.79, 95 % CI)); Settings described (rDOR = 1.15; (0.57-2.32), 95 % CI); Selection described (rDOR = 0.72 (0.28;1.86, 95 % CI)); Recruitment described (rDOR = 1.13 (0.58-2.21, 95 % CI)); Phonation (rDOR = 1.20 (0.63-2.30, 95 % CI)); Consecutive (rDOR = 1.40 (0.74-2.62, 95 % CI)). Limited no. evaluators (rDOR = 0.90 (0.47-1.70),

95 % CI)); Limited no. intubators (rDOR = 0.57 (0.30-1.06, 95 % CI)); High risk of bias (rDOR = 1.06 (0.54-2.08, 95 % CI)). In our meta-regression using obstetric and obesity as covariates, we excluded the case control studies evaluating obstetric vs. non-obstetric patients [70;72] and obese vs. non-obese patients [34;45]. Thus, the rDOR were: Obstetric (rDOR = 2.17 (0.76-6.23, 95 % CI)) and Obese (rDOR = 0.31 (0.09-1.03, 95 % CI)). Our evaluation of possible bias evaluated by the Egger's [19] regression intercept demonstrated no evidence of publication bias (t = 0.71, p = 0.48).

Among 92 092 patients from the Danish Anesthesia Database the prevalence of difficult tracheal intubation was 5.1 % (5.0 – 5.3, 95 % CI). Evaluating the performance of the modified Mallampati score as a prognostic test for the prediction of a difficult tracheal intubation demonstrated a sensitivity of 0.22 (0.21 – 0.24, 95 % CI), a specificity of 0.93 (0.92 – 0.93, 95 % CI), a predictive value of a positive test of 0.15 (0.14 – 0.16, 95 % CI), a predictive value of a negative test of 0.96 (0.96 – 0.96, 95 % CI), a positive likelihood ratio of 3.31 (3.12 – 3.51, 95 % CI) and negative likelihood ratio of 0.83 (0.82 – 0.85, 95 % CI). The diagnostic odds ratio was 3.98 (3.70 – 4.28, 95 % CI).

Discussion:

In the meta-analysis, the pooled frequency of difficult tracheal intubation was 6.8 %, which exceed the prevalence of 5.1 % found in our cohort study. None of the estimates derived from the Danish Anesthesia Database were included by the confidence interval of their corresponding pooled estimates of the meta-analyses. In a clinical context, especially the sensitivity and positive likelihood ratios differ. The pooled sensitivity was 0.35 in the meta-analysis and only 0.22 in the cohort study. Further, the positive likelihood ratios of the cohort study and the meta-analysis were 3.31 and 4.13, respectively. Concerning the sROC curve, the degree of accuracy of the test was good [75], as the AUC was greater than 0.75. However, as stand-alone tests both the cohort study and the meta-analysis demonstrated that the modified Mallampati score was an inadequate predictor of a difficult laryngoscopy or tracheal intubation. Hereby, we concur with both Shiga et al [7]and Lee et al [8]. Our assessments were not comparable with the meta-analyses performed by Shiga et al., as their assessment did not distinguish between the original and the modified Mallampati score. Nevertheless, our meta-analysis of the modified Mallampati test differs from the results reported by Lee et al. The pooled estimates of sensitivity reported by Lee et al ranged from 0.55 to 0.76, which was significantly and substantially greater than our findings. Likewise the specificity was remarkably lower than our findings, as it varied between 0.77 and 0.84. Compared with our estimates, Lee et al reported lower pooled positive likelihood ratios ranging from 3.30 to 3.44 and higher AUC ranging from 0.78 and 0.84.

There may be several explanations for these differences. In some of the studies the outcome measure was defined as a difficult tracheal intubation although the real outcome measure was the original Cormack and Lehane score [10]. Contrary to Lee et al, we actually used the Cormack and Lehane score as outcome measure in these studies. Further, our meta-analysis of all studies combines both difficult laryngoscopy and difficult tracheal intubation as one outcome measure. If a study both reported an intubation score and the Cormack and Lehane score based on the same population in the same assessment, only the intubation score was extracted for our assessment. We did that to avoid a wrong sampling error [76]. One aim of Lee et al was to distinguish between a difficult laryngoscopy and a difficult tracheal intubation, and they did not combine these measures. Because they evaluated the outcome measures separately, it seemed correct to

retrieve data on both outcome measures from the same patient population. Therefore, this difference may impact the comparison of our assessment with the previous one of Lee et al. However, the major reason for the differences may be caused by the increased number of studies and patients included in our updated meta-analyses. Thus the number of studies increased from 28 to 55 and the number of included patients increased nearly ten-fold from 17 902 to 177 088.

The meta-analyses all had a high degree of statistical heterogeneity. Additionally, the pooled estimates from our meta-analyses may be influenced by a high degree of clinical diversity. Thus, by whom and how the test was performed and the type of patient population evaluated, varied considerable between the individual studies. E.g., unblinded studies and case-control studies may tend to overestimate the diagnostic accuracy [77]. We suggested four criteria useable for quality and bias evaluation of the included studies. However, our exploration of possible explanations of the statistical heterogeneity with meta-regression analyses of numerous factors like blinding, consecutive recruitment, selected patient populations, estimates of possible bias etc., did not identify the reasons for this heterogeneity. Some studies may be categorized as studies with high-risk of bias, because they were poorly reported, even though the studies may have been properly conducted. Further, in our cohort study because of multiple numbers of evaluators of many patients in an everyday clinical set up, we cannot ensure controlled and uniform evaluation of the Mallampati score.

The number of patients evaluated in each study varied a lot. Together, two studies [13;29] evaluated 149 096 (84 %) of all patients, while the accumulated weight of the two studies in the random effect model evaluating the diagnostic odds ratio was only 6.3 %. Because of this discrepancy, it may not be entirely reasonable to emphasize the interstudy variance when pooling the estimates as it is done in the random-effects model. The random-effects model used for pooling diagnostic studies may have important shortcomings when large cohort studies comprising more than 80 % of the included patients may be inappropriately down-weighted [78;79]. Considering that the ultimate goal of the prognostic test is to guide clinicians in everyday practice, in a clinical environment with diverse settings the studies with very few evaluators adhering strictly to protocol procedures of both evaluation and settings for the intubation may exaggerate the prognostic value. Therefore,

large database studies may convey a more realistic picture of the prognostic value achieved by the Mallampati test. Contrarily, the smaller studies adhering strictly to protocols of both evaluation and settings for the tracheal intubation procedure may describe what is ultimately possible if education and training are optimized. Furthermore, it seems appropriate to emphasize that due to the apparent high precision of some of the studies estimate of diagnostic accuracy [13;29] and these particular estimates discrepancy with the estimates from other studies the statistical heterogeneity measured by I^2 may be exaggerated as pointed out by Rücker et al [80].

Shiga et al evaluated numerous screening tests for difficult tracheal intubation and concluded that they only had poor to moderate discriminative power when used alone [7]. Even though our assessments support that the modified Mallampati Score is inadequate as a stand alone test of a difficult laryngoscopy or tracheal intubation, it may still play a very important roll as a part of a multivariate model for the prediction of a difficult tracheal intubation [23;53]. Numerous studies have failed to present specific risk factors that could identify a difficult intubation or laryngoscopy by it self. Therefore it seems rational to focus even more than hitherto on the development, testing and modification of multivariate models from and in large scale cohort studies, hereby making the prognostication operational in everyday clinical practice.

Table 1. The Danish Anesthesia Database tracheal intubation score.

All patients in whom the primary airway management was planned and attempted for tracheal intubation by direct laryngoscopy were scored as follows:

Score = 1	Intubated by direct laryngoscopy by the first anesthetist and in two attempts maximally.
Score = 2	Intubated by direct laryngoscopy by the first anesthetist but with more than two attempts or intubated by a supervising anesthetist after one or more failed attempts of intubation.
Score = 3	Intubated by a method other than direct laryngoscopy.
Score = 4	Intubation abandoned after multiple attempts, no tracheal tube was inserted.

Difficult tracheal intubation was defined as an intubation score > 1

Table 2. Characteristics of the studies evaluating the modified Mallampati Score

	Outcome measure	No. of patients	Blinding	Setting	Selection	Recruit-ment	Risk of bias.
Adnet F	DTI	1171			Yes	Yes	High
Ali Z	DL	66	Yes		Yes	Yes	Medium
Allahyar E	DL	203	Yes	Yes	Yes	Yes	Low
Arne J	DTI	1200			Yes	Yes	High
Ayuso MA	DTI	181	Yes		Yes	Yes	Medium
Bouaggad A	DTI	320			Yes	Yes	High
Brodsky JB	DTI	100			Yes	Yes	High
Butler P	DL	220			Yes		High
Cattano D	DTI	1956			Yes	Yes	High
Charuluxananan S	DL	57005		Yes	Yes	Yes	Medium
Constantikes J	DL	30		Yes	Yes		High
Domi R	DL	426	Yes		Yes		High
Eberhart LHJ	DL	1107	Yes		Yes	Yes	Medium
Ezri T	DL	764		Yes	Yes	Yes	Medium
Ezri T	DL	1472			Yes	Yes	High
Ezri T	DL	50			Yes		High
Ezri T	DL	644			Yes	Yes	High
Frerk CM	DL	244		Yes			High
Gercek A	DTI	500	Yes		Yes		High
Gupta S	DTI	372	Yes				High
Hester CE	DL	50	Yes		Yes		High
Honarman A	DL	400	Yes		Yes	Yes	Medium
Huh J	DL	213	Yes		Yes	Yes	Medium
Iohom G	DL	212	Yes		Yes		High
Ita CE	DL	57			Yes		High
Juvin P	DTI	245			Yes	Yes	High
Kamalipour H	DL	100	Yes		Yes	Yes	Medium
Kaul TK	DL	500		Yes	Yes		High
Khan ZH	DL	300	Yes		Yes	Yes	Medium
Koh LK	DL	605			Yes	Yes	High
Komatsu R	DL	64			Yes		High
Krishna HM	DL	200	Yes		Yes	Yes	Medium
Krobbuaban B	DL	550	Yes		Yes	Yes	Medium
L'Hermite J	DTI	1023		Yes	Yes	Yes	Medium
Lundstrom LH	DTI	92091		Yes	Yes	Yes	Medium
Mashour GA	DL	346		Yes	Yes	Yes	Medium
Mashour GA	DTI	1133			Yes	Yes	High
Mashour GA	DL	60		Yes			High
Merah NA	DL	80		Yes	Yes	Yes	Medium
Merah NA	DL	380			Yes	Yes	High
Noorizad S	DL	379					High
Rocke DA	DTI	1500	Yes	Yes			High
Samra SK	DL	566			Yes		High
Savva D	DTI	350	Yes	Yes	Yes	Yes	Low
Schmitt H	DL	128		Yes	Yes	Yes	Medium
Siddiqi R	DL	338			Yes		High
Singh R	DL	300			Yes		High
Topcu I	DTI	208			Yes	Yes	High
Torres K	DTI	96				Yes	High
Tuzuner-Oncul A	DTI	208	Yes	Yes			High
Vani V	DL	50		Yes	Yes		High
Wong SH	DL	411	Yes		Yes	Yes	Medium
Yamamoto K	DL	3680	Yes		Yes	Yes	Medium
Yeo SW	DL	560			Yes	Yes	High
Yildiz TS	DTI	1674	Yes		Yes		High

Blinding = blinding of the Mallampati score; DL = difficult laryngoscopy; DTI = difficult tracheal intubation; Recruitment = if the recruitment of study population was described; Selection = if the selection of study population was described; Setting = if the setting of the test was described;

Table 3. Individual studies' evaluating the diagnostic performance of the modified Mallampati Score

	True positive	False positive	False negative	True negative	Prevalence DTI/DL	DOR	Weight (%)	Sens.	Spec.	PosLR
Adnet F	24	54	66	1027	7.7	6.92	2.6	0.27	0.95	5.34
Ali Z	5	13	6	42	16.7	2.69	1.4	0.46	0.76	1.92
Allahyar E	11	42	26	124	18.2	1.25	2.2	0.30	0.75	1.18
Arne J	39	168	11	982	4.2	20.72	2.4	0.78	0.85	5.34
Ayuso MA	29	26	25	101	29.8	4.51	2.4	0.54	0.80	2.62
Bouaggad A	7	8	10	295	5.3	25.81	1.6	0.41	0.97	15.60
Brodsky JB	7	26	5	62	12.0	3.34	1.6	0.58	0.71	1.97
Butler P	10	38	8	164	8.2	5.40	1.9	0.56	0.81	2.95
Cattano D	28	169	28	1731	2.9	10.24	2.6	0.50	0.91	5.62
Charuluxananan S	703	3122	1398	51782	3.7	8.34	3.1	0.34	0.94	5.88
Constantikes J	2	15	0	13	6.7	4.36	0.4	1.00	0.46	1.56
Domi R	30	10	38	348	16.0	27.47	2.2	0.44	0.97	15.79
Eberhart LHJ	92	381	39	595	11.8	3.68	2.9	0.70	0.61	1.80
Ezri T	68	196	13	487	10.6	13.00	2.5	0.84	0.71	2.93
Ezri T	116	354	36	966	10.3	8.79	2.9	0.76	0.73	2.85
Ezri T	3	6	6	35	18.0	2.92	1.1	0.33	0.85	2.28
Frerk CM	11	208	32	393	6.7	0.65	2.4	0.26	0.65	0.74
Gercek A	9	43	2	190	4.5	19.88	1.2	0.82	0.82	4.43
Gupta S	2	15	31	452	6.6	1.94	1.2	0.06	0.97	1.89
Hester CE	15	8	9	340	6.5	70.83	1.8	0.63	0.98	27.19
Honarman A	1	10	8	31	18.0	0.39	0.7	0.11	0.76	0.46
Huh J	22	12	13	353	8.8	49.78	2.1	0.63	0.97	19.12
Iohom G	3	12	23	175	12.2	1.90	1.4	0.12	0.94	1.80
Ita CE	8	22	12	170	9.4	5.15	1.9	0.40	0.89	3.49
Juvin P	0	4	1	52	1.8	3.89	0.4	0.00	0.93	3.17
Kamalipour H	2	75	3	165	2.0	1.47	1.0	0.40	0.69	1.28
Kaul TK	4	0	11	85	15.0	66.91	0.5	0.27	1.00	48.38
Khan ZH	31	24	11	434	8.4	50.96	2.2	0.74	0.95	14.09
Koh LK	14	94	3	189	5.7	9.38	1.5	0.82	0.67	2.48
Komatsu R	14	45	17	529	5.1	9.68	2.3	0.45	0.92	5.76
Krishna HM	6	16	14	28	31.3	0.75	1.7	0.30	0.64	0.83
Krobbuaban B	13	42	4	141	8.5	10.91	1.6	0.77	0.77	3.33
L'Hermite J	48	193	21	288	12.5	3.41	2.6	0.70	0.60	1.73
Lundstrom LH	24	104	36	859	5.9	5.51	2.6	0.40	0.89	3.70
Mashour GA	1042	5898	3620	81531	5.1	3.98	3.2	0.22	0.93	3.31
Mashour GA	7	79	10	250	4.9	2.22	1.9	0.41	0.76	1.72
Mashour GA	55	153	84	841	12.3	3.60	2.9	0.40	0.85	2.57
Merah NA	5	16	1	38	10.0	11.88	0.7	0.83	0.70	2.81
Merah NA	7	3	1	69	10.0	161.00	0.7	0.88	0.96	21.00
Noorizad S	8	7	5	360	3.4	82.29	1.4	0.62	0.98	32.26
Rocke DA	11	81	18	269	7.7	2.03	2.2	0.38	0.77	1.64
Samra SK	19	378	13	1090	2.1	4.21	2.4	0.59	0.74	2.31
Savva D	24	69	24	449	8.5	6.51	2.5	0.50	0.87	3.75
Schmitt H	11	113	6	220	4.9	3.57	1.9	0.65	0.66	1.91
Siddiqi R	25	53	8	42	25.8	2.48	2.1	0.76	0.44	1.36
Singh R	3	53	4	278	2.1	3.93	1.2	0.43	0.84	2.68
Topcu I	0	46	2	252	0.7	1.09	0.4	0.00	0.85	1.07
Torres K	5	11	7	185	5.8	12.01	1.5	0.42	0.94	7.42
Tuzuner-Oncul A	8	15	12	61	20.8	2.71	1.8	0.40	0.80	2.03
Vani V	19	30	13	146	15.4	7.11	2.2	0.59	0.83	3.48
Wong SH	1	4	7	38	16.0	1.36	0.7	0.13	0.91	1.31
Yamamoto K	6	150	1	254	1.7	10.16	0.8	0.86	0.63	2.31
Yeo SW	38	1723	18	1901	1.5	2.33	2.6	0.68	0.53	1.43
Yildiz TS	3	25	8	524	2.0	7.86	1.4	0.27	0.95	5.99
	28	172	52	1422	4.8	4.45	2.7	0.35	0.89	3.24

DL = difficult laryngoscopy; DOR= diagnostic odds ratio; DTI = difficult tracheal intubation; N = number of patients; NegLR = negativ
likelihood ratio; PosLR = positive likelihood ratio; Sens. = sensitivity; Spec = specificity; Weight = weight of each study in a pooled
diagnostic odds ration using a random effect model

Table 4: Pooled estimates of the total cohort and subgroup populations

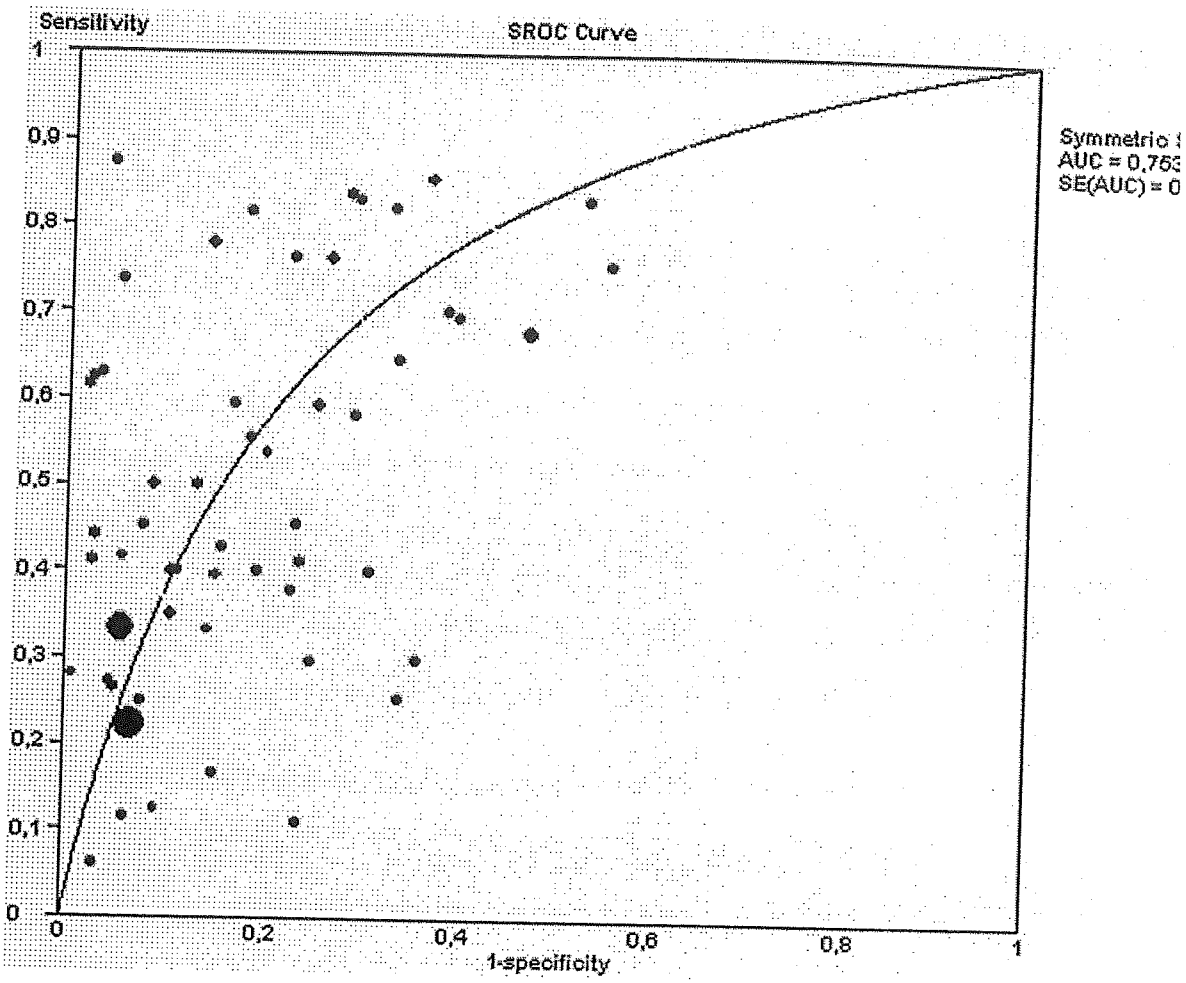
	No studies	No patients	AUC (SE)	Pooled estimates					
				Prev. DTI/DL %	Diagnostic Odds Ratio	Specificity.	Sensitivety	Positive Likelihood Ratio	Negative Likelihood Ratio
Total Population	55	177 088	0,75 (0.03)	7.6 (6.6–8.8)	5.89 (4.74-7.32)	0.91 (0.91-0.91)	0.35 (0.34-0.36)	4.13 (3.60-4.66)	0.70 (0.65–0.75)
Subgroup populations									
DTI	20	104 784	0.77 (0.04)	6.8 (5.3-8.7)	6.33 (4.71-8,49)	0.93 (0.92-0.93)	0.32 (0.31-0.33)	4.61 (3.91-4.30)	0.73 (0.66-0.80)
DL	35	72 304	0.75 (0.04)	8.0 (6.1-10.3)	5.58 (3.92-7.93)	0.90 (0.89-0.90)	0.38 (0.36-0.40)	3.83 (3.06-4.60)	0.69 (0.61-0.77)
Low /medium bias	20	159 198	0.75 (0.03)	8.5 (6.8-10.5)	5.12 (3.74-7.00)	0.92 (0.92-0.92)	0.31 (0.30-0.32)	3.85 (3.13-4.56)	0.75 (68.2-0.82)

AUC = area under the curve; DL = difficult laryngoscopy; DTI difficult tracheal intubation; Prev. = prevalence; SE = standard error. The ( ) of pooled estimates contain the 95 % confidence interval.

ive ıood o	Negative Likelihood Ratio
-4.66)	0.70 (0.65–0.75)
-4.30)	0.73 (0.66-0.80)
-4.60)	0.69 (0.61-0.77)
-4.56)	0.75 (68.2-0.82)

The ( ) of pooled

Figure 1. The summary receiver operator characteristics (sROC) curve of 55 studies evaluating the modified Mallampati score as a predictor for difficult tracheal intubation or difficult laryngoscopy. AUC = area under th SE = standard error.



Reference List

1. Cooper GM, McClure JH: Anaesthesia chapter from Saving mothers' lives; reviewing maternal deaths to make pregnancy safer. Br.J.Anaesth. 2008; 100: 17-22

2. Hove LD, Steinmetz J, Christoffersen JK, Moller A, Nielsen J, Schmidt H: Analysis of deaths related to anesthesia in the period 1996-2004 from closed claims registered by the Danish Patient Insurance Association. Anesthesiology 2007; 106: 675-80

3. Peterson GN, Domino KB, Caplan RA, Posner KL, Lee LA, Cheney FW: Management of the difficult airway: a closed claims analysis. Anesthesiology 2005; 103: 33-9

4. Rosenstock C, Moller J, Hauberg A: Complaints related to respiratory events in anaesthesia and intensive care medicine from 1994 to 1998 in Denmark. Acta Anaesthesiol.Scand. 2001; 45: 53-8

5. Mallampati SR, Gatt SP, Gugino LD, Desai SP, Waraksa B, Freiberger D, Liu PL: A clinical sign to predict difficult tracheal intubation: a prospective study. Can.Anaesth.Soc.J. 1985; 32: 429-34

6. Samsoon GL, Young JR: Difficult tracheal intubation: a retrospective study. Anaesthesia 1987; 42: 487-90

7. Shiga T, Wajima Z, Inoue T, Sakamoto A: Predicting difficult intubation in apparently normal patients: a meta-analysis of bedside screening test performance. Anesthesiology 2005; 103: 429-37

8. Lee A, Fan LT, Gin T, Karmakar MK, Ngan Kee WD: A systematic review (meta-analysis) of the accuracy of the Mallampati tests to predict the difficult airway. Anesth.Analg. 2006; 102: 1867-78

9. Deville WL, Buntinx F, Bouter LM, Montori VM, de Vet HC, van der Windt DA, Bezemer PD: Conducting systematic reviews of diagnostic studies: didactic guidelines. BMC.Med.Res.Methodol. 2002; 2: 9

10. Cormack RS, Lehane J: Difficult tracheal intubation in obstetrics. Anaesthesia 1984; 39: 1105-11

11. Yentis SM, Lee DJ: Evaluation of an improved scoring system for the grading of direct laryngoscopy. Anaesthesia 1998; 53: 1041-4

12. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J: The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC.Med.Res.Methodol. 2003; 3: 25

13. Lundstrom LH, Moller AM, Rosenstock C, Astrup G, Gatke MR, Wetterslev J: Avoidance of neuromuscular blocking agents may increase the risk of difficult tracheal intubation: a cohort study of 103,812 consecutiv adult patients recorded in the Danish Anaesthesia Database. Br.J.Anaesth. 2009; 103: 283-90

14. Lundstrom LH, Moller AM, Rosenstock C, Astrup G, Gatke MR, Wetterslev J: A documented previous difficult tracheal intubation as a prognostic test for a subsequent difficult tracheal intubation in adults. Anaesthesia 2009; 64: 1081-8

15. Higgins JP, Thompson SG, Deeks JJ, Altman DG: Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-60

16. DerSimonian R, Laird N: Meta-analysis in clinical trials. Control Clin.Trials 1986; 7: 177-88

17. Moses LE, Shapiro D, Littenberg B: Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. Stat.Med. 1993; 12: 1293-316

18. Jaeschke R, Guyatt GH, Sackett DL: Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Base Medicine Working Group. JAMA 1994; 271: 703-7

19. Egger M, Davey SG, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-34

20. Adnet F, Racine SX, Borron SW, Clemessy JL, Fournier JL, Lapostolle F, Cupa M: A survey of tracheal intubation difficulty in the operating room: a prospective observational study. Acta Anaesthesiol.Scand. 2001; 45: 327-32

21. Ali Z, Bithal PK, Prabhakar H, Rath GP, Dash HH: An assessment of the predictors of difficult intubation in patients with acromegaly. J.Clin.Neurosci. 2009; 16: 1043-5

22. Allahyary E, Ghaemei SR, Azemati S: Comparison of Six Methods for Predicting Difficult Intubation in Obstetric Patients. Iranian Red Crescent Medical Journal 2008; 10: 194-201

23. Arne J, Descoins P, Fusciardi J, Ingrand P, Ferrier B, Boudigues D, Aries J: Preoperative assessment for difficult intubation in general and ENT surgery: predictive value of a clinical multivariate risk index. Br.J.Anaesth. 1998; 80: 140-6

24. Ayuso MA, Sala X, Luis M, Carbo JM: Predicting difficult orotracheal intubation in pharyngo-laryngeal disease: preliminary results of a composite index. Can.J.Anaesth. 2003; 50: 81-5

25. Bouaggad A, Nejmi SE, Bouderka MA, Abbassi O: Prediction of difficult tracheal intubation in thyroid surgery. Anesth.Analg. 2004; 99: 603-6, table

26. Brodsky JB, Lemmens HJ, Brock-Utne JG, Vierra M, Saidman LJ: Morbid obesity and tracheal intubation. Anesth.Analg. 2002; 94: 732-6

27. Butler PJ, Dhara SS: Prediction of difficult laryngoscopy: an assessment of the thyromental distance and Mallampati predictive tests. Anaesth.Intensive Care 1992; 20: 139-42

28. Cattano D, Panicucci E, Paolicchi A, Forfori F, Giunta F, Hagberg C: Risk factors assessment of the difficult airway: An Italian survey of 1956 patients. Anesthesia and Analgesia.99(6)()(pp 1774-1779), 2004.Date of Publication: Dec 2004. 2004; 1774-9

29. Charuluxananan S, Suraseranivongse S, Punjasawadwong Y, Somboonviboon W, Nipitsukarn T, Sothikarnmanee T, Vasinanukorn M, Werawatganon T, Tanudsintum S, Lekprasert V, Hintong T: The Thai Anesthesia Incidents Study (THAI Study) of anesthetic outcomes: I description of methods and populations. Journal of the Medical Association of Thailand.88(SUPPL.7)()(pp S1-S13), 2005.Date of Publication: Jul 2005. 2005; S1-S13

30. Constantikes J: Predicting difficult tracheal intubation using a modified Mallampati sign: a pilot study report. CRNA. 1993; 4: 16-20

31. Domi R: A comparison of Wilson sum score and combination Mallampati, tiromental and sternomental distances for predicting difficult intubation. Macedonian Journal of Medical Sciences.2(2)()(pp 141-144), 2009.Date of Publication: 2009. 2009; 141-4

32. Eberhart LH, Arndt C, Cierpka T, Schwanekamp J, Wulf H, Putzke C: The reliability and validity of the upper lip bite test compared with the Mallampati classification to predict difficult laryngoscopy: an external prospective evaluation. Anesth.Analg. 2005; 101: 284-9, table

33. Ezri T, Warters RD, Szmuk P, Saad-Eddin H, Geva D, Katz J, Hagberg C: The incidence of class "zero" airway and the impact of Mallampati score, age, sex, and body mass index on prediction of laryngoscopy grade. Anesth.Analg. 2001; 93: 1073-5, table

34. Ezri T, Medalion B, Weisenberg M, Szmuk P, Warters RD, Charuzi I: Increased body mass index per se is not a predictor of difficult laryngoscopy. Can.J.Anaesth. 2003; 50: 179-83

35. Ezri T, Gewurtz G, Sessler DI, Medalion B, Szmuk P, Hagberg C, Susmallian S: Prediction of difficult laryngoscopy in obese patients by ultrasound quantification of anterior neck soft tissue. Anaesthesia 2003; 58: 1111-4

36. Ezri T, Weisenberg M, Khazin V, Zabeeda D, Sasson L, Shachner A, Medalion B: Difficult laryngoscopy: incidence and predictors in patients undergoing coronary artery bypass surgery versus general surgery patients. J.Cardiothorac.Vasc.Anesth. 2003; 17: 321-4

37. Frerk CM: Predicting difficult intubation. Anaesthesia 1991; 46: 1005-8

38. Gercek A, Lim S, Isler FB, Eti Z, Gogus FY: The prediction of difficult intubation with bedside scoring systems. Marmara Medical Journal.16(1)()(pp 16-19), 2003.Date of Publication: Jan 2003. 2003; 16-9

39. Gupta S, Pareek S, Dulara SC: Comparison of two methods for predicting difficult intubation in obstetric patients. Middle East J.Anesthesiol. 2003; 17: 275-85

40. Hester CE, Dietrich SA, White SW, Secrest JA, Lindgren KR, Smith T: A comparison of preoperative airway assessment techniques: the modified Mallampati and the upper lip bite test. AANA J. 2007; 75: 177-82

41. Honarmand A, Safavi MR: Prediction of difficult laryngoscopy in obstetric patients scheduled for Caesarean delivery. Eur.J.Anaesthesiol. 2008; 25: 714-20

42. Huh J, Shin HY, Kim SH, Yoon TK, Kim DK: Diagnostic predictor of difficult laryngoscopy: the hyomental distance ratio. Anesth.Analg. 2009; 108: 544-8

43. Iohom G, Ronayne M, Cunningham AJ: Prediction of difficult tracheal intubation. Eur.J.Anaesthesiol. 2003; 20: 31-6

44. Ita CE, Eshiet AI, Akpan SG: Recognition of the difficult airway in normal Nigerian adults (a prospective study). West Afr.J.Med. 1994; 13: 102-4

45. Juvin P, Lavaut E, Dupont H, Lefevre P, Demetriou M, Dumoulin JL, Desmonts JM: Difficult tracheal intubation is more common in obese than in lean patients. Anesth.Analg. 2003; 97: 595-600, table

46. Kamalipour H, Bagheri M, Kamali K, Taleie A, Yarmohammadi H: Lateral neck radiography for prediction of difficult orotracheal intubation. Eur.J.Anaesthesiol. 2005; 22: 689-93

47. Kaul TK, Deepika, Singh A, Bansal M: Prediction of difficult intubation - Analysis in 500 adult patients. Journal of Anaesthesiology Clinical Pharmacology.14(4)()(pp 323-328), 1998.Date of Publication: 1998. 1998; 323-8

48. Khan ZH, Kashfi A, Ebrahimkhani E: A comparison of the upper lip bite test (a simple new technique) with modified Mallampati classification in predicting difficulty in endotracheal intubation: a prospective blinded study. Anesthesia and Analgesia 2003; 96: 595-9, table

49. Koh LK, Kong CE, Ip-Yam PC: The modified Cormack-Lehane score for the grading of direct laryngoscopy: evaluation in the Asian population. Anaesth.Intensive Care 2002; 30: 48-51

50. Komatsu R, Sengupta P, Wadhwa A, Akca O, Sessler DI, Ezri T, Lenhardt R: Ultrasound quantification of anterior soft tissue thickness fails to predict difficult laryngoscopy in obese patients. Anaesth.Intensive Care 2007; 35: 32-7

51. Krishna HM, Agarwal M, Dali JS, Rampal P, Dua CK: Prediction of difficult laryngoscopy in indian population: Role of ratio of patient's height to thyromental distance. Journal of Anaesthesiology Clinical Pharmacology.21(3)()(pp 257-260), 2005.Date of Publication: Jul 2005. 2005; 257-60

52. Krobbuaban B, Diregpoke S, Kumkeaw S, Tanomsat M: The predictive value of the height ratio and thyromental distance: four predictive tests for difficult laryngoscopy. Anesth.Analg. 2005; 101: 1542-5

53. L'hermite J, Nouvellon E, Cuvillon P, Fabbro-Peray P, Langeron O, Ripart J: The Simplified Predictive Intubation Difficulty Score: a new weighted score for difficult airway assessment. Eur.J.Anaesthesiol. 2009; 26: 1003-9

54. Mashour GA, Kheterpal S, Vanaharam V, Shanks A, Wang LY, Sandberg WS, Tremper KK: The extended Mallampati score and a diagnosis of diabetes mellitus are predictors of difficult laryngoscopy in the morbidly obese. Anesth.Analg. 2008; 107: 1919-23

55. Mashour GA, Stallmer ML, Kheterpal S, Shanks A: Predictors of difficult intubation in patients with cervical spine limitations. J.Neurosurg.Anesthesiol. 2008; 20: 110-5

56. Mashour GA, Sandberg WS: Craniocervical extension improves the specificity and predictive value of the Mallampati airway evaluation. Anesth.Analg. 2006; 103: 1256-9

57. Merah NA, Foulkes-Crabbe DJ, Kushimo OT, Ajayi PA: Prediction of difficult laryngoscopy in a population of Nigerian obstetric patients. West Afr.J.Med. 2004; 23: 38-41

58. Merah NA, Wong DT, Ffoulkes-Crabbe DJ, Kushimo OT, Bode CO: Modified Mallampati test, thyromental distance and inter-incisor gap are the best predictors of difficult laryngoscopy in West Africans. Can.J.Anaesth. 2005; 52: 291-6

59. Noorizad S, Mahdian M: Mallampati and thyromental tests to predict difficult intubation. Journal of Medical Sciences.6(2)()(pp 169-172), 2006.Date of Publication: Mar 2006. 2006; 169-72

60. Rocke DA, Murray WB, Rout CC, Gouws E: Relative risk analysis of factors associated with difficult intubation in obstetric anesthesia. Anesthesiology 1992; 77: 67-73

61. Samra SK, Schork MA, Guinto FC, Jr.: A study of radiologic imaging techniques and airway grading to predict a difficult endotracheal intubation. J.Clin.Anesth. 1995; 7: 373-9

62. Savva D: Prediction of difficult tracheal intubation. Br.J.Anaesth. 1994; 73: 149-53

63. Schmitt H, Buchfelder M, Radespiel-Troger M, Fahlbusch R: Difficult intubation in acromegalic patients: incidence and predictability. Anesthesiology 2000; 93: 110-4

64. Siddiqi R, Kazi WA: Predicting difficult intubation--a comparison between Mallampati classification and Wilson risk-sum. J.Coll.Physicians Surg.Pak. 2005; 15: 253-6

65. Singh R, Jain A, Mishra S, Kohli P: Clinical evaluation for predicting difficult laryngoscopy in obstetric patients. Journal of Anaesthesiology Clinical Pharmacology.25(1)()(pp 38-42), 2009.Date of Publication: January 2009. 2009; 38-42

66. Topcu I, Ovali GY, Yentur EA, Kefi A, Tuncyurek O, Pabuscu Y: Clinical and radiologic evaluations for predicting difficult tracheal intubation. [Italian, English]. Acta Anaesthesiologica Italica / Anaesthesia and Intensive Care in Italy.57(4)()(pp 285-300), 2006.Date of Publication: 2006. 2006; 285-300

67. Torres K, Patel AA, Stylinski K, Blonski M, Torres A, Staskiewicz G, Maciejewski R, Wojtaszek M: The body constitution of patients and intubation scales as predictors of difficult intubation considered in relation to the experience of the intubator. Folia Morphol.(Warsz.) 2008; 67: 171-4

68. Tuzuner-Oncul AM, Kucukyavuz Z: Prevalence and prediction of difficult intubation in maxillofacial surgery patients. J.Oral Maxillofac.Surg. 2008; 66: 1652-8

69. Vani V, Kamath SK, Naik LD: The palm print as a sensitive predictor of difficult laryngoscopy in diabetics: a comparison with other airway evaluation indices. J.Postgrad.Med. 2000; 46: 75-9

70. Wong SH, Hung CT: Prevalence and prediction of difficult intubation in Chinese women. Anaesth.Intensive Care 1999; 27: 49-52

71. Yamamoto K, Tsubokawa T, Shibata K, Ohmura S, Nitta S, Kobayashi T: Predicting difficult intubation with indirect laryngoscopy. Anesthesiology.86(2)()(pp 316-321), 1997.Date of Publication: 1997. 1997; 316-21

72. Yeo SW, Chong JL, Thomas E: Difficult intubation: a prospective study. Singapore Med.J. 1992; 33: 362-4

73. Yildiz TS, Korkmaz F, Solak M, Toker K, Erciyes N, Bayrak F, Ganidagli S, Tekin M, Kizilkaya M, Karsli B, Turan A, Ozcan U: Prediction of difficult tracheal intubation in Turkish patients: a multi-center methodological study. Eur.J.Anaesthesiol. 2007; 24: 1034-40

74. Adnet F, Borron SW, Racine SX, Clemessy JL, Fournier JL, Plaisance P, Lapandry C: The intubation difficulty scale (IDS): proposal and evaluation of a new score characterizing the complexity of endotracheal intubation. Anesthesiology 1997; 87: 1290-7

75. Jones CM, Athanasiou T: Summary receiver operating characteristic curve analysis techniques in the evaluation of diagnostic tests. Ann.Thorac.Surg. 2005; 79: 16-20

76. Altman DG, Bland JM: Statistics notes. Units of analysis. BMJ 1997; 314: 1874

77. Lijmer JG, Bossuyt PM, Heisterkamp SH: Exploring sources of heterogeneity in systematic reviews of diagnostic tests. Stat.Med. 2002; 21: 1525-37

78. Higgins JP, Spiegelhalter DJ: Being sceptical about meta-analyses: a Bayesian perspective on magnesium trials in myocardial infarction. Int.J.Epidemiol. 2002; 31: 96-104

79. Li J, Zhang Q, Zhang M, Egger M: Intravenous magnesium for acute myocardial infarction. Cochrane.Database.Syst.Rev. 2007; CD002755

80. Rucker G, Schwarzer G, Carpenter JR, Schumacher M: Undue reliance on I(2) in assessing heterogeneity may mislead. BMC.Med.Res.Methodol. 2008; 8: 79