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ORIGINAL ARTICLE

# 'Do-not-intubate' orders in patients assisted by noninvasive respiratory support for acute hypoxaemic failure caused by coronavirus disease 2019; a systematic review and meta-analysis

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**BACKGROUND** Noninvasive respiratory support (NIRS) has been revealed feasible solutions to cope with the massive request for ventilatory support in patients subjected to 'do-not-intubate' order (DNI).

**OBJECTIVES** The aims of the present systematic review and meta-analysis was to estimate pooled incidence of DNI orders and the associated in-hospital mortality in patients undergoing NIRS for hypoxaemic acute respiratory failure (ARF) related to coronavirus disease 2019 (COVID-19).

**DESIGN** Systematic review of observational studies and randomized-controlled trials with meta-analyses

**DATA SOURCES** PUBMED, EMBASE, and Cochrane Controlled Clinical trials register were searched for observational studies and randomised-controlled trials from inception to the end of April 2022.

**ELIGIBILITY CRITERIA** Inclusion criteria were: observational studies enrolling $\geq$50 hospitalised patients with hypoxaemic COVID-19-related ARF requiring NIRS and DNI order application. Two authors independently extracted data from enrolled investigations. Data are presented as proportions with 95% confidence interval.

**RESULTS** Thirty-one observational studies were included for a total of 6645 COVID-19 patients undergoing NIRS, of whom 1590 received DNI orders. Among patients assisted by NIRS, a DNI order was expressed in a summary estimate of 25.4% [20.0–31.1] of the cases with a high between-study heterogeneity. The summary estimated of in-hospital mortality was 83.6% [75.3–90.7] for DNI patients and 20.0% [14.2–26.5] for full treatment patients, both with a high between-study heterogeneity.

**CONCLUSIONS** In COVID-19 patients assisted through NIRS for hypoxaemic ARF, a DNI order was frequently issued and associated with a high in-hospital mortality

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**KEY POINTS**

- Noninvasive respiratory support is feasible in patients subjected to 'do-not-intubate' orders.
- 'Do-not-intubate' order depends on patients' clinical status and wishes, and relatives' wishes.
- 'Do-not-intubate' orders are associated to a high in-hospital mortality.

## Introduction

Hypoxaemic acute respiratory failure (ARF) is the main cause of hospital admission in patients with coronavirus-19 disease (COVID-19).[1] Among patients admitted for hypoxaemic ARF related to COVID-19, invasive mechanical ventilation (IMV) onset has been described varying from 9% to 33%.[2–5] Due to the rapid spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak and massive demand for ventilatory assistance, the intensive care unit (ICU) surge capacity response was overloaded worldwide.[6,7] Several strategies had been developed to increase ICU capacity[6,8] and, at the same time, stabilise patients' respiratory status to avoid intubation.[9] In this context, noninvasive respiratory support (NIRS), that is, continuous positive airway pressure (CPAP), noninvasive bi-level ventilation, and high flow oxygen (HFO) therapy, played a key role in treatment of hypoxaemic ARF in the lower dependency wards outside the ICU.[9,10] In turn, NIRS modes have demonstrated to be effective strategies to avoid intubation[9–11] and, at the same time, to reduce mortality compared with conventional oxygen therapy in patients suffering from COVID-19 related hypoxaemic ARF.[11]

Since the very beginning of the COVID-19 pandemic, NIRS has been shown to be a feasible approach to cope with the massive demand for ventilatory support and also in those patients in whom a decision to not pursue IMV was taken, that is, with a 'do-not-intubate' (DNI) order.[9] According to recent data obtained principally from an Italian experience,[9] the rate of DNI order administration in patients undergoing noninvasive bi-level ventilation and CPAP during the first wave of COVID-19 outbreak reached 23%, with a pooled in-hospital mortality of 72%. Thus, after two years from the spread of COVID-19, describing updated insights on the rate of application of DNI orders and the associated in-hospital mortality in the cohort of COVID-19 patients undergoing NIRS for hypoxaemic ARF, including also HFO, could be particularly relevant for both the optimisation of patient care, as well as hospital resource allocation in pandemic scenarios. In addition, shedding light on the clinical and nonclinical factors underlying the decision-making process for the administration of such a DNI order could provide significant information on the clinical evaluation of patients in contexts such as that of the COVID-19 outbreak.

The aim of the present systematic review and meta-analysis was to estimate the pooled incidence of DNI orders in patients undergoing NIRS for COVID-19 related hypoxaemic ARF. As secondary aim, the associated intra-hospital mortality and all the factors underlying the use of NIRS as a ceiling ventilatory support therapy were assessed in the same population. We hypothesised that, in the COVID-19 pandemic context, the application of DNI orders might have been exceptionally elevated due to the imbalance between the massive influx of patients requiring NIRS and the hospital surge capacity response also reported worldwide.

## Methods

The present systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines[12] and was registered on PROSPERO (CRD42021271313).

### Patients, intervention, comparator, outcome) questions

We sought information about the application of NIRS (CPAP, noninvasive bi-level ventilation, and HFO (I) in adult patients admitted for hypoxaemic ARF consequent to COVID-19 (P) with or without comparator (C) and aimed to ascertain the rate of application of DNI orders and the related intra-hospital mortality (O). Regarding the rate of application of DNI orders and in-hospital mortality we took the time-points of applications of the DNI and in-hospital mortality reported by each enrolled study at database closure.

### Search strategy and study selection

We searched PUBMED, EMBASE and the Cochrane Controlled Clinical trials register from inception to April 2022 for observational studies and randomised controlled trials without language restrictions. The search was carried out applying the following terms, combined according to database syntax (search strategy in additional file 1, Supplemental Digital Content, http://links.lww.com/EJAIC/A21):

'COVID-19', 'Novel Coronavirus 2019', 'SARS-CoV-2', 'SARS-CoV-19', 'Severe Acute Respiratory Syndrome', 'Severe Acute Respiratory Syndrome Coronavirus related', 'Positive Pressure Respiration', 'NIV', 'Non Invasive Ventilation', 'CPAP', 'Continuous Positive Airway Pressure', 'noninvasive positive pressure respiration', 'NIPPV', 'NIRS', 'Non-Invasive Respiratory Support', 'High flow oxygen therapy', 'high flow nasal cannula', 'Do not intubate orders', 'limitations of care', 'ceiling therapy', 'ceiling therapies'.

In addition, we reviewed the references of the selected papers, review articles, commentaries, and editorials on

the same topic to discover other relevant studies missed during the primary search.

The titles and abstracts of the investigations retrieved from the search were independently evaluated by two authors (G.C. and T.E.) according to the following inclusion criteria: observational studies or randomised clinical trials enrolling ≥50 patients admitted for hypoxaemic ARF related to COVID-19 requiring NIRS and applications of DNI orders. In case of potentially overlapping cohorts from multiple publications of the same research group/centre, the most recent publication was selected. The same authors separately evaluated the full texts, and any divergence was resolved by discussion or involving a senior review author (EDR). When necessary, the corresponding authors of the selected studies were contacted to obtain essential information not available in the published format.

### Data extraction, study quality, and bias assessment

Once study screening and selection were completed, two authors (G.C. and T.E.) independently extracted data from these. Similarly, any disagreement was resolved by discussion or involving a senior review author (E.D.R.). Data extracted included: investigation features (e.g., study design, setting), demographic characteristics (e.g., age, sex, body mass index), presence of comorbidities (with special attention to hypertension, diabetes, kidney disease, respiratory disease, and cardiac disease), Charlson comorbidity index,[13] characteristics at hospital admission, e.g., arterial oxygen tension to inspired oxygen fraction ratio ($PaO_2/FIO_2$), peripheral oxygen saturation ($SpO_2$), respiratory rate, laboratory tests, NIRS regulations, rescue therapies, DNI order application, and clinical outcomes.

The articles selected were evaluated for methodological quality according to the classification of the different items of methodological index for nonrandomized studies (MINORS) tool, namely prospective calculation of the study size, loss to follow-up less than 5%, follow-up period appropriate to the study aim, unbiased assessment of the study endpoint, endpoints appropriate to the study aim, prospective data collection, inclusion of consecutive patients, and a clearly stated aim, as adequate, inadequate, or unclear.[14]

### Statistical analysis

The analysis was conducted on the data obtained from peer-reviewed manuscripts.

All the selected variables considered in the included studies were descriptively analysed. Continuous or non-continuous variables were reported as appropriate. Proportions with 95% confidence intervals (CIs) and model fitting weights were calculated through the Der Simonian-Laird method[9] with a random-effects model, based on the expected heterogeneity. The Freeman–Tukey double-arcsine transformations were considered to stabilise and weigh the variances of incidence measures.[15]

Heterogeneity across the studies was assessed through both $Q$ and $I^2$ tests, which were considered significant when the $P$-value was $<0.05$ and $I^2 > 75\%$,[16] along with graphical evaluation of forest plots for the summary estimate of patients who received DNI orders assisted by NIRS and the related in-hospital morality, summary estimate of patients who deemed as deserving full treatment assisted by NIRS and the related in-hospital morality, and the summary estimate of patients assisted by NIRS overall.

A general linear (mixed-effects) meta-regression model was carried out by using the outcome as the dependent variable and the study size as the independent variable. In patients admitted for hypoxaemic ARF consequent to COVID-19 and undergoing NIRS, meta-regression was conducted to assess the impact of study type (retrospective *vs.* prospective), country where study was conducted (Italian vs. non-Italian study), in-hospital setting (in- *vs.* outside ICU), and center characteristics (university *vs.* hospital center). The variables were chosen if reported in all the studies included in the meta-analysis. The observations were weighted by the inverse variance of the estimate to allow for possible heteroscedasticity.

The analyses have been conducted with the R 4.2.1 (R Core Team 2022) System with the meta and metafor packages.[17,18]

## Results

The search identified a total of 1825 potentially eligible records, as illustrated in additional File 2, Supplemental Digital Content, http://links.lww.com/EJAIC/A22. Once duplicates were excluded, titles and abstracts were screened and full texts were evaluated (additional File 3, Supplemental Digital Content, http://links.lww.com/EJAIC/A23). Thirty-one eligible observational studies were identified for a total of 26 100 patients with COVID-19 related infection on hospital admission, of whom 6645 received NIRS.[10,19,28–37,20,38–47,21,48,49,22–27] Among the patients receiving NIRS, 5055 subjects were deemed as deserving 'full treatment' while 1590 patients received a DNI order (additional file 4-Table 1, Supplemental Digital Content, http://links.lww.com/EJAIC/A24).

### Characteristics of the studies included

The main characteristics of the selected studies are described in additional File 4-Table 2, Supplemental Digital Content, http://links.lww.com/EJAIC/A24. Among the 31 investigations included, three were prospective studies and 14 were multicenter studies; 42.5% of the enrolled studies were carried out in Italy from the end of February to the end of May 2020, and 38.7% of the included investigations was performed in ICU. Moreover, as reported in additional File 4-Table 2, Supplemental Digital Content, http://links.lww.com/EJAIC/A24, 48.4% of the included studies were performed in university centres.

The MINORS tool, assessing the methodological quality of the investigations included, is described in additional File 4-Table 3, Supplemental Digital Content, http://links.lww.com/EJAIC/A24 and additional File 5, Supplemental Digital Content, http://links.lww.com/EJAIC/A25.

### Patient characteristics

The overall demographic characteristics of the patients' population subjected to NIRS are reported in additional File 4-Table 4, Supplemental Digital Content, http://links.lww.com/EJAIC/A24, whereas the demographic characteristics of 'full treatment' patients and DNI patients undergoing NIRS are described in additional File 4-Table 5, Supplemental Digital Content, http://links.lww.com/EJAIC/A24 and additional File 4-Table 6, Supplemental Digital Content, http://links.lww.com/EJAIC/A24, respectively.

In additional File 4 -Table 7, Supplemental Digital Content, http://links.lww.com/EJAIC/A24, additional File 4 -Table 8, Supplemental Digital Content, http://links.lww.com/EJAIC/A24, and additional File 4 -Table 9, Supplemental Digital Content, http://links.lww.com/EJAIC/A24, $PaO_2/FiO_2$, respiratory rate, and $SpO_2$ acquired on hospital admission are reported for the total population, 'full treatment' patients, and DNI patients undergoing NIRS, respectively.

The settings of NIRS are shown in additional File 4-Table 10, Supplemental Digital Content, http://links.lww.com/EJAIC/A24, additional File 4-Table 11, Supplemental Digital Content, http://links.lww.com/EJAIC/A24, and additional File 4-Table 12, Supplemental Digital Content, http://links.lww.com/EJAIC/A24 for the total study population, full treatment patients, and DNI patients under NIRS, respectively.

The studies providing criteria for the application of DNI orders are presented in additional File 4-Table 13, Supplemental Digital Content, http://links.lww.com/EJAIC/A24. In the 32 studies enrolled, 12 investigations reported criteria for the application of DNI orders.[10,20–22,26,29,32,36–38,46,49] Among these, 16.7% of the studies were conducted in nonuniversity centres whereas 50% were conducted in exclusively university centres. In additional File 4-Table 14, Supplemental Digital Content, http://links.lww.com/EJAIC/A24, the criteria for application of DNI orders are presented. The presence of comorbidities was the most commonly described criterion (9/12 investigations), followed by patient refusal (7/12 investigations), frailty (6/12 investigations), and age (5/12 investigations). In additional File 6, Supplemental Digital Content, http://links.lww.com/EJAIC/A26, DNI criteria and the countries where the studies were conducted are presented. As depicted in additional File 6, Supplemental Digital Content, http://links.lww.com/EJAIC/A26, clinical judgment, low predicted hospital survival, and disease severity were DNI criteria reported only in the Italian studies.[10,20–22,26,37,38,46] According to our dataset, relatives' wishes were not considered as a DNI criterion in the Italian investigations. ICU capacity was taken in account in the DNI application decision-making process in the French study only.[36]

### Clinical outcomes

The pooled incidence of DNI orders in patients undergoing NIRS is depicted in Fig. 1. Among patients assisted through NIRS, a DNI order was expressed in a summary estimate of 25.4% [20.0–31.1] of the cases with a high between-study heterogeneity ($P < 0.01$, $I^2 = 97.0\%$). As depicted in additional File 7-Figure 1, Supplemental Digital Content, http://links.lww.com/EJAIC/A27, patients were deemed as deserving full treatment in a summary estimate of 74.2% [68.5–79.5] of the cases with a high between-study heterogeneity ($P < 0.01$, $I^2 = 97.0\%$).

The pooled in-hospital mortality for patients undergoing NIRS who received DNI order is illustrated in Fig. 2. The summary estimated of in-hospital mortality for DNI patients was 83.6% [75.3–90.7] with a high between-study heterogeneity ($P < 0.01$, $I^2 = 98.0\%$). As depicted in Fig. 3, the summary estimate of in-hospital mortality of DNI patients on overall in-hospital mortality of general population assisted by NIRS ratio was 58.7% [48.0–69.0] with a high between-study heterogeneity ($P < 0.01$, $I^2 = 97.0\%$).

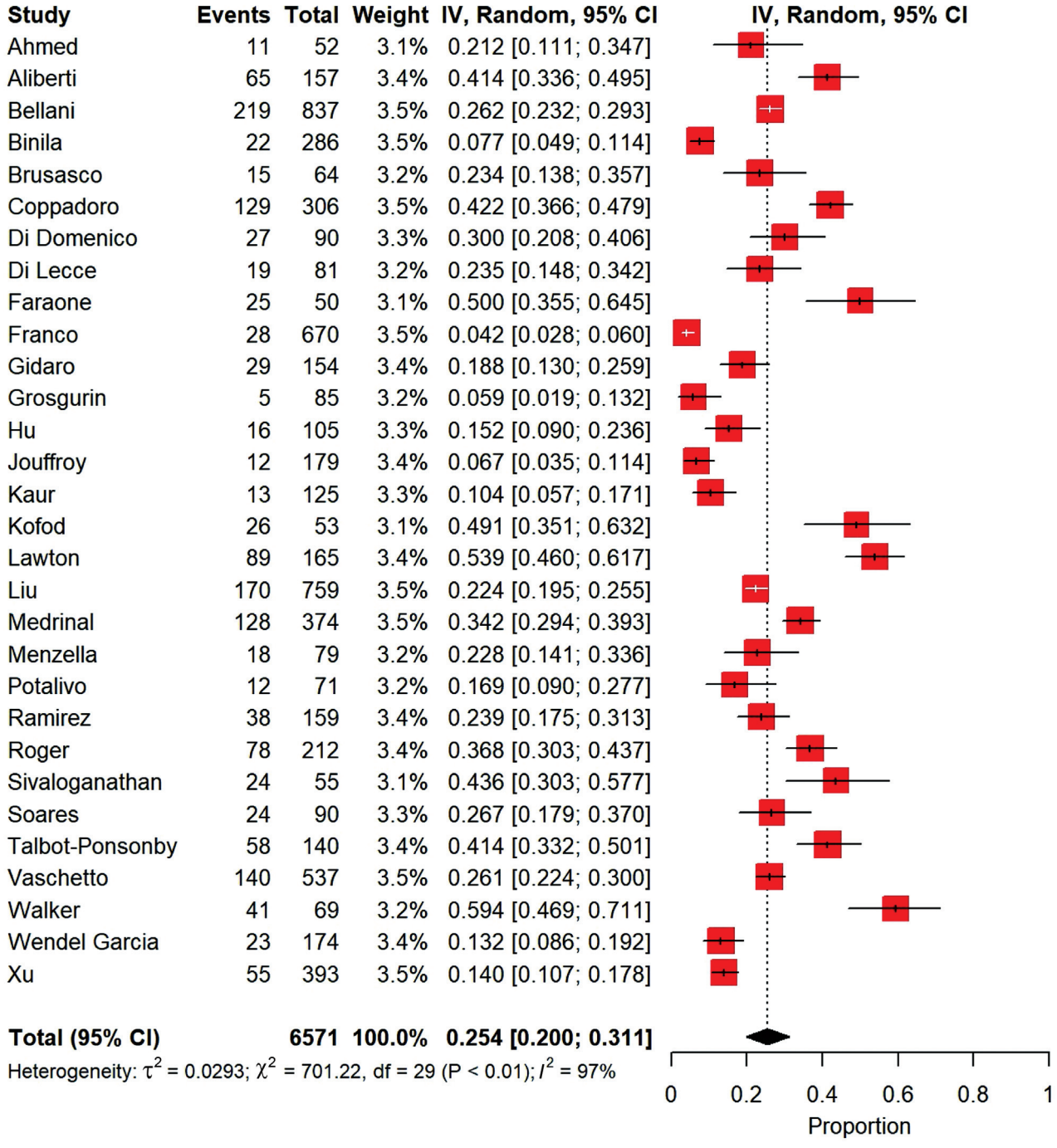
The summary estimate of in-hospital mortality of overall patients' population undergoing NIRS was 37.0% [31.2–43.0] with a high between-study heterogeneity ($P < 0.01$, $I^2 = 96.0\%$) (additional File 7-Figure 2, Supplemental Digital Content, http://links.lww.com/EJAIC/A27). In Fig. 4, the pooled in-hospital mortality of patients subjected to NIRS deemed to deserve full treatment. The summary estimate of in-hospital mortality of patients subjected to NIRS deemed to deserve full treatment was 20.0% [14.2–26.5] with a high between-study heterogeneity ($P < 0.01$, $I^2 = 97.0\%$). At meta-regression, heterogeneity among studies did not change when examining study type (retrospective *vs.* prospective), country where study was conducted (Italian *vs.* non-Italian study), in-hospital setting (in- *vs.* outside ICU), and centre characteristics (university *vs.* hospital center).

Duration of NIRS as well as hospital length of stay are described in additional File 4-Table 15, Supplemental Digital Content, http://links.lww.com/EJAIC/A24 for the overall study population, full treatment patients, and DNI patients under NIRS.

## Discussion

In patients with hypoxaemic ARF related to COVID-19 and assisted by NIRS, we found that the pooled incidence of DNI orders reached 25%,with a pooled intra-hospital mortality higher than 80%. According to the availability data, factors underlying the use of NIRS as a ceiling

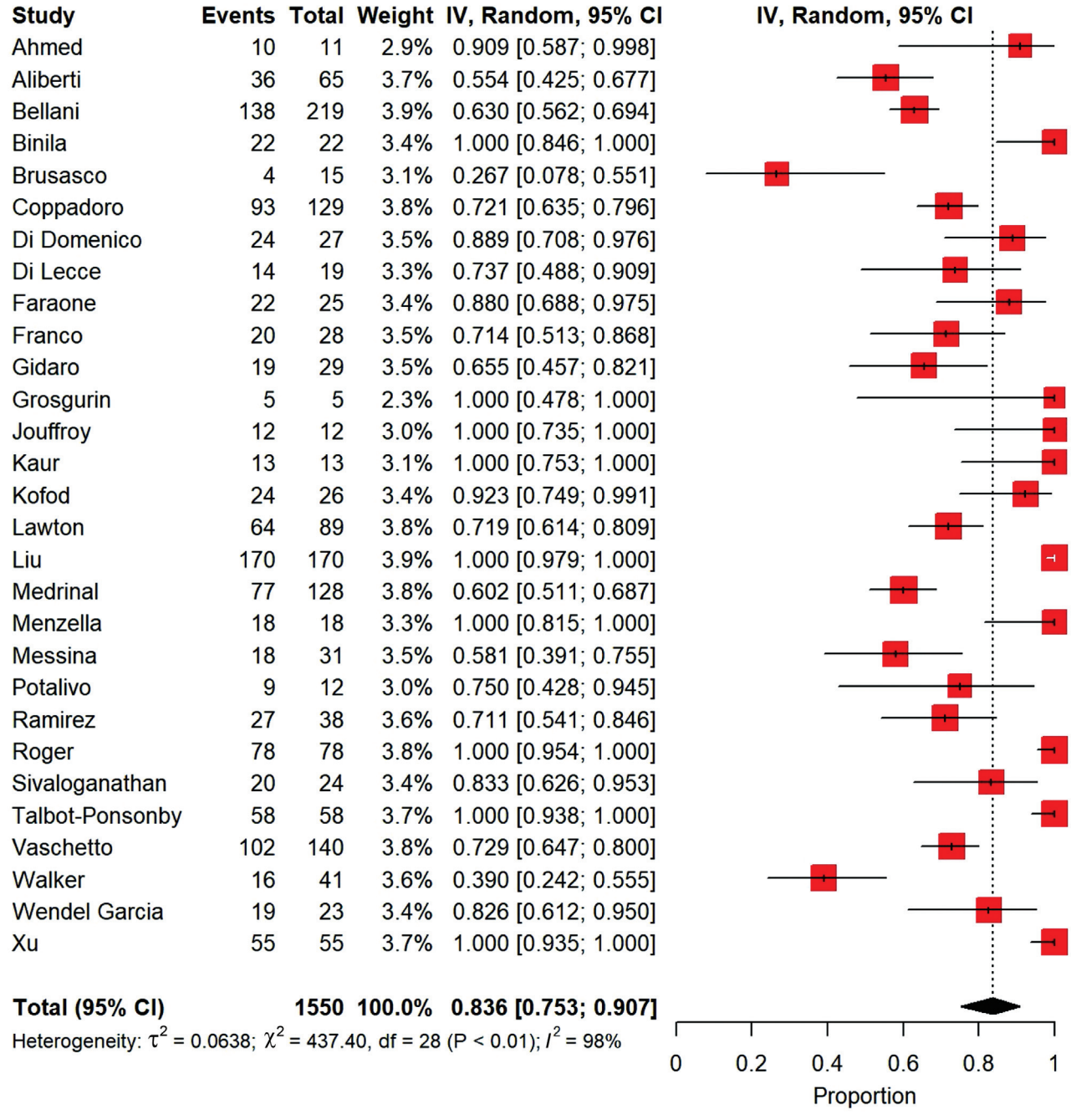
**Fig. 1** Summary estimate of patients with 'do-not-intubate' orders receiving noninvasive respiratory support. Vertical dotted line: summary estimate of 'do-not-intubate' orders. Red squares: study estimates of 'do-not-intubate' orders. Black horizontal lines: 95% confidence intervals. Diamond: summary estimate 95% confidence intervals. IV, interval variable.




ventilatory support were principally related to patients' clinical status and wishes, as well as relatives' wishes.

The present systematic review and meta-analysis was performed two years after the beginning of the COVID-19 pandemic. Compared with those data reported mainly from the Italian experience on the rate of application of DNI orders in COVID-19 patients undergoing NIRS, excluding HFO, and outside the ICU (17 investigations, 822 DNI patients),[9] the present investigation was performed on data retrieved from 31 studies conducted worldwide that addressed the role of

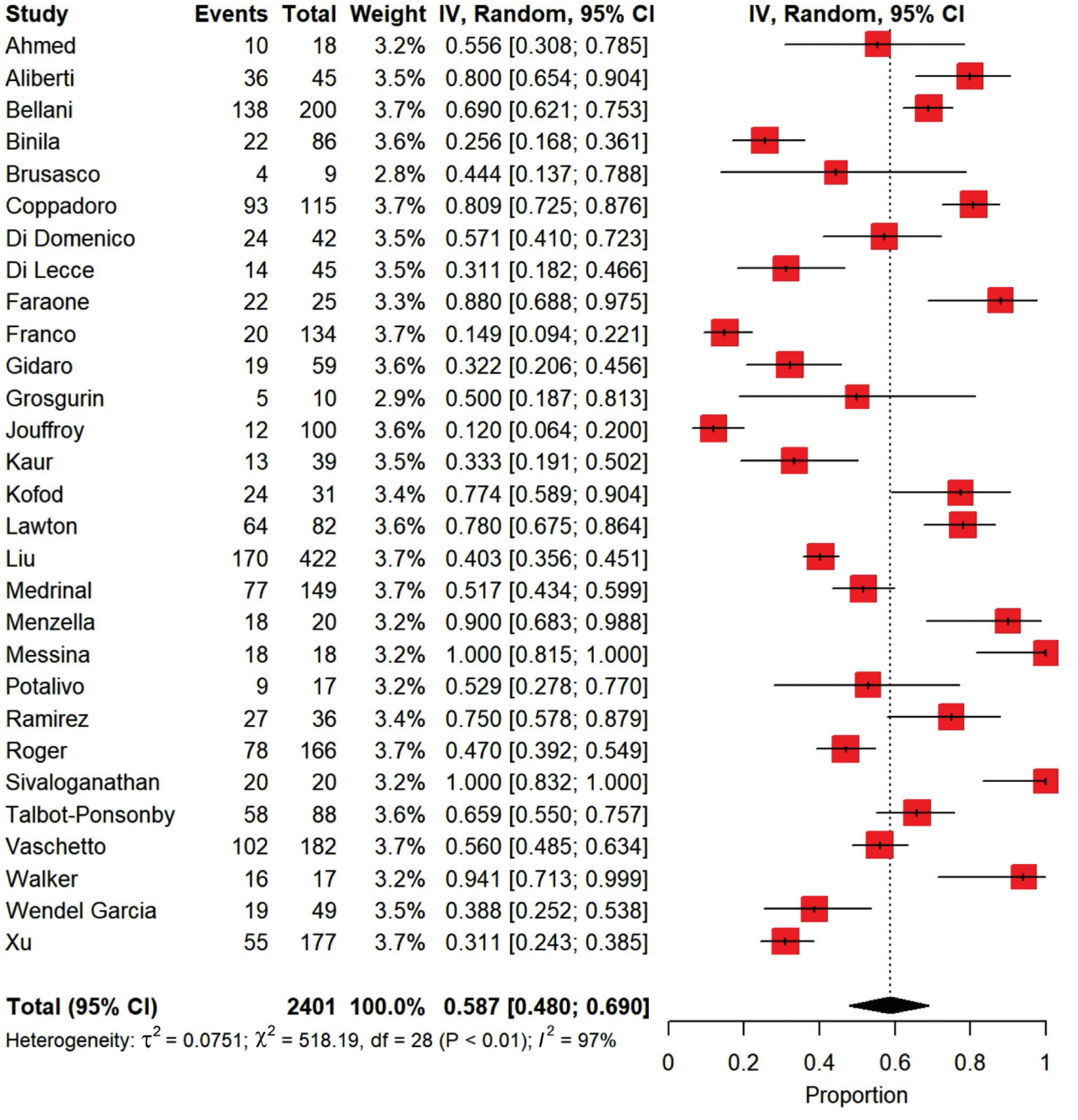
**Fig. 2** Pooled in-hospital mortality of patients who received 'do-not-intubate' orders assisted by noninvasive respiratory support. Vertical dotted line: summary estimate of in-hospital mortality of patients receiving DNI orders. Red squares: study estimates of intra-hospital mortality of patients receiving DNI orders. Black horizontal lines: 95% confidence intervals. Diamond: summary estimate 95% confidence intervals. DNI, do-not-intubate; IV, interval variable.




NIRS, including HFO therapy, in COVID-19 ARF, with a higher population of DNI patients (1590). Additionally, our investigation provided an in-depth analysis on the criteria used for the DNI decision-making process in these studies.

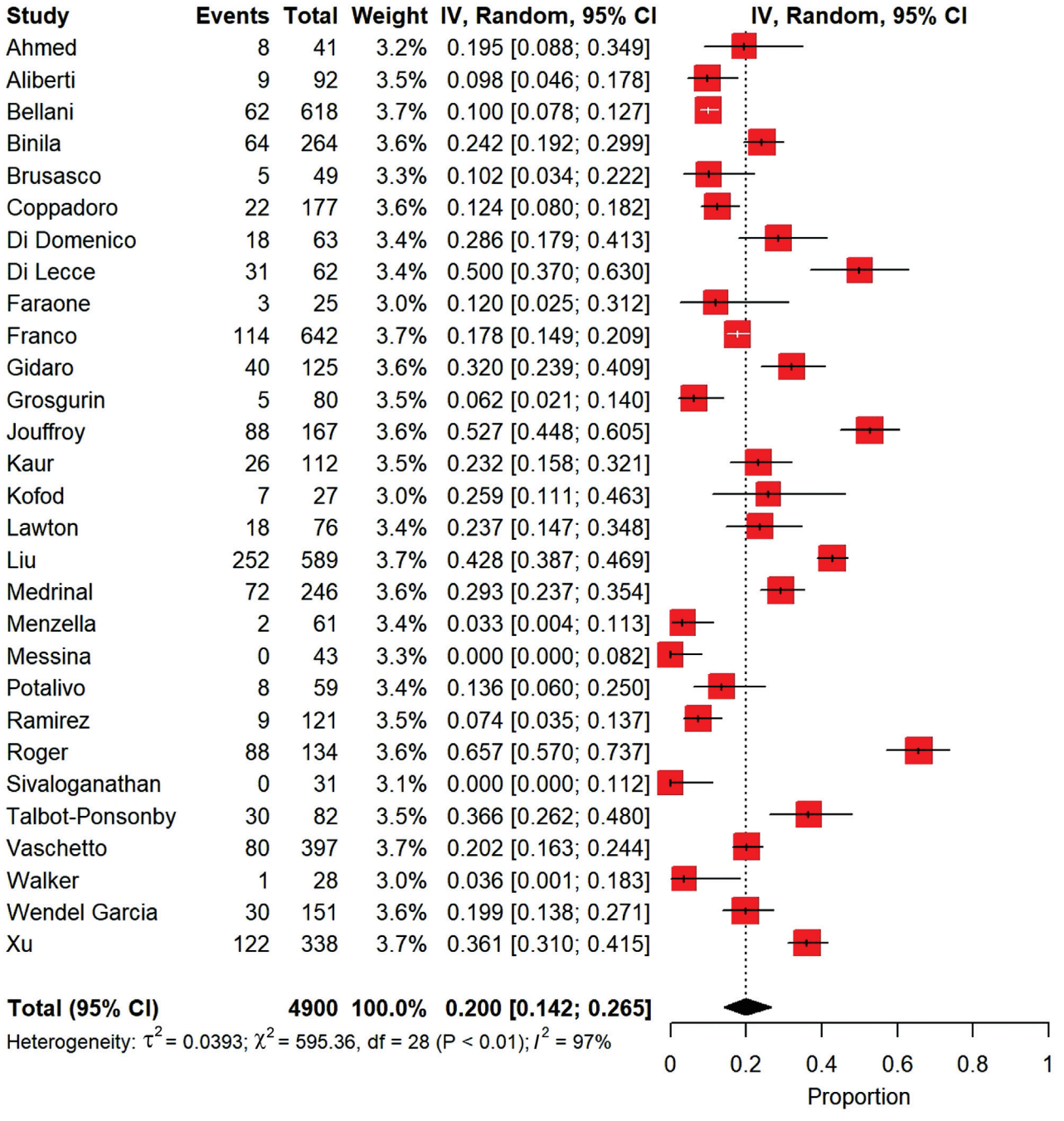
NIRS has been extensively employed to defer the frequent requests for ventilatory assistance during COVID-19 pandemic, within and outside the ICU.[9,11] In this context, the decision-making process for applications of DNI orders would have been particularly complex due to

**Fig. 3** Summary estimate of in-hospital mortality of 'do-not-intubate' patients on overall in-hospital mortality ratio of patients assisted by noninvasive respiratory support. Vertical dotted line: summary estimate of in-hospital mortality of patients with DNI orders on overall in-hospital mortality ratio of patients receiving noninvasive support. Red squares: estimates of in-hospital mortality of DNI patients on overall in-hospital mortality ratio of patients receiving noninvasive support. Black horizontal lines: 95% confidence intervals. Diamond: summary estimate 95% confidence intervals. DNI, do-not-intubate; IV, interval variable.




the crisis facing ICU surge capacity.[6,7,50] In patients suffering from hypoxaemic ARF related to COVID-19 who underwent NIRS outside the ICU, the rate of application of DNI orders has been recently described as 23%,[9] consistent with our findings obtained in a greater worldwide population of patients receiving NIRS both within and outside of the ICU. Also our results were consistent with a previous investigation conducted in non-COVID-19 ARF, which reported a rate of administration of DNI orders during NIRS of 32%.[51]

**Fig. 4** Pooled in-hospital mortality of patients on 'full treatment' receiving noninvasive support. Vertical dotted line: summary estimate for in-hospital mortality. Red squares: study estimates of the in-hospital mortality. Black horizontal lines: 95% confidence intervals. Diamond: summary estimate 95% confidence intervals. IV, interval variable.




Orders to limit life-sustaining treatment have appreciably increased over the years in patients suffering from non-COVID-19 ARF assisted by NIRS.[51] In issuing a DNI order, several factors must be considered that will depend on the characteristics of the patients, their families, physicians, and hospitals.[51] Also, the variability in DNI order applications depends on differences in policies, practices, medical ethics, social attitudes, culture, and religion.[51]

In our subset of COVID-19 patients, DNI criteria were reported in <40% of the investigations included, of which <20% were conducted in non-university centres. In our dataset, the factors influencing DNI order applications

were principally related to patients' clinical status and wishes in ≥50% of the 12 studies reporting DNI,[10,20–22,26,29,32,36–38,46,49] 66.7% of which were conducted in Italy.[10,20–22,26,37,38,46] DNI orders also relied on factors not strictly related to the patient's condition, that is, relatives' wishes and ICU capacity, as described in those investigations conducted in countries other than Italy. In particular, the involvement of patients' relatives in the ceiling of therapies was described only in 25% of the enrolled studies reporting DNI criteria (3/12 investigations). However, these findings are in clear contradiction with the latest end-of-life care recommendations, supporting the participation of patients' relatives and family members in life-sustaining therapies withdrawal.[52] Of course, in interpreting our data, it is worth considering the effects of 'lockdown', social restrictions, and social distancing policies adopted worldwide in order to contain the spread of COVID-19.

The in-hospital mortality of COVID-19 patients undergoing NIRS outside the ICU and subjected to DNI orders was reported as 71.7%.[9] In our study, we describe a high in-hospital mortality (>80%) for DNI patients undergoing NIRS, accounting for 60% of the overall in-hospital mortality characterising global patient populations assisted by NIRS. As expected, from our COVID-19 cohort, in-hospital mortality of DNI patients was greater than in-hospital mortality described for patients deserving full treatment undergoing NIRS (20%) as well as in-hospital mortality reported from countries where DNI is not legally allowed.[53] Regarding this optimistically, the survival rate in patients with DNI was reported close to 20%, suggesting that NIRS was not strictly employed as palliative therapy, but also as a curative strategy, and supported in some cases also by the awake prone position as a rescue therapy.[27]

Our systematic review and meta-analysis addressed the application of DNI orders in patients assisted by NIRS for COVD-19 ARF. Nevertheless, in the light of our results, new questions arise for DNI patients concerning the quality of life in the days following NIRS onset, quality of death in nonsurvivor patients, quality of life in the survivors, and the characteristics of hospital wards/units essential to provide high-quality support.

Regarding clinical implications, our data would encourage the use of NIRS in dealing with DNI patient. This is even more true in consideration of the survival rate observed in our subset of patients, despite hospital surge capacity crisis and limitations imposed by a 'lockdown' policy. In the management of DNI patients it is of pivotal importance to undertake a therapeutic strategy directed at solving the condition responsible for ARF and dyspnoea and, at the same time, be respectful of patients' and family wishes[51] with the focus of avoiding discomfort, distress, and agonizing situations. Hence, future investigations should be targeted toward the identification of all the clinical and nonclinical factors affecting the quality of life of DNI patients assisted by NIRS, with particular regard to those strategies focused on the assessment and enhancement of comfort.

Surprisingly, data from our cohort of patients are consistent with the crude intrahospital mortality (35.8%) observed in conventional ARF patients undergoing NIRS.[54] These findings validate the use of NIRS outside the ICU in dealing with acute respiratory failure regardless of COVID-19, provided that proper clinical monitoring is ensured to avoid undue prolongation of NIRS and a consequent delay in intubation upon clinical deterioration.

Our study has several limitations that require mention. The studies included in our systematic review and meta-analysis were mainly conducted during the first wave of COVID-19 pandemic when ICU surge capacity was profoundly compromised by overwhelming requests for ventilatory assistance.[3,55,56] A large part of the investigations included were retrospective studies. Accordingly, the retrospective nature of most studies included, along with the great proportion of single-center investigations (17/31), led to the high heterogeneity observed in the study analysis. However, the random-effect model adopted yielded summary estimates that adequately reflected this situation. We retrieved data regarding the criteria for application of DNI orders in less than 50% of the studies enrolled. As a consequence, the role of factors other than those reported in the present investigation, i.e., ICU capacity, might be underestimated. Also, our data might be also underestimate because, in some countries, DNI orders are not legally permitted.[53] Thus, no definitive conclusions can be drawn on the factors leading to the application of DNI orders in our cohort of COVID-19 patients. A high proportion of studies enrolled were conducted in Italy. Thus, our findings cannot be generalised to different contexts and countries.

In conclusion, during COVID-19 pandemic, in patients assisted by NIRS for hypoxaemic ARF, both within and outside the ICU, DNI orders were frequently issued and were associated with a high in-hospital mortality.

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