Intensive Care Med (2020) 46:36–45
https://doi.org/10.1007/s00134-019-05828-2

ORIGINAL

Do-not-intubate orders in patients with acute respiratory failure: a systematic review and meta-analysis

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Abstract

Purpose: To assess the rates and variability of do-not-intubate orders in patients with acute respiratory failure.

Methods: We conducted a systematic review of observational studies that enrolled adult patients with acute respiratory failure requiring noninvasive ventilation or high-flow nasal cannula oxygen from inception to 2019.

Results: Twenty-six studies evaluating 10,755 patients were included. The overall pooled rate of do-not-intubate orders was 27%. The pooled rate of do-not-intubate orders in studies from North America was 14% (range 9–22%), from Europe was 28% (range 13–58%), and from Asia was 38% (range 9–83%), $p = 0.001$. Do-not-intubate rates were higher in studies with higher patient age and in studies where do-not-intubate decisions were made without reported patient/family input. There were no significant differences in do-not-intubate orders according to illness severity, observed mortality, malignancy comorbidity, or methodological quality. Rates of do-not-intubate orders increased over time from 9% in 2000–2004 to 32% in 2015–2019. Only 12 studies (46%) reported information about do-not-intubate decision-making processes. Only 4 studies (15%) also reported rates of do-not-resuscitate.

Conclusions: One in four patients with acute respiratory failure (who receive noninvasive ventilation or high-flow nasal cannula oxygen) has a do-not-intubate order. The rate of do-not-intubate orders has increased over time. There is high inter-study variability in do-not-intubate rates—even when accounting for age and illness severity. There is high variability in patient/family involvement in do-not-intubate decision making processes. Few studies reported differences in rates of do-not-resuscitate and do-not-intubate—even though recovery is very different for acute respiratory failure and cardiac arrest.

Keywords: Intensive care units, Critical care, Acute respiratory failure, Do-not-intubate, Noninvasive ventilation, Palliative care

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Introduction

Acute respiratory failure is a common reason for admission to the intensive care unit (ICU), accounting for approximately one-third of ICU admissions [1–3]. In addition to treating the underlying etiology, the range of supportive treatments for patients with acute respiratory failure includes supplemental oxygen, high-flow nasal cannula oxygen, noninvasive ventilation, invasive mechanical ventilation via endotracheal tube or tracheostomy, extracorporeal membrane oxygenation (ECMO), as well as palliative treatments such as opioids.

While intubation and invasive mechanical ventilation is a cornerstone of supportive treatment for acute respiratory failure, a proportion of patients do not receive invasive mechanical ventilation due to factors such as patient preference for no intubation, physician belief that intubation would not offer any therapeutic benefit (e.g., for a dying patient), or lack of resource availability resulting in triaging ICU beds and ventilators to other patients. A decision to not pursue invasive mechanical ventilation may be reflected in the patient's medical record with a do-not-intubate (DNI) order. Decisions to pursue DNI may occur at any point in a patient's medical course—in the outpatient setting, on the medical ward or emergency department, or when the patient has respiratory failure in the ICU. Such decisions may be revisited when the patient's diagnosis, prognosis, or goals of medical treatment change.

Decisions to place a DNI order may have important consequences for individual patients. While patients with DNI orders have a significantly increased risk of hospital mortality (up to five times greater) compared to patients without DNI orders [4], it remains unclear if this is due to the DNI order or merely a reflection of the increased severity of illness and comorbid conditions in patients for whom a DNI order is placed. Placement of DNI orders and thus withholding of invasive mechanical ventilation may facilitate delivery of treatment that is in agreement with patient preferences and goals [5]. Notwithstanding, more than half of all patients with acute respiratory failure who receive noninvasive ventilation and also have a DNI order survive to hospital discharge—often with no worse quality of life compared to those without a DNI order [4].

While prior studies have identified considerable variability in decisions to withhold or withdraw life support therapies [7–9], the rates of DNI and inter-hospital variability in DNI orders are unknown—especially in patients with acute respiratory failure who are at the highest risk of requiring intubation. Understanding the rates of DNI and DNI-specific variability is an important step in improving DNI decision making. The objectives of this study were to (1) assess the rates of DNI in patients with acute respiratory failure and (2) determine if there was inter-study variability in rates of and methods to decide DNI status.

Take home message

One in four patients with acute respiratory failure has a do-not-intubate order and rates of do-not-intubate orders appear to be increasing over time. There is high inter-study variability in rates of do-not-intubate—even when accounting for age, illness severity, and decision making processes.

Methods

We conducted a systematic review of observational studies of adult patients with acute respiratory failure which reported rates of DNI orders. Eligible studies enrolled hospitalized patients who received noninvasive ventilation or high-flow nasal cannula oxygen. The manuscript follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements [10]. The protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO #: CRD42017059914).

Data sources and searches

We searched CINAHL, PubMed, MICROMEDEX, MEDLINE, EMBASE, Scopus, and Web of Science databases from inception to February 18, 2019 using a medical librarian-designed search strategy (Supplemental Table 1). Independent reviewers, working in pairs, screened the titles, and abstracts of all citations using pre-specified inclusion and exclusion criteria. Studies included by either reviewer were retrieved for full-text screening. Independent reviewers, again working in pairs, screened the full-text version of eligible references. Discrepancies between the reviewers were resolved through consensus. If consensus could not be reached, a third reviewer resolved the difference.

Outcomes measures and analysis

The primary outcome was rates of DNI. Secondary outcomes were decision-making process to determine DNI and rates of DNR. We conducted subgroup analyses, identified a priori, based on country, patient age (< 60, 60–75, and > 75 years), treatment received (noninvasive ventilation, high flow nasal cannula, both), cancer comorbidity (vs no cancer comorbidity), predicted hospital mortality using severity of illness scores, observed hospital mortality rates, and methodological quality (high vs low). A post hoc analysis was conducted to evaluate the possible change in rate of DNI orders

over time (publication year categories of 1970–1999, 2000–2004, 2005–2009, 2010–2014, and 2015–2019). Methodological quality of studies was independently assessed by 2 authors using a modified Newcastle–Ottawa Quality Assessment Scale for cohort studies (Supplemental Table 2) [11]. Pooled estimates were generated using random effects meta-analyses with variance stabilization using the Freeman Turkey double arcsine method [12]. I^2 was used to estimate variation across studies attributable to heterogeneity. I^2 ranges from 0 to 100% with low I^2 representing low heterogeneity [13]. Two-tailed p value < 0.05 is considered as statistically significant. All statistical analyses were conducted using Stata/SE version 15.1 (StataCorp LLC, College Station, TX).

Results

Study characteristics

Twenty-six unique studies (published in 27 manuscripts) evaluating 10,755 patients with acute respiratory failure were included [6, 14–39]. Supplemental Figure 1 shows the results of search strategy. Table 1 summarizes the characteristics of included studies. Studies were conducted in North America ($n=6$), Europe ($n=12$), and Asia ($n=8$). Mean/median age of patients ranged from 50 to 82 years. Studies treated patients in the ICU, respiratory care units, hospital wards, emergency departments or a combination of these settings. Studies described patients who utilized noninvasive ventilation ($n=17$), high-flow nasal cannula oxygen ($n=8$) or both ($n=1$). Nineteen studies recruited patients with acute respiratory failure of any cause. Seven studies reported results of DNI in cancer patients only. The methodological quality of included studies was high in 9 studies and low in 17 studies (Supplemental Table 3). Sources of low methodological quality included poor sample representativeness (single center studies only), small sample size, no clear distinction between patients with DNI orders and comfort measure only orders, and limited description of the decision making process for DNI orders.

Rates of do-not-intubate orders

The overall pooled rate of DNI orders was 27%. Rates of DNI from individual studies widely varied and ranged from 9 to 58%. The pooled rate of DNI in studies from North America was 14% (range 9–22%), from Europe was 28% (range 13–58%), and from Asia was 38% (range 9–83%), $p=0.001$ (Fig. 1). The pooled rates of DNI according to age were 20% (age < 60 years), 22% (age 60–75 years), and 49% (age ≥ 75 years), $p=0.001$ (Fig. 2).

There were no statistically significant differences in rate of DNI orders based on predicted mortality using severity of illness scores or based on observed mortality rates (Supplemental Figures 2 and 3). There were no statistically significant differences in rates of DNI when looking at studies enrolling cancer patients only vs studies who enrolled patients without cancer (20% vs 30%) or studies using noninvasive ventilation compared to high-flow nasal cannula oxygen (23% vs 37%) (Supplemental Figures 4 and 5). There was also no difference in DNI rates among studies with high vs low methodological quality (Supplemental Figure 6).

The pooled rates of DNI orders increased over time (Fig. 3 and Supplemental Figure 7). For studies published from 2000 to 2004 ($n=1$ study), the pooled rate of DNI was 9%. For studies published from 2005 to 2009 ($n=4$ studies), the pooled rate of DNI was 19%. For studies published from 2010 to 2014 ($n=7$ studies), the pooled rate of DNI was 26%. For studies published from 2015 to 2019 ($n=14$ studies), the pooled rate of DNI was 32%.

Methods for decision making

Only 12 of 26 studies reported information about the decision-making process for DNI (Table 2). Seven studies reported patient or family involvement in decision making and 5 studies reported that patients or families were not involved in the decision making process. Studies, where patients or families were not reported to be involved in DNI decision making, had higher rates of DNI (36% vs 18%, $p=0.015$) (Supplemental Figure 8). Factors reported to be considered when making DNI decisions: age, prognosis, baseline health (functional status, cognition, quality of life, living in a nursing home), patient wishes, family wishes, and comorbidities.

Differentiating do-not-resuscitate from do-not-intubate

Only 4 out of 26 studies also reported a rate of DNR (Table 1). In three studies, the rates of DNR were the same as DNI (i.e., all patients were DNR and DNI). In one study, the reported rate of DNI was 12% and the reported rate of DNR was 55% [19].

Discussion

This systematic review demonstrates several findings. First, 1 in 4 patients who utilize noninvasive ventilation or high-flow nasal cannula for acute respiratory failure has a DNI order. Second, there is high inter-study variability in published rates of DNI orders, even when

Table 1 Studies reporting rates of do-not-intubate orders of hospitalized patients

Study	Country	Location within hospital	Included only patients with cancer?	Patients with DNI order % (*n*)	Patients with DNR orders % (*n*)	Reported patient/family involvement in DNI decision making	Age	Severity of illness	Observed hospital mortality (%)
Levy et al. 2004 [25]	USA	ICU, Ward	No	9% (114/1211)		Yes	78 (72–84)[b] (DNI)		57
Meert et al. 2005 [14]	Belgium	ICU	Yes	21% (18/87)		No	68 (29–81)[b] (DNI)	SAPS II: 42(15-58)[b]	
Farha et al. 2006 [29]	USA	Ward	No	18% (14/76)			63 (13)[a]		
Bulow et al. 2007 [31], Bulow and Thorsager 2009 [30]	Denmark	ICU	No	24% (38/157)		Yes	73 (47–91)[b] (DNI hospital survivors) 73(54–98)[b] (DNI hospital non-survivors)	APACHE: 18 (10–26)[b] (DNI hospital survivors) 21(15–42)[b] (DNI hospital non-survivors)	
Fernandez et al. 2007 [28]	Spain	ICU	No	15% (34/233)			74 (9.4)[a] (DNI) 67 (14.6)[a] (full code)	APACHE II: 20 (7.9)[a] (DNI) 18 (7.1)[a] (full code)	34
Epstein et al. 2011[19]	USA	ICU, Ward	Yes	12% (22/183)	55% (101/183)		67 (20–95)[b]		44
Soler Barnes et al. 2011 [23]	Spain	ICU	No	25% (658/2590)					
Schortgen et al. 2012 [24]	France	ICU	No	16% (61/376)					44
Azoulay et al. 2013 [6]	France, Belgium	ICU	No	26% (206/780)		Yes	76 (65–83)[b] (DNI) 66(57–76)[b] (full code)	SAPS II: 41(35–51)[b] (DNI) 36(27–47)[b] (full code)	18
La Regina et al. 2013 [27]	Italy	Ward	No	58% (85/147)		No	82 (47–96)[a]		28
Lemyze et al. 2013 [26]	France	ICU	No	13% (74/573)		Yes	75 (64–80)[b] (DNI)	SAPS II: 40(35–49)[b]	23
Del Campo Molina et al. 2014 [22]	Spain	RCU	No	45% (95/211)	45% (95/211)	No	78 (41–97)[a]	APACHE II: 18(12–33)[a]	32
Bugov et al. 2015 [17]	USA	ICU, Ward	Yes	22% (8/36)	22% (8/36)		54 (19)[a]		31
Lee et al. 2015 [16]	South Korea	ICU, Ward	Yes	14% (7/52)			50 (2)[a]	APACHE II: 17 (0.6)[a]	62
Durey et al. 2016 [15]	South Korea	ED	Yes	36% (4/11)			72 (10.6)[a]	APACHE II: 23 (4)[a]	36
Harada et al. 2016 [18]	Japan		Yes	41% (23/56)			59 (24–82)[b]	SAPS II: 43 (14–88)[b]	
Ugurlu et al. 2016 [21]	USA	ICU, Ward, ED	No	19% (97/499)					
Vilaca et al. 2016 [20]	Portugal	ED	No	29% (70/243)		No	82 (75–87)[b] (DNI)		57
Hibi et al. 2017 [34]	Japan		No	38% (188/495)					
Duan et al. 2018 [33]	China	ICU	No	9% (140/1539)		Yes	69 (14)[a] (NIV < 14 days) 72 (14)[a] (NIV ≥ 14 days)	APACHE II: 16 (4)[a] (NIV < 14 days) 17 (4)[a] (NIV ≥ 14 days)	17
Ito et al. 2018 [37]	Japan	ICU, Ward, ED	No	37% (120/321)			76 (66–83)[b]		36
Kang et al. 2018 [39]	South Korea	ICU, Ward	No	55% (50/91)			65 (12)[a]	APACHE II: 22 (5)[a]	63

Table 1 (continued)

Study	Country	Location within hospital	Included only patients with cancer?	Patients with DNI order % (*n*)	Patients with DNR orders % (*n*)	Reported patient/family involvement in DNI decision making	Age	Severity of illness	Observed hospital mortality (%)
Makino et al. 2018 [38]	Japan		No	83% (48/58)			78[a]		50
Brambilla et al. 2019 [35]	Italy	ED, Respiratory ward	No	30% (103/347)		No	77 (66–85)[b] 74 (14)[a]	APACHE II: 18 (6)[a]	24
Hedsund et al. 2019 [36]	Denmark	Ward	No	49% (141/304)	49% (141/304)	Yes	76[a]		30
Liu et al. 2019 [32]	Canada	ICU	Yes	9% (7/79)		Yes	56 (14)[a]	APACHE II: 28 (5)[a]	41

All values are for entire cohort (Full Code + DNI patients) unless otherwise specified. Blank boxes signify the result was not reported

DNI do not intubate, *DNR* do not resuscitate, *ICU* intensive care unit, *NIV* noninvasive ventilation, *HFNC* high-flow nasal cannula, *RCU* respiratory care unit, *ED* emergency department, *USA* United States of America

[a] Mean (standard deviation)

[b] Median (interquartile range)

accounting for factors such as age, country, and illness severity. Third, there is high variability in the reported decision-making processes of individual studies to determine DNI. Fourth, few studies reported differences in rates of DNR and DNI—even though chances for recovery are better for acute respiratory failure compared with cardiac arrest. Fifth, published rates of DNI increased over time from 9% in 2000–2004 to 32% in 2015–2019.

Variability in DNI orders according to global location may reflect differences in policies, practices, medical ethics, social attitudes, culture, and religion [7, 40–42]. Characteristics of patients, families, physicians, and hospitals (including ethical climates, implementation of advance care planning, as well as availability of ICU beds and ventilators) also play important roles [7, 8, 43–58]. A recent global analysis of clinicians' views on ethical aspects of withholding and withdrawing life support showed that although there are important differences between countries and hospitals within a country, the largest differences are accounted for by differences between individual clinicians within a hospital [40]. Increasing rates of DNI orders over the past 20 years may reflect increased focus on high quality end-of-life care, changing ethical climates [55, 56], or increased recognition of the utility of noninvasive ventilation in patients who are not candidates for intubation. Higher rates of DNI orders in Europe and Asia (compared to North America) could also reflect these same principles (e.g., increased physician anticipation of end-of-life).

Patients with DNI orders have variable goals of care (ranging from curative intent to solely symptom relief). Therefore, it is important to evaluate DNI orders in the context other potential treatment limitations such as DNR orders or orders to stop all life-prolonging treatments such as antibiotics, dialysis, surgery, etc. ("comfort measures only"). Shared decision making, a collaborative decision-making process involving both physician and patient/family input, has been endorsed by a panel of experts from 32 countries worldwide [59]. Nevertheless, integration of shared decision making into practice is variable and there are few tools to help clinicians, patients, and families. In some settings, written DNI orders may not accurately reflect patient wishes—as some patients with written DNI orders may actually prefer a trial of intubation as long as the ventilator would be withdrawn if intubation becomes prolonged [60]. Nevertheless, in countries where life support withdrawal may be culturally unacceptable or even illegal, there may be a greater tendency to avoid intubation altogether.

Our manuscript has several limitations. First, there was significant heterogeneity of included studies and we were methodologically unable to perform a multivariate analysis. Second, we could not account for institutional variation in multi-center studies which reported pooled estimates only. Third, data regarding patient/family involvement may be limited as reporting these data was not a primary purpose of many included studies. Fourth, we presented observational data only and did not evaluate the association of DNI status or treatments used on

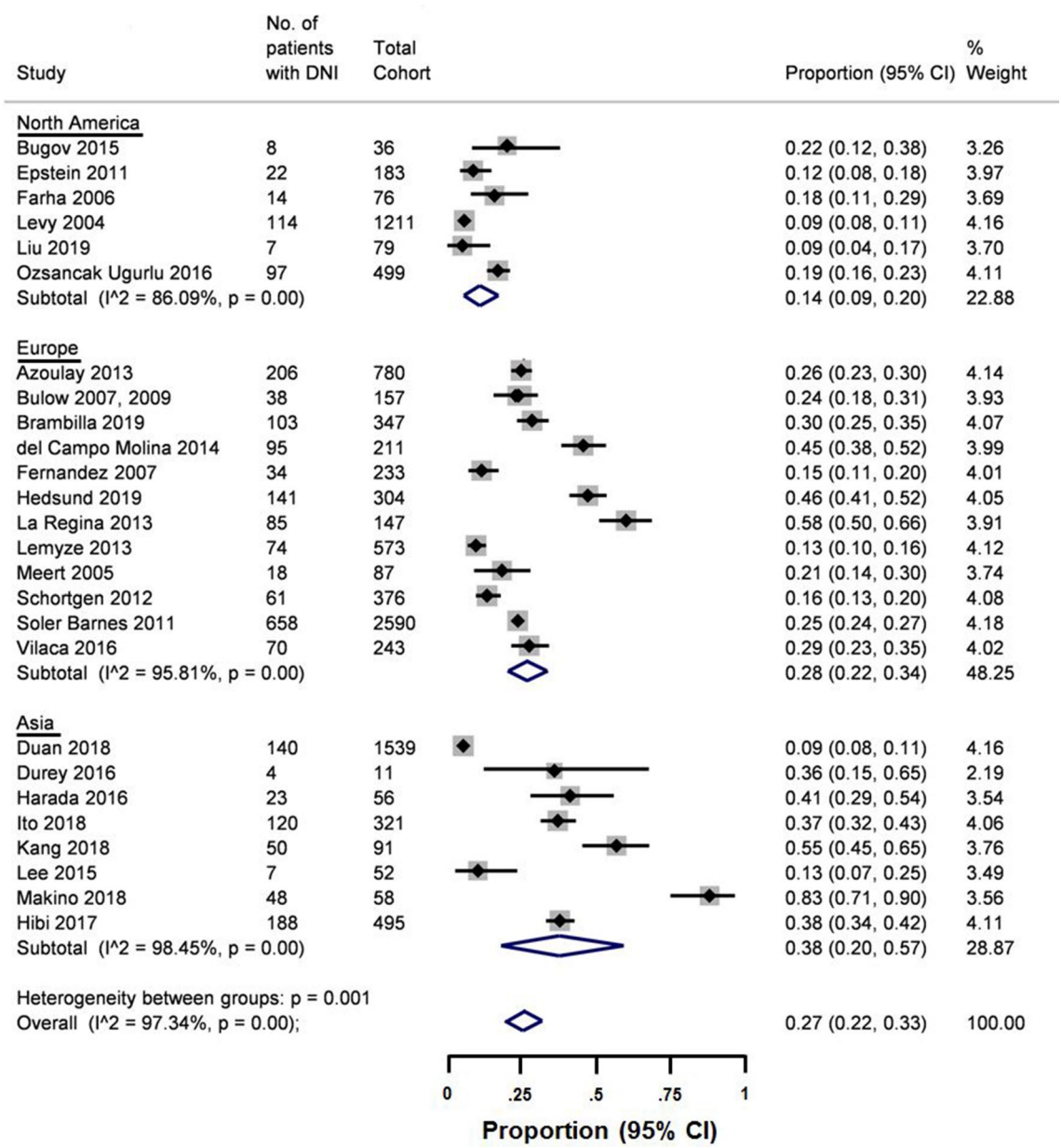

Fig. 1 Rates of do-not-intubate orders in patients with acute respiratory failure according to study location. The diamond under each subgroup represents the pooled proportion of patients with do-not-intubate (DNI) orders. The width of the diamond represents the 95% confidence interval (CI) of the pooled proportion

clinical outcomes. Fifth, study results may not generalize to institutions, where such epidemiological studies have not been performed. Sixth, DNI rates may be different in patients who were not receiving noninvasive ventilation or high-flow nasal cannula oxygen. Seventh, evaluations for characteristics such as patient age and illness severity were based on study population means, as we were unable to perform individual patient data analysis. Eighth, 65% of included studies were of low methodological quality; nevertheless, there were no significant DNI rate differences based on quality.

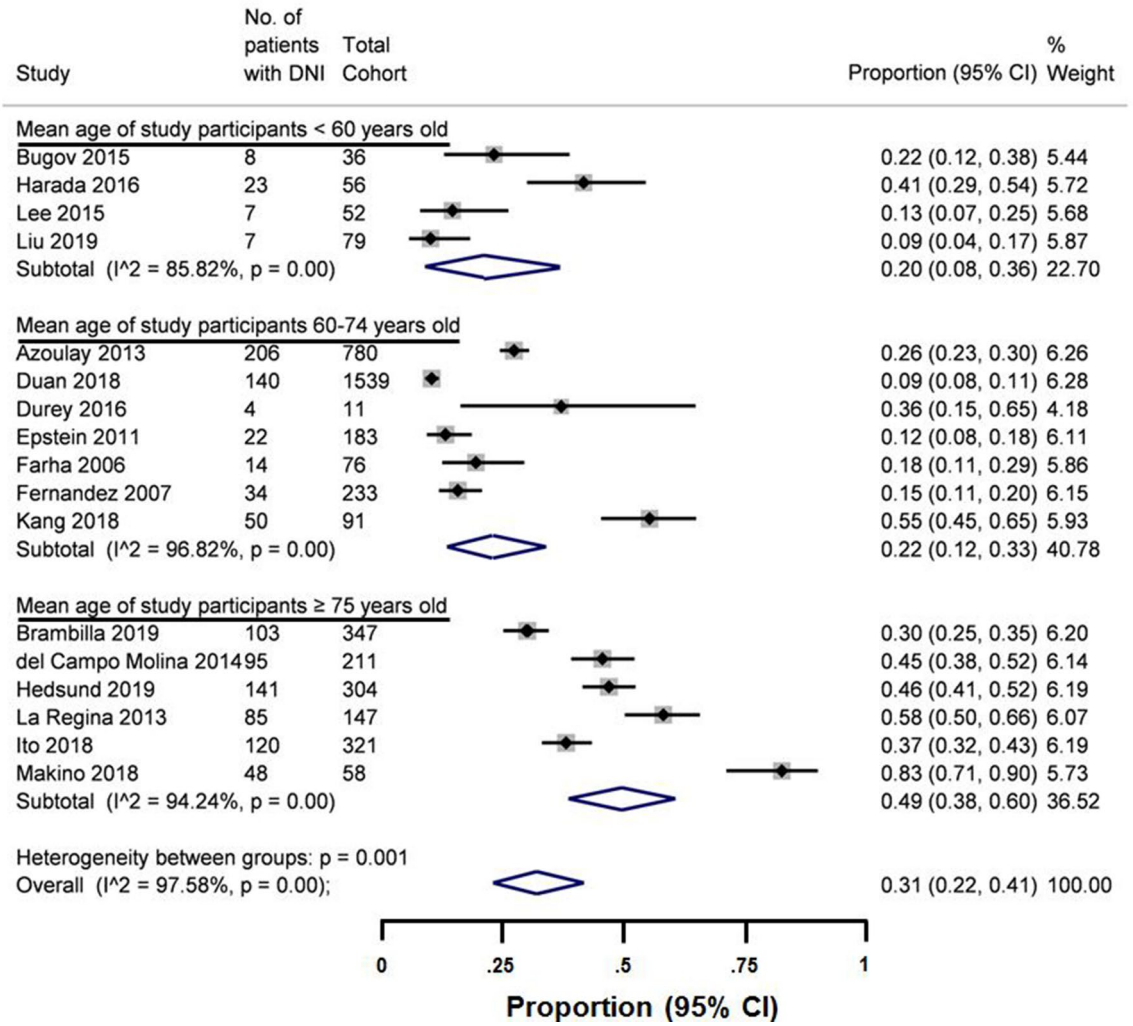

Fig. 2 Rates of do-not-intubate orders in patients with acute respiratory failure according to mean age of study participants. The diamond under each subgroup represents the pooled proportion of patients with do-not-intubate (DNI) orders. The width of the diamond represents the 95% confidence interval (CI) of the pooled proportion. Median age was used when the mean was not available

In conclusion, while this manuscript builds on the previous work to categorize DNI-specific variability, significant work remains to explore the non-physiological indications for clinician choice to provide non-invasive oxygenation support to patients in respiratory failure. Future considerations also include evaluating the impact of DNI orders and treatments (e.g., noninvasive ventilation) on short- and long-term outcomes when adjusted for individual patient characteristics, as well as the development and testing of interventions to improve DNI decision making. Truly understanding DNI variability across continents can only be achieved by benchmarking long-term outcomes in patients with and without DNI orders across geographical regions, cultures, and ethical climates.

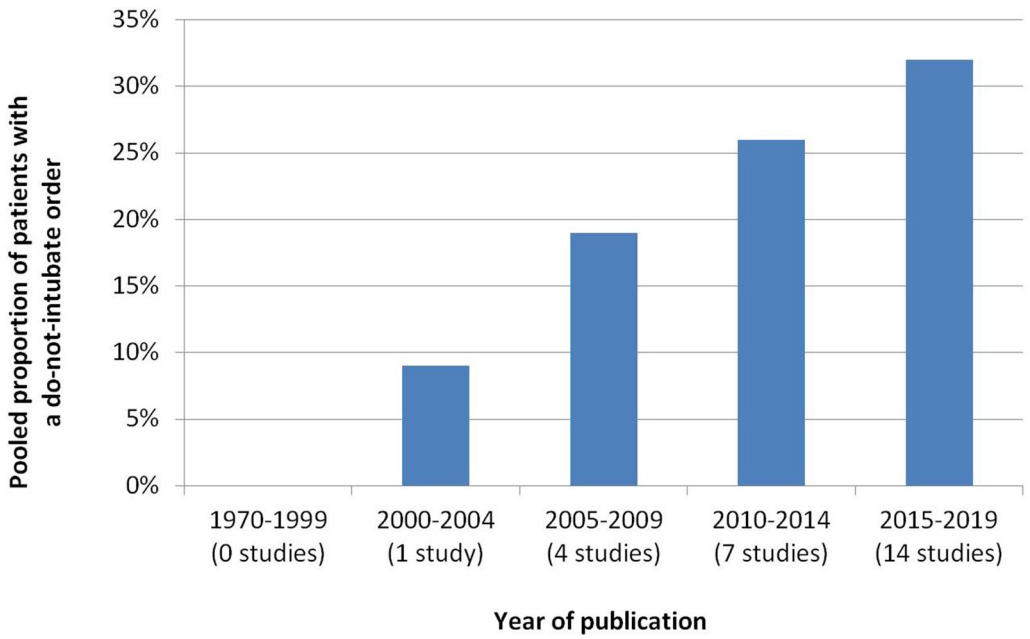

Fig. 3 Rates of do-not-intubate orders in patients with acute respiratory failure according to publication year

Table 2 Description of do-not-intubate decision-making process

Study	Country	Description of DNI decision making process
La Regina et al. [27]	Italy	"We considered DNI patients to be those of advanced age, bed-ridden, with severe cognitive impairment, and/or severe and multiple comorbidities and/or short life expectancy."
Del Campo Molina et al. [22]	Spain	DNI was based on physician assessment of "age, comorbidities, or poor prognosis." DNI status was then "reported to the family."
Vilaca et al. [20]	Portugal	"Withholding therapy decision" group, comprised patients for whom a decision was made by the attending physician not to start or increase a life-sustaining intervention."
Azoulay et al. [6]	France, Belgium	DNI was defined as "patients who themselves declined tracheal intubation and those in whom the healthcare staff considered that tracheal intubation was not appropriate"
Bulow et al. [31], Bulow and Thorsager [30]	Denmark	"The reasons for DNI orders were patient's own wish, or very low pulmonary capacity, very low physical ability at home with a low quality of life, referred from a nursing home, concomitant severe disease with a low life expectance and often a combination of these reasons."
Lemyze et al. [26]	France	"This decision was made by the patient himself whenever possible, or by a multidisciplinary team including physicians and nurses caring for the patient when the latter does not have the capacity to make such a decision. Clinicians involved in the decision process included at least an intensivist and either a pulmonologist or a cardiologist, who did not participate in the present study. Patients were classified as do-not-intubate when their physical disability and their underlying debilitating conditions made them poor candidates for intubation. The patient's family was informed in a clear and loyal manner, and all efforts were provided to make them understand and adhere to the medical decision."
Levy et al. [25]	USA	"23 of the DNI patients had advanced directives and had declared their wishes prior to admission, and the remainder had their DNI status established following admission."
Brambilla et al. [35]	Italy	"Do Not Intubate (DNI) order was defined as the decision of the physician in charge to withhold intubation and to use NIV as "ceiling" treatment considering the characteristics of the patients (e.g., extremely poor functional status prior on admission, very low predicted probability of hospital survival)"
Hedsund et al. [36]	Denmark	"DNR/DNI orders were placed after assessment of the patient's general daily activity level and functional impairment, severity of disease, comorbid conditions, and patient's own wish and with less consideration to the course of current treatment. Senior physicians were always consulted and if possible, the patient and their relatives too."
Duan et al. [33]	China	"A do-not-intubate (DNI) order can be made at ICU admission or at NIV as a first-line treatment failure. It was decided by patients themselves or their families."
Meert et al. [14]	Belgium	"The staff consisting of physicians, including intensivists, decides this [life support limitation order] during regular meetings in the department."
Liu et al. [32]	Canada	"We included patients who had a do-not-intubation (DNI) advance directive at the time of NIV initiation or whose goals of care were changed to DNI during ICU admission."

DNI do not intubate, *DNR* do not resuscitate, *NIV* noninvasive ventilation

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05828-2) contains supplementary material, which is available to authorized users.

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Funding
This project received no funding.

Compliance with ethical standards

Conflicts of interest
The authors have no conflicts of interest to disclose.

Publisher's Note

Received: 26 August 2019 Accepted: 7 October 2019
Published online: 28 October 2019

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