

REVIEW OF RANDOMIZED CONTROL TRIALS ASSESSING
THE EFFICACY OF NONINVASIVE VENTILATION (NIV)
IN ACUTE HYPOXEMIC RESPIRATORY FAILURE (AHRF)
IN NON-COPD AND NON-TRAUMA CASES

by

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Thesis Title: Review of Randomized Control Trials Assessing the Efficacy of
Noninvasive Ventilation (NIV) in Acute Hypoxemic Respiratory Failure
(AHRF) in Non-COPD and Non-Trauma Cases

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ABSTRACT

Introduction: In the last two decades, there has been strong evidence supporting the use of noninvasive ventilation (NIV) in COPD cases. While there are advocates in favor of the use of NIV in patients presented with acute hypoxemic respiratory failure (AHRF) non-related to COPD nor chest trauma, efficacy of NIV in these cases is still heatedly debated in the medical research field.

Objective: To critically assess the existing scientific evidence regarding efficacy of NIV as an adjunct therapy, the endotracheal intubation rate, intensive care and hospital length of stay, fatal complications, and mortality rate in patients presented with AHRF in non-COPD, non-trauma situations.

Data Source: A search of PubMed, MEDLINE database from 1990 to 2010, Cochrane Library, and EMBASE from 1990 to 2010 were also conducted.

Study Selection: Randomized controlled trials (n=11) that assessed the efficacy of NIV in patient with AHRF not related to COPD nor trauma, in addition to various cohort studies, observational studies, and some selective conference proceedings that are considered potentially relevant to the topic.

Results: The use of NIV showed a statistically significant decrease in intubation and mortality rates in patients with immunosuppression who developed AHRF. There were also encouraging results in patients who underwent lung resection, and post-abdominal surgical procedures who received NIV to treat AHRF.

Conclusion: This systematic review of a number of RCTs suggests that the use of NIV decreases the need for endotracheal intubation, fatal complications, and mortality rate. However, due to the diversity of study population, there is a great need for more specific trials on less heterogeneous patients with AHRF.

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CHAPTER I: BACKGROUND

What Is Acute Hypoxemic Respiratory Failure?

Acute hypoxemic respiratory failure (AHRF) is severe arterial hypoxemia (low oxygenation in arterial blood) that does not respond to supplemental oxygen provided. It is caused by intrapulmonary shunting of blood (i.e. the availability of perfusion without ventilation) secondary to collapsed or fluid-filling air sacs (alveoli). Symptoms include dyspnea (shortness of breath) and tachypnea (abnormally rapid breathing). AHRF can be diagnosed by obtaining arterial blood gas samples (ABG) and chest radiography. Treatment usually requires mechanical ventilation whether invasive or noninvasive (Beers, Porter, Jones, Kaplan, & Berkwits, 2006).

Noninvasive ventilation (NIV) is the delivery of mechanical ventilation without using an invasive artificial airway for the management of acute respiratory failure caused by various etiologies.

Historical Overview

NIV was first introduced in the early 20th century in the form of negative pressure ventilation in which a patient is placed in a large metal cylinder (iron lung), which encases the patient, who lay on his/her back on a mattress with the head protruding through an air-tight rubber neck seal (see Figure 1). It was widely used during the polio epidemics in the 1900s. The bulk and lack of portability of early tank ventilators stimulated the development of more portable negative pressure devices, including the

chest cuirass (see Figure 2) or “shell” ventilator and raincoat (or wrap) ventilator. The first cuirass, developed in 1876 by Ignaz von Hauke in Austria, consisted of an iron shell covering the anterior part of the thorax with an air-filled rubber edge that created a tight seal around the chest (Mehta & Hill, 2001).



Figure 1. “Iron Lung” is a well-known negative pressure ventilator. Retrieved from: <http://colgurchemistry.com/Science9/Biology/iron%20lung%202.jpg>



Figure 2. “Chest Cuirass” is another type of negative pressure ventilator. Retrieved from United Hayek: <http://nivusers.tripod.com/psfolder/Hayek2.jpg>

Prior to 1950, invasive positive pressure ventilation was exclusively used for the delivery of anesthesia during surgical procedures. However, in 1952 in Copenhagen, Denmark, and during the peak outbreak of the polio epidemic, and due to the overwhelming number of patients who required mechanical ventilation, there was a

massive shortage of negative pressure machines. At that point, positive pressure ventilation was first deployed to treat patients outside the anesthesia departments and the survival rates were much better with the positive pressure ventilation than with the negative pressure ventilation. That success during the difficult epidemic caused clinicians to switch to invasive positive pressure ventilation supported by the first use of intensive care units (ICUs) and by the less expensive, and user-friendly ventilators. Invasive ventilation delivered via endotracheal tube then became the first choice method to provide mechanical ventilation to patients with acute respiratory insufficiency (Mehta & Hill, 2001).

Reemergence of Noninvasive Ventilation

Because of the major complications associated with the use of invasive positive pressure ventilation, the practice of using NIV has increased to avoid such complications. Although invasive positive pressure ventilation is practically reliable in ensuring effective alveolar ventilation, endotracheal intubation involves serious risks of adverse complications: during the process of insertion or removal of the endotracheal tube; during the ventilation application such as barotrauma (i.e., airway injury due to excessive pressure); or those caused by the accidental loss of artificial airways; the bypassing of the patient's natural upper airway filtering and humidification mechanisms (Pingleton, 1988).

Types of Noninvasive Ventilation

NIV comes in two forms, noninvasive positive pressure ventilation (NIPPV) and continuous positive airway pressure (CPAP). NIPPV is a combination of inspiratory pressure support (also known as inspiratory positive airway pressure [IPAP]) plus positive end expiratory pressure (PEEP) (also known as expiratory positive airway pressure [EPAP]) delivered to the patient via a mask interface. Biphasic positive airway pressure (BiPAP1) (Respironics, Murrayville, PA) (see Figures 3 and 4), Bilevel, and noninvasive pressure support ventilation (NIPSV) are also used to describe NIPPV. CPAP provides a baseline constant positive airway pressure throughout inspiration and expiration, whereas BIPAP provides two levels of pressure: IPAP during inspiration and EPAP during expiration phase.



Figure 3. Nasal NIV Mask. Retrieved from:
www.aic.cuhk.edu.hk/web8/NIV%20masks.htm



Figure 4. Respironics Bipap-Vision with full face mask. Retrieved from Respironics.com: www.healthcare.philips.com/main/products/Hospital_Respiratory/Products/Noninvasive_ventilation/respironics_bipap_vision.wpd

Golden Age of Noninvasive Ventilation

Over the last two decades, there has been tremendous development in the field of NIV. In the 1980s, CPAP was delivered via face mask to treat sleep apnea. Later, volume and pressure-control were used to treat cases of chest wall deformity diseases, neuromuscular respiratory disorders, and acute respiratory failure (ARF) (Benditt, 2009).

The implementation of noninvasive positive pressure ventilation (NIV) as a first-line treatment in selected cases of acute respiratory failure is considered the single most important progress in the field of mechanical ventilation in the past two decades. In this review, NIV will be defined as the application of NIV, most commonly in the form of BiPAP, which provides pressure support in addition to positive end expiratory pressure (PEEP), and the other form is continuous positive airway pressure (CPAP), which is the equivalence of PEEP alone. It differs from BiPAP by having no added ventilatory support during the inspiratory cycle (Elliott, Steven, Phillips, & Branthwaite, 1990; Meduri et al., 1991).

CHAPTER II: INTRODUCTION

Strong evidence involving several randomized controlled trials (RCTs) supports the use of NIV as an adjunct to standard therapy for the management of acute exacerbation of chronic obstructive pulmonary disease (COPD) particularly when used in early phases of the disease (Keenan, Powers, McCormack et al., 2002; Ram, Picot, Lightowler, & Wedzicha, 2004). However, evidence supporting the efficacy of NIV in patients with hypoxemic respiratory failure due to causes other than COPD is still debated and has produced conflicting results (Hill, Brennan, Garpestad, & Nava, 2007).

The aim of this study is to conduct a systematic review of RCTs in the medical literature of patients with AHRF unrelated to exacerbation of COPD and chest trauma to assess the efficacy of NIV when combined with the usual medical care (UMC) as compared to the UMC alone. The main outcome measures are endotracheal intubation, ICU and hospital length of stay, complications, and mortality rate.

CHAPTER III: METHOD & PROCEDURES

Search Strategy

A search of PubMed using the terms “non-invasive ventilation”, “noninvasive ventilation”, “non-invasive positive pressure ventilation”, “BiPAP”, and “CPAP” was conducted. Literature searches on NIV in MEDLINE from 1990 to 2010, Cochrane database, EMBASE from 1990 to 2010 were also conducted. In this review, the focus is limited to RCTs only (see Figure 4), and included other articles in the background and the introduction. All of the RCTs are available in full texts using the Albertson Library, Boise State University website (<http://library.boisestate.edu/>).

Selection Criteria

The following criteria were used to select articles:

1. Study design was a randomized controlled trial.
2. Study population consisted of a majority of patients (>60%) with acute hypoxemic respiratory failure not associated with an exacerbation of COPD and not requiring immediate ventilatory assistance.
3. The intervention included noninvasive ventilation (NIV) plus usual medical care (UMC) vs. UMC alone.
4. Outcomes included the need for endotracheal intubation, length of ICU or hospital stay, or ICU and/or hospital mortality.

Study Selection

Initial electronic searches identified 315 studies as potentially relevant to the topic. Of these, studies were excluded for the following reasons:

1. They were not randomized controlled trials or did not evaluate noninvasive ventilation (n = 232).
2. The patients did not have acute hypoxemic respiratory failure or the study population was mixed and patients with acute hypoxemic respiratory failure were not reported separately (n = 72).

The remainder, a total of eleven randomized controlled trials, all fully published, met the set selection criteria (see Figure 5, Table1).

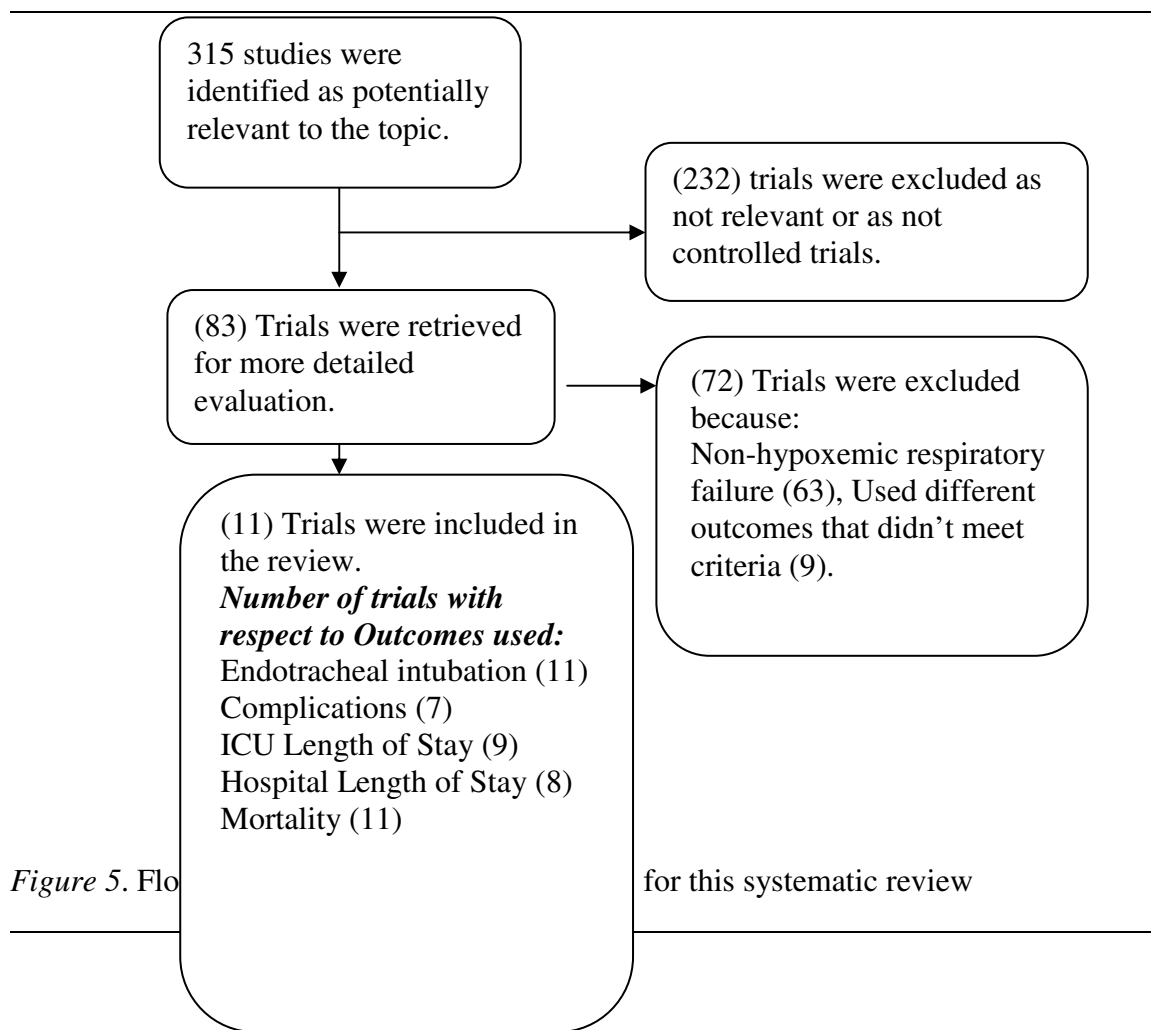


Table 1.

RCTs Included in this Review

<i>Study, year (No. of Participants)</i>	<i>Age (Yrs)</i>	<i>Gender M/F</i>	<i>Disease</i>	<i>Sample size</i>	<i>Informed Consents Obtained</i>
1-Wysocki et al., 1995 (n=41)	NIV=64±18 UMC=62±11	NIV= 12/9 UMC=12/8	ARF (no COPD) PaCO ₂ >45 (n=17) PaCO ₂ ≤45 (n=24)	NIV=21 UMC=20	yes
2- Confalonieri et al., 1999 (n=56)	NIV=66±14 UMC=61±21	NIV=23/5 UMC=17/11	CAP+ARF (n=23), AHRF (n=33)*	NIV=28 UMC=28	yes
3- Antonelli et al., 2000. (n=40)	NIV=45 UMC=44	NIV; 13/7 UMC=12/8	ARF solid organ transplantation	NIV=20 UMC=20	yes
4- Delclaux et al., 2000. (n=123)	NIV=62 UMC=61	NIV=38/24 UMC=40/21	ALI/ARDS	NIV=62 UMC=61	yes
5-Auriant et al., 2001. (n=48)	NIV=58.9±10 UMC=63±9	NR	AHRF post-lung resection	NIV=24 UMC=24	yes
6-Hilbert et al., 2001. (n=52)	NIV=48±14 UMC=50±12	NIV=18/8 UMC=19/7	AHRF-immunosuppressed	NIV=26 UMC=26	yes
7-Keenan et al., 2002. (n=81).	NIV=68.3 (13.1) UMC=68.6 (12.4)	NR	ARF, post-extubation AHRF	NIV=39 UMC=42	yes

Table 1 continues

Table 1 (continued)

<i>Study, year (No. of Participants)</i>	<i>Age (Yrs)</i>	<i>Gender M/F</i>	<i>Disease</i>	<i>Sample size</i>	<i>Informed Consents Obtained</i>
8- Ferrer et al., 2003. (n=105)	NIV=61±17 UMC= 62±18	NIV= 30/32 UMC = 28/26	AHRF	NIV=51 UMC=54	yes
9-L'Her et al., 2004. (n=89)	NIV= 84±6 UMC= 84±6	NIV= 18/28 UMC = 19/24	ACPE Elderly (>75 yrs old)	NIV=43 UMC=46	yes
10-Squadrone et al., 2005. (n=209)	NIV= 65(10) UMC= 66(9)	NIV= 71/34 UMC = 64/40	AHRF Post- operative	NIV=105 UMC=104	yes
11-Gray et al., 2008. (n=1069)	NIV= 77±10 UMC= 79±9	NIV= 393/309 UMC= 213/154	ACPE	NIV=702 UMC=367	yes

NIV: noninvasive ventilation; UMC: usual medical care; ARF: acute respiratory failure;
AHRF: acute hypoxemic respiratory failure; CAP: community acquired pneumonia;
ACPE: acute cardiogenic pulmonary edema; ALI: acute lung injury.

CHAPTER IV: RESULTS

Study Description

Studies included in this review involve an international experience, as they included data from five different countries (France 1, 4, 5, 6 & 9; Italy 2, 3 & 10; Spain 8; Canada 7; and the United Kingdom 11). Five studies involved multiple center trials (2, 4, 8, 10 & 11). Patient populations with hypoxemic respiratory failure enrolled in these 11 RCTs were diverse. Two trials focused on immunocompromised patients (3, 6), two on acute cardiogenic pulmonary edema (ACPE) patients (9, 11), one on post-lung resection surgery patients (5), one on community-acquired pneumonia (CAP) (2), one on post-extubation respiratory failure (7), one on acute lung injury (ALI) (4), one study on post-abdominal surgery (10), and two on more heterogeneous groups of patients (1, 8) (see Table 1).

Study Results

Wysocki et al. Total of 41 patients with non-COPD ARF were included in this RCT between July 1990 and October 1992. Twenty were randomly assigned for UMC, and twenty one were assigned for NIV treatment. Fourteen of the 20 patients (70%) who received UMC alone were endotracheal intubated versus 13 of the 21 patients (62%) who were treated with NIV in addition to UMC ($P=0.88$) (Table 2). The ICU length of stay was 25 ± 23 days in the case of UMC patients and 17 ± 19 days in the case of NIV patients ($P=0.16$). In the UMC group, 10 of the 20 patients (50%) died, and in the NIV

group, 7 of the 21 (33%) patients died ($P=0.46$) (Table 2). In this study population, the authors performed a subgroup analysis between those patients who had hypercapnea $\text{PaCO}_2 > 45$ mm Hg, and the second subgroup that had their $\text{PaCO}_2 \leq 45$ mm Hg. Endotracheal intubation was required in all 6 hypercapnic patients (100%) who received UMC, while only 4 of the 11 hypercapnic patients (36%) required intubation in the NIV group ($P=0.02$). The ICU length of stay was significantly lower in hypercapnic patients treated with NIV (13 ± 15 days versus 32 ± 30 days, $P=0.04$) and 4 of the 6 hypercapnic patients from UMC group died (66%), while one of the 11 hypercapnic patients (9%) died who received the NIV ($P=0.06$). Oppositely, in the subgroup of patients with $\text{PaCO}_2 \leq 45$ mm Hg ($n=24$), there were no positive effects with the use of NIV (Table 2).

Confalonier et al. The study took place between November 1996 and March 1998 and included 56 patients with community-acquired pneumonia (CAP) and ARF from multi-center settings. The population was divided equally, 28 to be treated with UMC alone and 28 with NIV intervention. Twenty-three patients had a history COPD and they were analyzed separately. The other non-COPD patients ($n=33$) were also analyzed separately, which is the group considered in the analysis. In the UMC group, 8 of the 17 patients (47.1%) required endotracheal intubation while 6 of the 16 patients (37.5%) in the NIV group required intubation ($P=0.73$). In the UMC group, the ICU length of stay was 4.8 ± 1.7 days versus 2.9 ± 1.8 days in the NIV group ($P=0.44$). The overall hospital stay was 15.1 ± 2.8 days in the UMC group versus 17.9 ± 2.9 days in the NIV group (0.48). In the UMC group, 4 of the 17 patients (23.5%) died versus 6 of 16 patients (37.5%) in the NIV group ($P=0.47$) (Table 2).

Antonelli et al. The study was conducted between December 1995 and October 1997 and involved 40 patients who received a solid organ transplant (liver, kidney, or lung) and were treated in ICU for AHRF, which occurred post transplantation. There were 20 patients randomly assigned in each group. Fourteen patients (70%) in the UMC group required intubation and 4 patients (20%) in the NIV group ($P = 0.002$). The length of stay among the survivors in the ICU was better in the NIV group (5.5 days versus 9 days in the UMC group; $P=0.03$). The mortality rate in the ICU was 10 patients (50%) in the UMC group versus 4 patients (20%) in the NIV group ($P=0.05$). Finally, serious fatal complications leading to death were significantly higher in the UMC group than the NIV group (10 vs 4; $P= 0.05$) (Table 2).

Delclaux et al. Between September 1997 and January 1999, 123 adult patients admitted with acute respiratory insufficiency secondary to pulmonary edema were recruited at the medical ICUs of 6 hospitals from France, Spain, Tunisia, and Italy. One hundred and two (83%) patients were presented with acute lung injury (ALI) ($\text{PaO}_2/\text{FIO}_2$ ratio ≤ 300 mm Hg), while 21(17%) were classified as having pure cardiac decompensation. Patients with an underlying cardiac disease were equally distributed between the UMC and the CPAP groups. There were 61 patients in the UMC group versus 60 patients in the CPAP plus UMC group. No significant differences were found between the two treatment groups for any of the clinical outcome measures studied, including rate of endotracheal intubation, length of hospital stay, and hospital mortality rate. However, the complications were more common in the CPAP group: 18 (29%) versus 6 (10%) in the UMC group ($P = 0.01$) (Table 2).

Auriant et al. Between May 1999 and July 2000, 48 patients with AHRF following lung resection were enrolled in this RCT. The indication for lung resection was lung cancer for all patients in this population. All the patients were extubated in the operating room after surgery. The study population was randomly assigned to UMC alone (n=24) and NIV plus UMC (n=24). In the UMC alone group, 12 of the 24 patients (50%) required intubation versus only five of the 24 patients (20.8%) in the NIV group ($P=0.035$) (Table 2). Nine patients in the UMC group (37.5%) died, versus only three (12.5%) in the NIV group ($P=0.045$). The ICU and hospital length of stay were similar in the two groups. There was no death in either group after hospital discharge, so that in both groups, in-hospital mortality was equal to 120-d mortality (Table 2).

Hilbert et al. The study took place between May 1, 1998 and December 31, 1999. A total of 52 patients with immunosuppression were admitted to the ICU with AHRF associated with pulmonary infiltrates and fever. There were 26 patients in the UMC group and 26 in the NIV group. Twenty patients of the 26 (77%) in the UMC group required endotracheal intubation versus 12 patients of the 26 (46%) in the NIV group ($P=0.03$). In the UMC group, 18 of the 26 (69%) died in the ICU versus 10 of the 26 (38%) in the NIV group ($P=0.03$). The ICU length of stay among survivors was 9 ± 4 days in the UMC group versus 7 ± 3 days in the NIV group. In the UMC group, hospital mortality was 21 of the 26 (81%) versus 13 of the 26 (50%) in the NIV group ($P=0.02$) (see Table 2).

Keenan et al. The study was conducted between August 1, 1996 and October 31, 1999. Eighty-one patients who required ventilator support for more than 48 hours, or had

a history of either congestive heart failure or chronic lung disease, and developed respiratory distress were randomly assigned to this study (42 patients in the UMC group and 39 patients in the NIV group). There was no statistically significant difference in the reintubation rate between the UMC group and the NIV group. In the UMC group, 29 of the 42 (69%) patients required reintubation versus 28 of the 39 (72%) patients in the NIV group ($P=0.79$). The ICU length of stay was 19.4 days in the UMC group and 15.1 days in the NIV group ($P=0.32$). The UMC group had 29.8 days hospital stay, whereas the NIV group had 32.2 days ($P=0.69$). Both groups had the same mortality rate: 29 of the 42 (69%) in the UMC died versus 27 of the 39 in the NIV group (69%) ($P=0.99$) (Table 2).

Ferrer et al. This study involved 105 patients from three different ICUs diagnosed with severe AHRF, defined as a PaO₂ less than 60 mm Hg for more than 6-8 hours or arterial oxygen saturation via pulse oximetry (SpO₂) persistently below 90% while breathing 50% FIO₂ via Venturi mask. They were randomly assigned to both groups: 54 in the UMC group and 51 in the NIV group. In those who received the UMC alone, 28 of the 54 (52%) required endotracheal intubation while only 13 of 51 (25%) needed intubation in those who were treated with adjunct NIV ($P=0.01$). In the UMC group, 17 patients of the 54 (31%) developed septic shock versus 6 patients of the 51 (12%) in the NIV group ($P=0.02$). In the ICU, 21 patients of the 54 (39%) died in the UMC group versus 9 patients of the 51 (18%) in the NIV group ($P=0.28$) (Table 2).

L'Her et al. The study was conducted in three different emergency departments (EDs) and involved a total of 89 elderly patients (≥ 75 years) admitted to EDs with AHRF related to cardiogenic pulmonary edema (CPE). The population was randomly

assigned to receive UMC (n=46) or NIV, particularly CPAP therapy. In the UMC group, 14 of the 46 (30%) required intubation versus 4 patients (9%) in the NIV group. There were 17 (37%) patients who experienced serious complications in the UMC group versus 4 (9%) in the NIV group. Early 48-hour mortality was significantly lower in the NIV group; 3 of the 43 (7%) patients died versus 11 of the 46 (24%) in the UMC group (P=0.017). In-hospital length of stay was 9±7 days in the UMC group versus 12±11 days in the NIV group (P=0.07) (Table 2).

Squadrone et al. The study took place between June 2002 and November 2003 in multi-center ICUs. A total of 209 patients were randomly assigned to the study if they had AHRF post-elective abdominal surgery, with an arterial oxygen tension to inspiratory oxygen fraction ($\text{PaO}_2/\text{FiO}_2$) ≤ 300 while breathing 50% oxygen via Venturi mask, and had no underlying cardiac or chronic lung diseases. There were 104 patients in the UMC group and 105 patients in the NIV group (which used CPAP in this study). The rate of intubation was lower in the NIV group; only one patient (1%) of the 105 patients required intubation versus 10 patients (10%) in the UMC group (P=0.005). The ICU length of stay was 2.6 days in the UMC group versus 1.4 days in the NIV group (P=0.09). Hospital length of stay was almost similar in the two groups. Serious complications were significantly less in the NIV group: only 2 (2%) of the 105 patients in the NIV group developed pneumonia versus 10 (10%) of the 104 patients in the UMC group (P=0.02). There were no deaths (0%) among the NIV group while three (3%) patients died in UMC group (P=0.12) (Table 2).

Gray et al. This is a multi-center study conducted in 26 emergency departments in district and regional hospitals in the United Kingdom between July 2003 and April 2007. A total of 1069 patients were assigned to a UMC group (367 patients), and 702 patients to a NIV group. There was no significant difference in one week or one month mortality between patients receiving the UMC and those undergoing the NIV. The mortality rate for one week was 9.8% in the UMC group and 9.5% in the NIV group ($P = 0.87$). The mortality rate for one month was 16.4% in the UMC group and 15.2% in the NIV group ($P = 0.64$) (Table 2).

Table 2.

RCTs Results

Study, year (No. of Participants)	ETI & MV (%) UMC vs. NIV	ICU LOS (days) UMC vs. NIV	Hosp. LOS (days) UMC vs. NIV	Complications UMC vs. NIV	Mortality (%) UMC vs. NIV
1-Wysocki et al., 1995 (n=41) PaCO ₂ >45 (n=17) PaCO ₂ ≤45 (n=24)	14(70) vs 13(62) p=0.88 PaCO ₂ >45: 6 (100) vs 4 (36) p=0.02 PaCO ₂ ≤45: 8 (57) vs 9 (90) p=0.19	25±23 vs 17±19 p=0.16 PaCO ₂ >32±30 vs 13+ 15 p=0.04 PaCO ₂ ≤45: 22 ±20 vs 22 ± 22 P = 0.83	NR	NR	10 (50) vs 7(33) P=0.46 PaCO ₂ >45: 4(66) vs 1(9) p=0.06 PaCO ₂ ≤45: 6(43) vs 6 (60) P = 0.76
2- Confalonieri et al., 1999 (n=56) AHRF (n=33) considered	8 (47.1) vs 6 (37.5) P = 0.73	4.8±1.7 vs 2.9±1.8 P=0.44	15.1±2.8 vs 17.9±2.9 P= 0.48	NR	4(23.5) vs 6(37.5) P=0.17
3- Antonelli et al., 2000. (n=40)	14(70) vs 4(20) P= 0.002	9 vs 5.5 P=0.03	NR	10(50) vs 4(20) P= 0.05	10(50) vs 4(20) P= 0.05 ^{icu} 11(55) vs 7(35) P= 0.17 ^{hosp}
4- Delclaux et al., 2000. (n=123)	24(39) vs 21(34) P=0.53	12 vs 15 P=0.43	32 vs 30.5 P=0.77	6(10) vs 18(29) P= 0.01 ↑	18(29) vs 19(31) P= 0.24
5-Auriant et al., 2001. (n=48)	12(50) vs 5(20.8) P=0.035	14 vs 16.65 P= 0.52	22.8 vs 27.1 P= 0.61	NR	9(37.5) vs 3(12.5) P=0.045
6-Hilbert et al., 2001. (n=52)	20(77) vs 12(46) P= 0.03	10±4 vs 7±3 P=0.06	NR	21(81) vs 13(50) P=0.02	21(81) vs 13(50) P= 0.02

Table continues

Table 2 (continued)

Study, year (No. of Participants)	ETI & MV (%) UMC vs. NIV	ICU LOS (days) UMC vs. NIV	Hosp. LOS (days) UMC vs. NIV	Complications UMC vs. NIV	Mortality (%) UMC vs. NIV
7-Keenan et al., 2002. (n=81).	29(69) vs 28(72) P= 0.79	19.4 vs 15.1 P= 0.32	29.8 vs 32.2 P= 0.69	17 (40) vs 16 (41) P = 0.61	29(69) vs 27(69) P=0.99
8- Ferrer et al., 2003. (n=105)	28(52) vs 13(25) P= 0.01	11.3 vs 9.6 P=0.51	26.8 vs 20.7 P=0.09	17(31) vs 6(12) P= 0.028	21(39) vs 9(18) P= 0.028
9-L'Her et al., 2004. (n=89)	14(30) vs 4(9) P=0.01	NR	9 vs 12 P=0.07	17(37) vs 4(9) P=0.002	14(30) vs 12(28) P= 0.8
10-Squadrone et al., 2005. (n=209)	10(10) vs 1(1) P= 0.005	2.6 vs 1.4 P=0.09	17 vs 15 P=0.10	10(10) vs 1(2) P= 0.02	3(3) vs 0(0) P =0.12
11-Gray et al., 2008. (n=1069)	10(2.8) vs 20(2.9) P=0.9	NR	39(10.5) vs 77(11.4) P=0.10	148(40.5) vs 317(45.2) P= 0.15	60(16.4) vs 107(15.2) P= 0.64

ETI & MV: endotracheal intubation and mechanical ventilation; ICU: intensive care unit; LOS: length of stay; UMC: usual medical care; NIV: noninvasive ventilation; ARF: acute respiratory failure; CAP: cardiogenic pulmonary edema; AHRF: acute hypoxemic respiratory failure; ALI: acute lung injury; ACPE: acute cardiogenic pulmonary edema; NR: not recorded.

CHAPTER V: ANALYSIS

The results of this systematic review of the RCTs suggest that the early application of NIV therapy in patients presented with acute hypoxemic respiratory failure decreases the likelihood of endotracheal intubation. By avoiding the endotracheal intubation, there is great potential in improving patient outcome. There is a reduction trend in the rate of endotracheal intubation, ICU length of stay, and ICU mortality in these RCTs (see Table 3). These results were consistent when patients with COPD were excluded.

Immunosuppressed Patients with AHRF

Two of the studies in which immunosuppressed patients with AHRF who received NIV showed statistically significant results in terms of need of endotracheal intubation, rate of complications, and, most importantly, decreased mortality rates (Antonelli et al., 2000; Hilbert et al., 2001) (see Table 3, Figure 6). The success of the NIV in such cases was probably a result of the avoidance of complications associated with the invasive mechanical ventilation in those vulnerable populations (Hill, 2001).

Acute Lung Injury/Acute Respiratory Distress Syndrome (ALI/ARDS)

A study conducted on patients with ALI revealed no benefits from adding CPAP to the UMC in those types of cases. In addition, there were more patients from the CPAP group who developed significantly higher rates of adverse events (Declaux et al., 2000) (see Table 3, Figure 7). This could be due to the delay of conventional mechanical ventilation these patients needed to improve ventilation rather than oxygenation alone. In a similar population, a multi-center cohort study was conducted on a total of 299 patients at 70 ICUs. All patients were labeled as having ALI/ARDS after excluding those who had COPD or CPE. Of those, 209 (70%) were intubated directly without undergoing a NIV trial. The remainder 90 (30%) patients underwent NIV as a first-line therapy. Fifty-four (60%) patients in the NIV group required intubation. The overall ICU mortality was 40% in the NIV group. However, the authors concluded that although the successful NIV trial had a lower mortality rate, the group who failed the NIV trial had a much higher mortality rate than those who were intubated initially without undergoing NIV trials (Demoule et al., 2006a & 2006b). Another cohort study conducted on patients with ALI/ARDS used PS+ PEEP as NIV with limited tidal volume (VT of 6 ml/kg) and adjusted the PS and PEEP according to the patient's need. They managed to avoid intubation in 54% of the NIV patients. There was a statistical significance in the ICU mortality rate between those who avoided intubation (6%), as compared to those who failed the NIV trial (53%). Hospital mortality was also significantly lower in those who avoided intubation (19%) as compared to 54% in the NIV failures (Antonelli et al., 2007) (Table 3).

Post-Extubation AHRF

Keenan and colleagues conducted a study on 81 post-extubation patients who developed AHRF within 48 hours post-extubation, which showed no advantages from the use of the NIV therapy (see Table 3, Figure 8). In addition, another RCT, which is not included in this review, involved 224 patients from various medical centers and went further into this issue: it showed that the mortality rate was higher in the NIV group than in the UMC group (25% versus 14%, $P = 0.048$) (Esteban et al., 2004).

Community-Acquired Pneumonia

The use of the NIV did not result in significant benefits in patients who were presented with CAP and developed AHRF and had no underlying COPD disease (Confalonieri, Potena, & Carbone et al., 1999) (see Figure 9). However, the same author in a non-randomized clinical trial of AIDS patients presented with severe pneumocystis pneumonia and managed by NIV showed improvement in their outcomes as compared to the group who received invasive mechanical ventilation (Confalonieri, Calderini, & Terraciano, et al., 2002). Interestingly enough, in a RCT that involved 105 patients presented with AHRF from heterogeneous causes, the authors indicated a significantly lower intubation rate and death rate in a subgroup of 34 patients with pneumonia treated with NIV as compared to the UMC group (Ferrer et al., 2003) (see Table 3, Figure 9) .

Acute Cardiogenic Pulmonary Edema

One of the RCTs that included 89 patients showed statistically significant improvements in the first 48-hour mortality, the need for intubation, and in the serious complications in elderly patients ≥ 75 years of age admitted to the ED with ACPE and treated with CPAP as compared to another group treated with the UMC (L'Her et al., 2004; Figure 10). However, in contrast to most of the trials that were conducted on ACPE, a larger RCT, which had 1069 patients from various medical centers in the UK, despite showing that the NIV improved dyspnea and arterial blood gases (ABG) in one hour, there were no statistically significant differences between the NIV group and the UMC group, in rate of intubation and in one-week mortality rate (Gray et al., 2008) (see Table 3, Figure 10). A large randomized patient study, (which included 130 patients) from multiple EDs in Italy showed that there were improvements only in PaO₂/FiO₂ ratios, but showed a reduction in hypercapnic patients and not the other patients with PaCO₂ ≤ 45 , which agreed with Gray's conclusion (Nava et al., 2003). On the other hand, Potts in his meta-analysis indicated that there is strong evidence of the efficacy of NIV in the treatment of ACPE (Potts, 2009).

Post-Surgical AHRF

Two RCTs were conducted on post-lung resection (Auriant et al., 2001), and the second assessed the efficacy of NIV to treat AHRF in patients who underwent major abdominal surgery (Squadrone et al., 2005). Both studies showed statistically significant differences in the rate of intubation. NIV successfully treats atelectasis (collapsed lung units), which is very common in post-abdominal surgery. In the post-lung resection

study, the benefit of NIV is probably because of the presence of ACPE, which usually responds well to NIV therapy. Aurient et al. did not assess complications, which showed a significant decrease in Squadrone et al. However, there was a significant reduction in mortality rate in the post-lung resection surgery population, yet there was no statistically significant improvement in post-abdominal surgery when treated with the NIV as compared to the UMC (see Table 3, Figure 11). The noticeable improvements in the post-abdominal surgery could be because those elective cases were not considered a high risk population.

Table 3.

Efficacy of NIV+ UMC versus UMC Alone in This Review:

Study, year (No. of Participants)	Disease	ETI & MV (%) UMC vs. NIV	ICU LOS (days) UMC vs. NIV	Hosp. LOS (days) UMC vs. NIV	Complications UMC vs. NIV	Mortality UMC vs. NIV
1-Wysocki et al., 1995 (n=41)	ARF (no COPD) PaCO ₂ >45 (n=17) PaCO ₂ ≤45 (n=24)	•	•	NR	NR	•
2- Confalonieri et al., 1999 (n=56)	CAP+ARF (n=23), AHRF (n=33)*	•	•	•	•	•
3- Antonelli et al., 2000. (n=40)	ARF solid organ transplantation	↓	↓	NR	↓	↓ ^{ICU}
4- Delclaux et al., 2000. (n=123)	ALI/ARDS	•	•	•	↑	•
5-Auriant et al., 2001. (n=48)	AHRF post-lung resection	↓	•	•	NR	↓
6-Hilbert et al., 2001. (n=52)	AHRF-immunosuppressed	↓	↓	NR	↓	↓
7-Keenan et al., 2002. (n=81).	ARF, AHRF postextubation	•	•	•	•	•

Table continues

Table 3 (continued)

Study, year (No. of Participants)	Disease	ETI & MV (%) UMC vs. NIV	ICU LOS (days) UMC vs. NIV	Hosp. LOS (days) UMC vs. NIV	Complications UMC vs. NIV	Mortality UMC vs. NIV
10-Squadrone et al., 2005. (n=209)	AHRF Post- operative	↓	•	•	↓	•
11-Gray et al., 2008. (n=1069)	ACPE	•	NR	•	•	•

ETI & MV: endotracheal intubation and mechanical ventilation; ICU: intensive care unit; LOS: length of stay; UMC: usual medical care; NIV: noninvasive ventilation; ARF: acute respiratory failure; CAP: cardiogenic pulmonary edema; AHRF: acute hypoxemic respiratory failure; ALI: acute lung injury; ARDS: acute respiratory distress syndrome; ACPE: acute cardiogenic pulmonary edema; •: no significant change; ↓: significant decrease after the use NIV; ↑: increase after the use NIV; NR: not recorded.

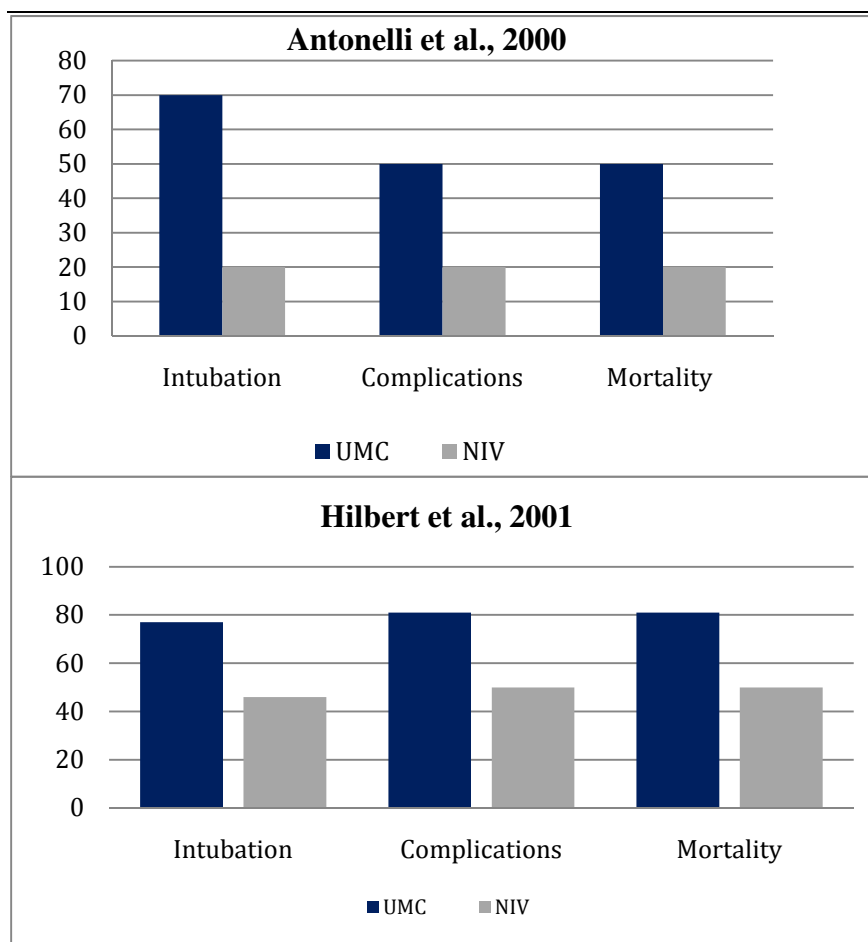


Figure 6. Summary of the subgroup studies of patients with immunosuppression who treated NIV or UMC, which showed a statistically significant decrease in intubation, complication, and mortality rate ($p = 0.02$, $p=0.03$, & $p=0.05$) respectively, and ($p=0.03$, $p= 0.02$ & $p=0.02$) respectively.

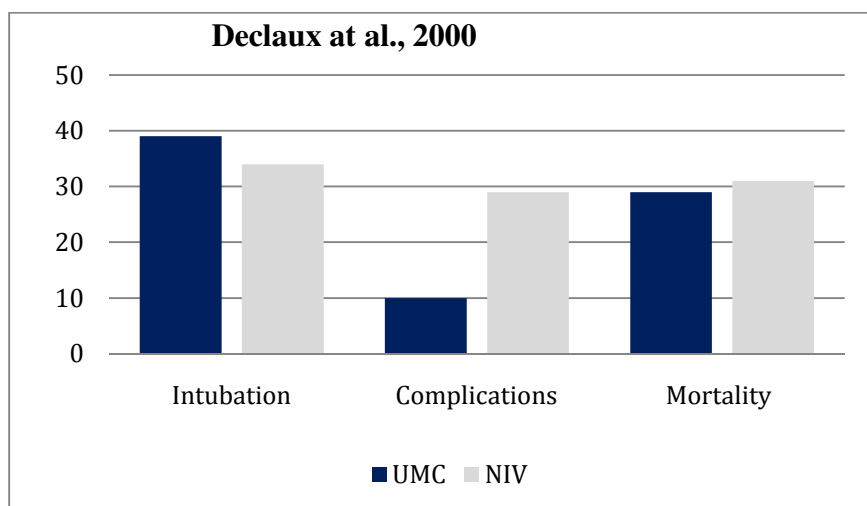


Figure 7. Summary of the subgroup study of patient populations with ALI/ARDS who were treated with NIV or just UMC showing no statistically significant improvement with worse complications in the NIV group.

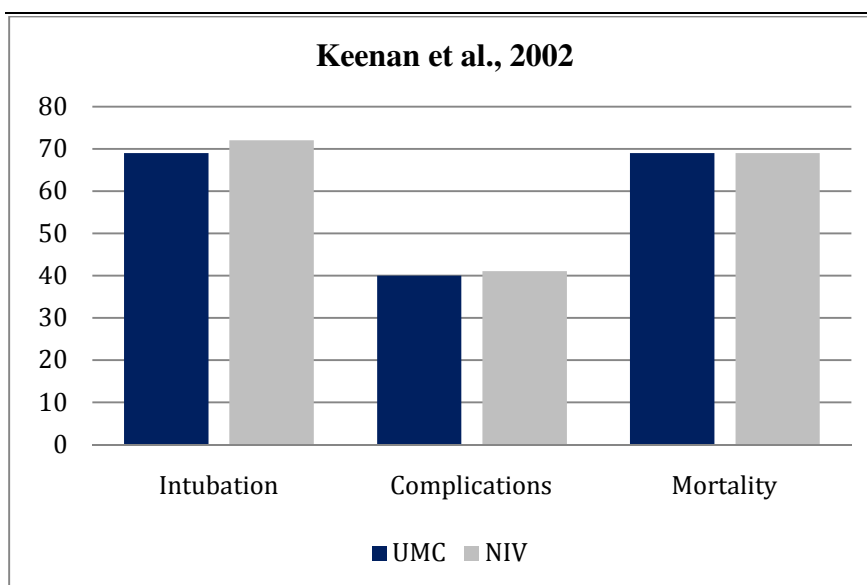


Figure 8. Results of the study of patients with developed AHRF post-extubation and either received NIV or just UMC showing no benefits from the use of NIV in this patients' group.

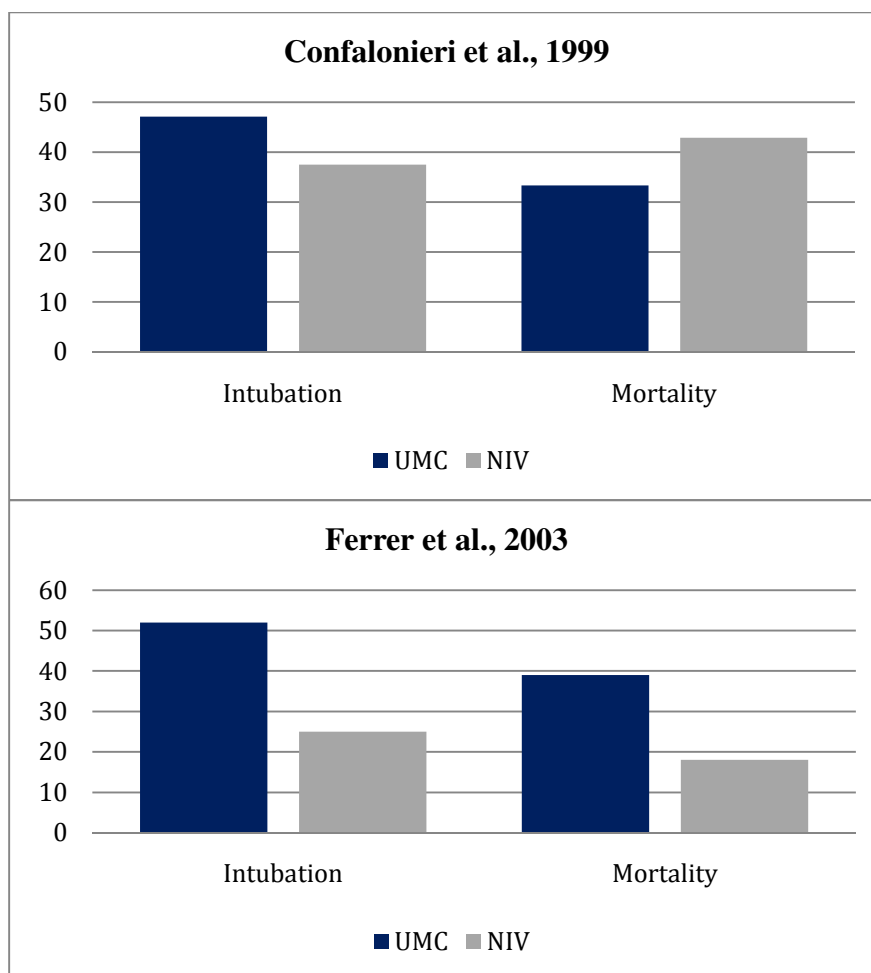


Figure 9. Studies that assessed the effect of NIV as compared to UMC in patients with community-acquired pneumonia who did not have underlying COPD disease. Confalonieri et al. did not show a significant improvement in intubation nor in mortality rates after using NIV, unlike Ferrer et al., which showed a statistically significant improvement in intubation rate ($p = 0.01$) and mortality rate ($p = 0.028$).

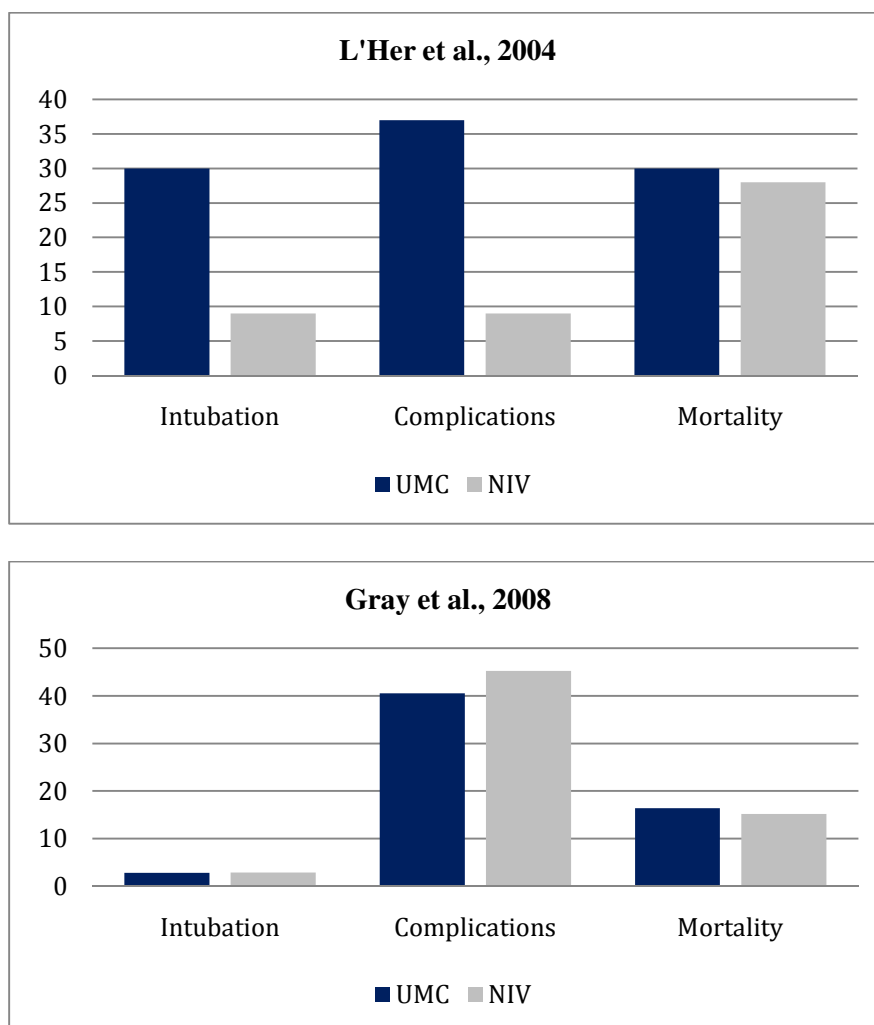


Figure 10. Two studies that assess the efficacy of NIV versus UMC on acute cardiogenic pulmonary edema (ACPE). L'Her et al. showed a significant improvement in both intubation rate ($p = 0.01$) and complications rate ($P = 0.002$), but did not show a significant drop in the mortality rate in elderly patients with ACPE. Gray et al., which involved a larger study sample, didn't show a significant improvement in intubation, complications, or mortality rate.

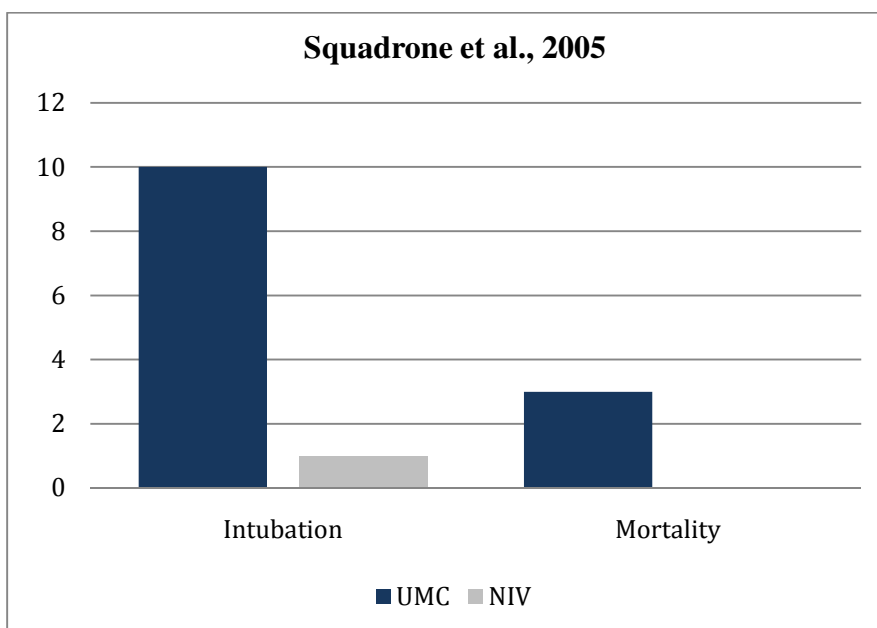
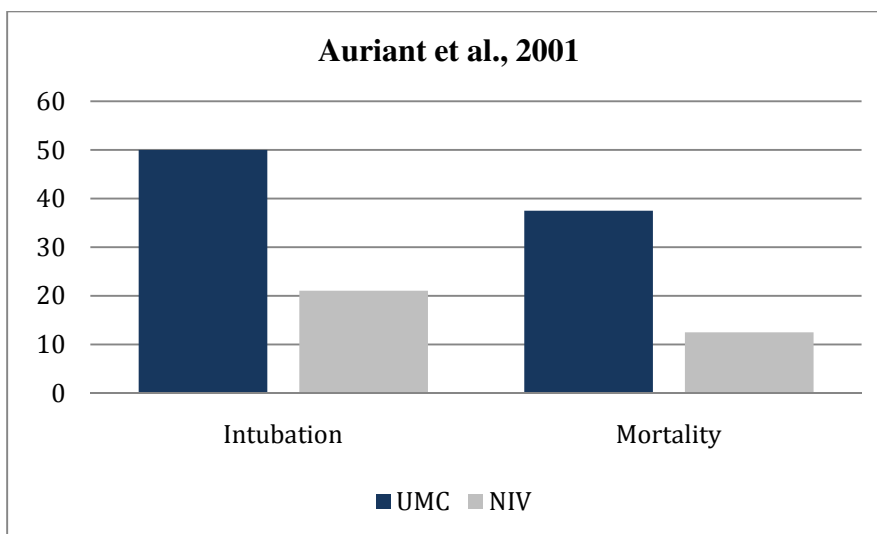


Figure 11. Results of the subgroup in two studies of patients presented post-lung resection AHRF(Auriant et al.), and post-elective abdominal surgery with AHRF, who were treated with NIV versus UMC, showed a statistically significant improvement in intubation rates ($p=0.03$, $p=0.05$). Both also showed a drop in mortality rates. In addition, Squadrone et al. showed a statistically significant improvement in the complications rate ($P=0.02$), which was not recorded in Auriant et al.

CHAPTER VI: CONCLUSION

In the last few years, several randomized and non-randomized trials showed strong evidence of the benefit of using NIV therapy in COPD exacerbation cases. This researcher reviewed the literature to assess the efficacy of NIV in patients with acute hypoxemic respiratory failure (AHRF).

From the analysis of the eleven RCTs that were included in this systematic review, the overall results suggest that the use of NIV in AHRF patients decreases the need for endotracheal intubation, ICU length of stay, and mortality rate. However, it is difficult to generalize these results on most of the AHRF cases due to the wide heterogeneity in the populations of these RCTs and due to small sample sizes in some of the trials. Some subgroups showed clear benefits from the use of NIV as compared to the UMC alone. This was seen in patients with immunosuppression after lung resection, and in patients who underwent abdominal surgery, although the study involved only elective procedures. Nevertheless, there was strong evidence of a significant benefit from the use of NIV in reducing the death rate in ACPE, regardless of the RCT in Gray's et al. In other etiologies, the use of NIV showed various results.

More focused studies that concentrate on patient groups with AHRF, with less heterogeneity in etiology would likely be more reliable. It is noteworthy that increased clinical experience with the application, patient tolerance, and selection of the most appropriate interface is fundamentally important (Kallet, 2009). Additionally, patient monitoring has an important role in improving the outcomes.

The use of NIV should not be a reason to delay endotracheal intubation when it is indicated. Competent personnel such as respiratory therapists and registered nurses in highly monitored clinical settings are always a critical factor for optimal use of NIV and to ensure patient safety.

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