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SYSTEMATIC REVIEW

# Cardiac arrest and complications during non-invasive ventilation: a systematic review and meta-analysis with meta-regression

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## Abstract

**Purpose:** The aim of this study was to perform a systematic review and meta-analysis to investigate the incidence rate of cardiac arrest and severe complications occurring under non-invasive ventilation (NIV).

**Methods:** We performed a systematic review and meta-analysis of studies between 1981 and 2020 that enrolled adults in whom NIV was used to treat acute respiratory failure (ARF). We generated the pooled incidence and confidence interval (95% CI) of NIV-related cardiac arrest per patient (primary outcome) and performed a meta-regression to assess the association with study characteristics. We also generated the pooled incidences of NIV failure and hospital mortality.

**Results:** Three hundred and eight studies included a total of 7,601,148 participants with 36,326 patients under NIV (8187 in 138 randomized controlled trials, 9783 in 99 prospective observational studies, and 18,356 in 71 retrospective studies). Only 19 (6%) of the analyzed studies reported the rate of NIV-related cardiac arrest. Forty-nine cardiac arrests were reported. The pooled incidence was 0.01% (95% CI 0.00–0.02, $I^2 = 0\%$ (0–15)). NIV failure was reported in 4371 patients, with a pooled incidence of 11.1% (95% CI 9.0–13.3). After meta-regression, NIV failure and the study period (before 2010) were significantly associated with NIV-related cardiac arrest. The hospital mortality pooled incidence was 6.0% (95% CI 4.4–7.9).

**Conclusion:** Cardiac arrest related to NIV occurred in one per 10,000 patients under NIV for ARF treatment. NIV-related cardiac arrest was associated with NIV failure.

**Keywords:** Non-invasive ventilation, Cardiac arrest, Complications, Meta-analysis, ICU

## Introduction

Non-invasive ventilation (NIV) has been associated with a reduction in reintubation rate compared with standard oxygen in several types of acute respiratory failure (ARF) of variable causes: decompensation of chronic obstructive pulmonary disease (COPD) [1], cardiogenic pulmonary edema [2] and following abdominal surgery [3]. For these indications, the use of NIV has become more and more frequent in the past number of years [4]. For other etiologies of ARF, despite controversies [5], NIV is still widely used in the acute care setting [6, 7], including in patients affected by coronavirus disease 2019 (COVID-19) [8, 9]. In this setting, the benefit-risk ratio of performing NIV has to be assessed and re-assessed before and during NIV [10–12]. Some adverse effects of NIV are commonly reported such as gastric insufflation, skin lesions and lack of tolerance [13]. More severe complications (hemodynamic, respiratory and neurological) may also occur, leading to cardiac arrest and death. To prevent side effects during NIV use, guidelines have been implemented [6].

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In-hospital cardiac arrest is a major patient safety concern with a high mortality rate (more than 50%) [14]. In a post hoc analysis of intubated critically ill patients [15], intubation-related cardiac arrest in the intensive care unit (ICU) was recorded in 49 of 1847 intubation procedures (2.7%). Intubation-related cardiac arrest was associated with a high immediate and 28-day mortality rate (28.5% and 71.4%, respectively) and was determined to be an independent risk factor for day-28 mortality.

To our knowledge, there is no study which has specifically reported the incidence of cardiac arrest occurring under NIV and not during intubation.

We aimed to perform a systematic review and meta-analysis of studies to establish the incidence of cardiac arrest and other severe life-threatening complications occurring under NIV to treat ARF. The secondary objectives were to assess the relationship between the incidence of NIV-related cardiac arrest and study characteristics.

**Take-home message**

Three hundred and eight studies included a total of 7,601,148 participants with 36,326 patients under non-invasive ventilation (NIV), NIV-related cardiac arrest per patient was reported in 49 patients (pooled incidence of 0.01% (95% CI 0.00–0.02), 1 per 10,000 procedures). NIV failure was reported in 4371 patients, with a pooled incidence of 11.1% (95% CI 9.0–13.3); NIV-related cardiac arrest was strongly related to NIV failure.

## Methods

This article reports the results of a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [16] and was registered in PROSPERO (CRD42019132801).

### Search strategy

We performed a computerized search of MEDLINE (1966 to September 31, 2020), PubMed (1966 to September 31, 2020), Embase (1977 to September 31, 2020) and the Cochrane Central Register of Controlled Trials (CENTRAL) (1943 to September 31, 2020) for studies concerning NIV to treat ARF in the critical care setting. We excluded non-English publications.

For the bibliographic review, keywords and MESH terms ("non-invasive" OR "non invasive" OR "positive pressure" OR "positive-pressure" OR "pressure support" OR "positive airway" OR "intermittent positive pressure" OR "airway* pressure" OR "pressure-control*" OR "volume control*" OR "continuous positive airway pressure*" OR "CPAP*" OR "Helmet*" OR "bi-level" OR "ventilatory* support" OR "NIPPV" OR "NPPV" OR "NIV in ARF") were used in our Boolean search strategy. References in the retrieved articles were also examined for relevant publications. We identified and deleted any duplicate papers. All potential eligible papers were retrieved in full.

### Selection criteria and outcome measures

We screened for relevant studies that enrolled adults (> 18 years) in whom NIV was used to treat ARF (in ICU, an emergency setting, operating rooms and pre-hospital). NIV included one pressure support level (continuous positive airway pressure (CPAP)) and two pressure support levels, performed via non-invasive interfaces (without tracheal intubation or tracheotomy). We excluded studies performed for preventing ARF. Then we made a quantitative synthesis performing a systematic review and meta-analysis. For this purpose, we selected randomized controlled trials (RCTs) and observational studies (prospective and retrospective) and excluded case reports. The primary outcome was the pooled incidence of cardiac arrest occurring during NIV, defined as the absence of a palpable pulse (in addition to loss of consciousness and absence of normal breathing) [17], in the absence of a decision to withdraw life-sustaining treatment or do-not-resuscitate orders. Only cardiac arrests for which resuscitation was attempted were included. Cardiac arrests occurring during intubation for NIV failure or later during ICU stay and not during a NIV session were not reported. We categorized studies according to their reporting or not of cardiac arrest during NIV. The secondary outcomes (post hoc analysis) were NIV failure, defined as the need for endotracheal intubation during the ICU stay [18], hospital mortality (whenever hospital mortality was not available, we selected 30-day mortality, and then ICU mortality, as outcome), and other reported severe complications related to NIV (respiratory arrest, severe collapse, pneumothorax, pneumonia, gastric insufflation, agitation and encephalopathy).

### Data collection and analysis

First, two authors (AR and ADJ) independently screened the retrieved studies by title and then by abstract for exclusion. They assessed the full text of the possible relevant studies for inclusion and exclusion criteria. Disagreement was resolved by discussion and arbitrated, if necessary, by a third author (SJ). Data were then added to an Excel database, specifically designed for this review, and analyzed using R software. The indication for NIV [6] and the interface used during NIV were assessed. Study design, rank, impact factor, year of publication (assessed as a categorical variable (before 2000, 2000–2004, 2005–2009,

2010–2014, after 2015) and the positive or negative main result of the study were assessed.

### Statistical analysis

Data were extracted as they were reported in the original paper. We used the package "robvis" (Risk-Of-Bias VISualization, R software) to perform publication-quality risk-of-bias assessment [19].

Mean pooled incidences (and corresponding confidence intervals (95% CIs)) of the primary outcome were estimated by pooling incidence measures for the primary outcome per patient, for studies reporting cardiac arrest and for all studies included [20]. Mean pooled incidences of the secondary outcomes were estimated by pooling incidence measures for the secondary outcomes per patient, for all studies included. The pooled means incidences were estimated using DerSimonian and Laird random effects models [21]. The variances of incidence measures were stabilized using arcsine transformation [22], and then weighted using the inverse-variance method [22]. A funnel plot (plot of treatment effect against trial precision) was created for the primary outcome to assess publication bias [23]. Statistical heterogeneity was quantified by the Q-Cochrane heterogeneity test (Q statistic with degree of freedom (df)) and the $I^2$ statistic with CI [24] for the primary outcome. The pooled incidence rate with random effects was considered.

We used random effects meta-regression models to identify variables associated with NIV-related cardiac arrest [25]. The following independent variables were specified a priori because of relevance to the study's questions: study design (retrospective studies, prospective studies, and RCTs versus non-RCTs), year of study publication, rank of journal, impact factor, positive or negative main result of the study, interface used, indication for NIV and NIV failure. Inverse variance weighting was used in all meta-regressions, and only the significant variables were kept in the final model. We calculated the pooled incidence for each outcome (hospital mortality and NIV-related complications, primary and secondary outcomes analyzed separately) by the inverse method [25]. We plotted those results in a histogram plot. We compared the outcomes between RCTs and non-RCTs by the test for subgroup differences (in a random effects model) [25].

Finally, we calculated the pooled incidence for the NIV-related cardiac arrest, NIV failure and hospital mortality according to the year (from 1981 to 2020) and the study design (RCTs and non-RCTs). We presented those results in a spaghetti plot, with the package "Ggplot2" and the function "ggparcoord" to add the line between each point representing the pooled incidence. A time effect and a study design effect (RCTs versus non-RCTs) were analyzed.

For the studies in which NIV-related cardiac arrest was reported, the corresponding authors were contacted and asked about the outcome of the patient(s) who presented NIV-related cardiac arrest (i.e., whether the patient(s) died or not during the NIV session or during the ICU stay).

We then performed post hoc analyses: one combining RCTs and prospective studies, and another including only retrospective studies.

Post hoc subgroup analyses were also performed among patient populations identified: obstructive lung disease, hypoxemic respiratory failure and heart failure. Subgroup analyses were also performed among different interfaces: facial mask, nasal mask, full face mask, helmet.

To further explore heterogeneity, we performed a subgroup analysis of the studies having the worst outcomes (defined by more than 5% of cardiac arrests within a single study) and checked differences formally with the other studies with an interaction test.

To avoid multiplicity, no comparison between subgroups was performed.

All tests were two sided and $p$ values less than 0.05 were considered statistically significant. All analyses were performed using R 3.4.4 (R Project) and the "metafor" package [26].

## Results

### Study selection

We identified 2632 articles using the search strategy. We excluded 684 citations because of duplication and 1495 citations on the initial abstract screen because inclusion criteria were not met. After examination of the full text of the selected papers, we included 308 studies (138 RCTs, 99 observational prospective, 71 observational retrospective) for the systematic review and meta-analysis. Among them, 302 (98%) were performed in ICU and 6 (2%) were performed in intermediate care units with close monitoring. Figure 1 shows the study selection flowchart.

### Study description

The 308 included studies involved a total of 7,601,148 participants. Overall, 36,326 patients under NIV (8187 in 138 RCTs, 9783 in 99 prospective observational studies, and 18,356 in 71 retrospective studies) were included for analysis. Among the 308 included studies, 19 reported NIV-related cardiac arrest (6%), while the other 289 (94%) did not report NIV-related cardiac arrest (Fig. 1). Table 1 presents the main characteristics of the patients included in the studies. The risk of bias summary is presented in Supplementary Fig. S1.

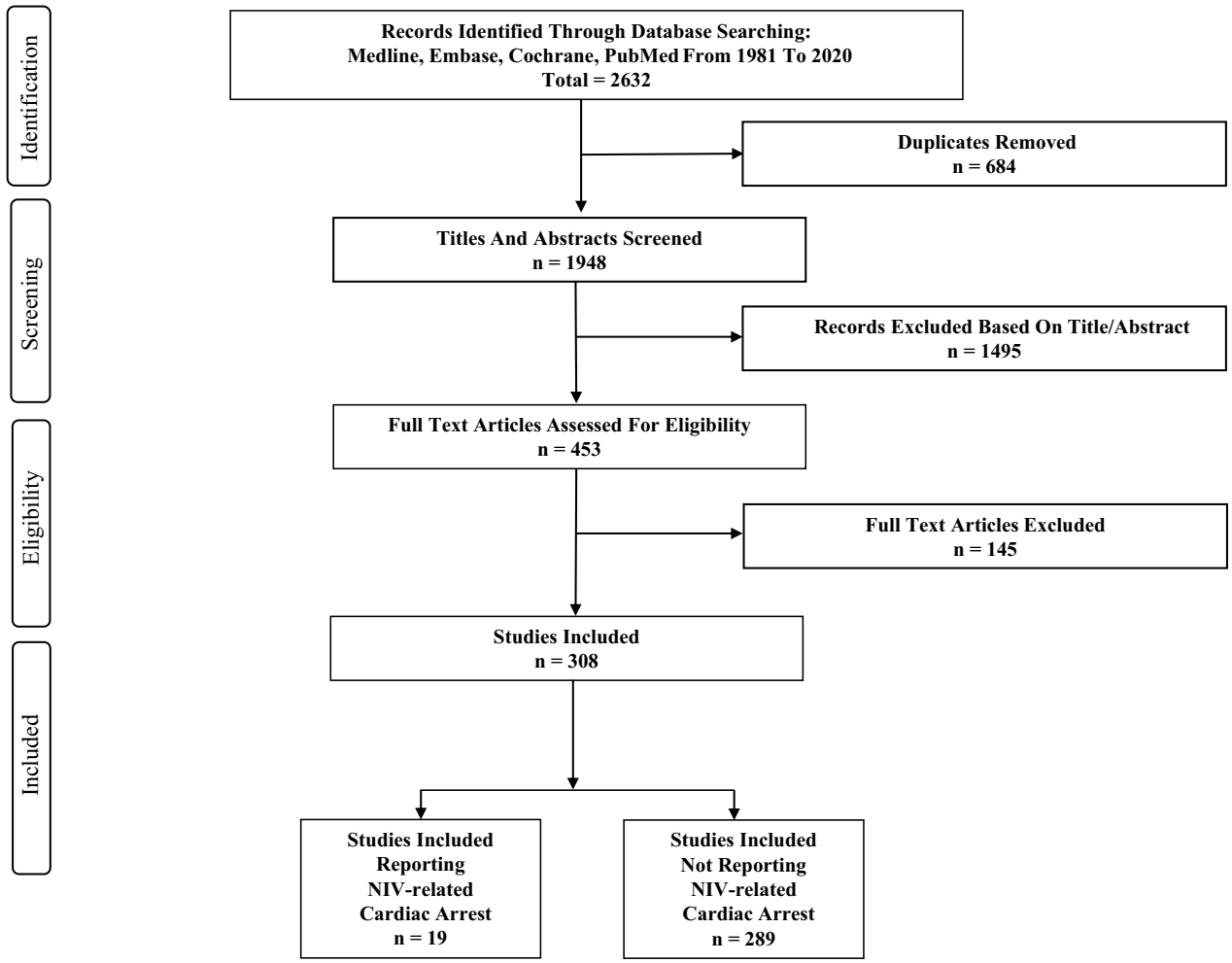


**Fig. 1** Flow chart of the study. Between 1981 and 2020, we identified 2632 articles using the search strategy. A total of 308 studies were included (138 RCTs, 99 observational prospective, 71 observational retrospective), 19 (6%) studies reported a NIV-related cardiac arrest and 289 (94%) studies did not report a NIV-related cardiac arrest. *NIV* non-invasive ventilation

#### Pooled incidence of NIV-related cardiac arrest

Among the 1729 patients under NIV with assessed NIV-related cardiac arrests, 49 cardiac arrests were reported. The pooled incidence among all the studies included (reporting and not reporting cardiac arrests) was 0.01% (95% CI 0.00–0.02, $I^2 = 0\%$ (0–15)) (Fig. 2 and Supplementary Fig. S2). The pooled incidence among the 19 studies reporting cardiac arrests was 2.6% (95% CI 1.9–3.4, $I^2 = 0\%$ (0–49)).

Among the 14 corresponding authors of studies reporting NIV-related cardiac arrests who responded, 10 could not determine if the patients had died after successful resuscitation later during the ICU stay or directly during the NIV session after unsuccessful resuscitation. Four of the studies' authors could provide the prognosis of eight patients with NIV-related cardiac arrest: three (38%) died during the NIV session, and five (62%) died during the ICU stay.

The pooled incidence of NIV-related cardiac arrest significantly differed between the two periods ("Before 2010" and "After 2010", $p < 0.001$), and between studies with and without NIV failure ($p = 0.01$). No significant difference was reported according to the journal rank ($p = 0.51$), the impact factor of the journal ($p = 0.52$), the study design ($p = 0.19$) or the positive or negative result of the study ($p = 0.12$). NIV-related cardiac arrest did not differ according to the indication for NIV ($p = 0.62$) or interface used ($p = 0.18$).

After meta-regression, NIV failure ($p = 0.041$, OR = 1.43 (1.02–2.02)) and the study period (before 2010, $p < 0.001$, OR = 2.06 (1.47–2.88)) were significantly associated with NIV-related cardiac arrest.

**Table 1 Characteristics of studies and patients according to non-invasive ventilation-related cardiac arrest reporting**

| Characteristics<br>Study (*n*)* | Overall<br>(*n* = 308) | Reported cardiac arrest<br>(*n* = 19) | Not reported cardiac arrest<br>(*n* = 289) |
|---|---|---|---|
| **Patients included (*N*)** | **(*N* = 7,601,148)** | **(*N* = 2389)** | **(*N* = 7,598,759)** |
| **Patients under NIV (*N*)** | **(*N* = 36,326)** | **(*N* = 1729)** | **(*N* = 34,597)** |
| **Indication for NIV** | | | |
| COPD exacerbation with hypercapnia, *n* (%) | 71 (23) | 4 (20) | 67 (23) |
| COPD exacerbation without hypercapnia, *n* (%) | 3 (1) | 0 (0) | 3 (1) |
| Hypercapnia, *n* (%) | 2 (1) | 0 (0) | 2 (1) |
| Cardiogenic pulmonary edema, *n* (%) | 56 (18) | 3 (16) | 53 (18) |
| Immunocompromised, *n* (%) | 18 (6) | 1 (5) | 17 (6) |
| De novo hypoxemic respiratory failure, *n* (%) | 61 (20) | 7 (37) | 54 (19) |
| Postoperative surgical patients, *n* (%) | 29 (10) | 2 (11) | 27 (9) |
| Palliation, *n* (%) | 3 (1) | 0 (0) | 3 (1) |
| Chest trauma, *n* (%) | 6 (2) | 0 (0) | 6 (2) |
| Pandemic viral illness, *n* (%) | 2 (1) | 0 (0) | 2 (1) |
| Post-extubation treatment, *n* (%) | 4 (1) | 0 (0) | 4 (1) |
| Asthma exacerbation, *n* (%) | 9 (3) | 0 (0) | 9 (3) |
| Severe acute pancreatitis, *n* (%) | 1 (0) | 0 (0) | 1 (1) |
| Mixed indications, *n* (%) | 43 (14) | 2 (11) | 41 (14) |
| **Study design, *n* (%)** | | | |
| Randomized, *n* (%) | 138 (45) | 6 (32) | 128 (44) |
| Prospective, *n* (%) | 99 (32) | 10 (53) | 93 (32) |
| Retrospective, *n* (%) | 71 (23) | 3 (15) | 68 (24) |
| **Year of publication, *n* (%)** | | | |
| Before 2000, *n* (%) | 57 (19) | 2 (11) | 55 (19) |
| 2000–2004, *n* (%) | 66 (21) | 5 (26) | 61 (21) |
| 2005–2009, *n* (%) | 59 (19) | 4 (20) | 55 (19) |
| 2010–2014, *n* (%) | 72 (23) | 2 (11) | 70 (24) |
| From 2015, *n* (%) | 54 (18) | 6 (32) | 48 (17) |
| **Median of patients included by study** | 57 (30–122) | 89 (57–139) | 53 (30–113) |
| **Median of patients under NIV by study** | 39 (21–118) | 50 (37–128) | 36 (21–84) |

Data expressed as median (25–75% IQR) or proportion (%)

*NIV* non-invasive ventilation, *COPD* chronic obstructive pulmonary disease

*The denominator of all the percentages is the number of studies

After including only RCTs, the pooled incidence was 0.01% (95% CI 0.00–0.05, $I^2 = 0\%$). After including prospective studies and RCTs, the pooled incidence was 0.02% (95% CI 0.00–0.04, $I^2 = 0\%$). After including only retrospective studies, the pooled incidence was 0.009% (95% CI 0.00–0.01, $I^2 = 0\%$).

The pooled incidences of NIV-related cardiac arrest among patient populations were computed: obstructive lung disease (0.001% (95% CI 0.00–0.01), $I^2 = 0\%$), hypoxemic respiratory failure (0.03% (95% CI 0.00–0.09), $I^2 = 0\%$) and heart failure (0.00001% (95% CI 0.00–0.04), $I^2 = 0\%$). The pooled incidences were also computed among different interfaces: facial mask (0.01% (95% CI 0.00–0.02), $I^2 = 0\%$), nasal mask (0.00001% (95% CI 0.00–0.24), $I^2 = 0\%$), full face mask (0.01% (95% CI 0.00–0.07), $I^2 = 0\%$) and helmet (0.01% (95% CI 0.00–0.27), $I^2 = 0\%$).

In Supplementary Tables S1 and S2, we present the characteristics of studies and patients having the worst outcomes. The pooled incidence in the group "worst outcome" was 0.006% (95% CI 0.0007–9.8, $I^2 = 0\%$), whereas it was 0.005% (95% CI 0.0003–0.02, $I^2 = 0\%$) in the group "not worst outcome" ($p$-value for interaction: $p = 1.00$).

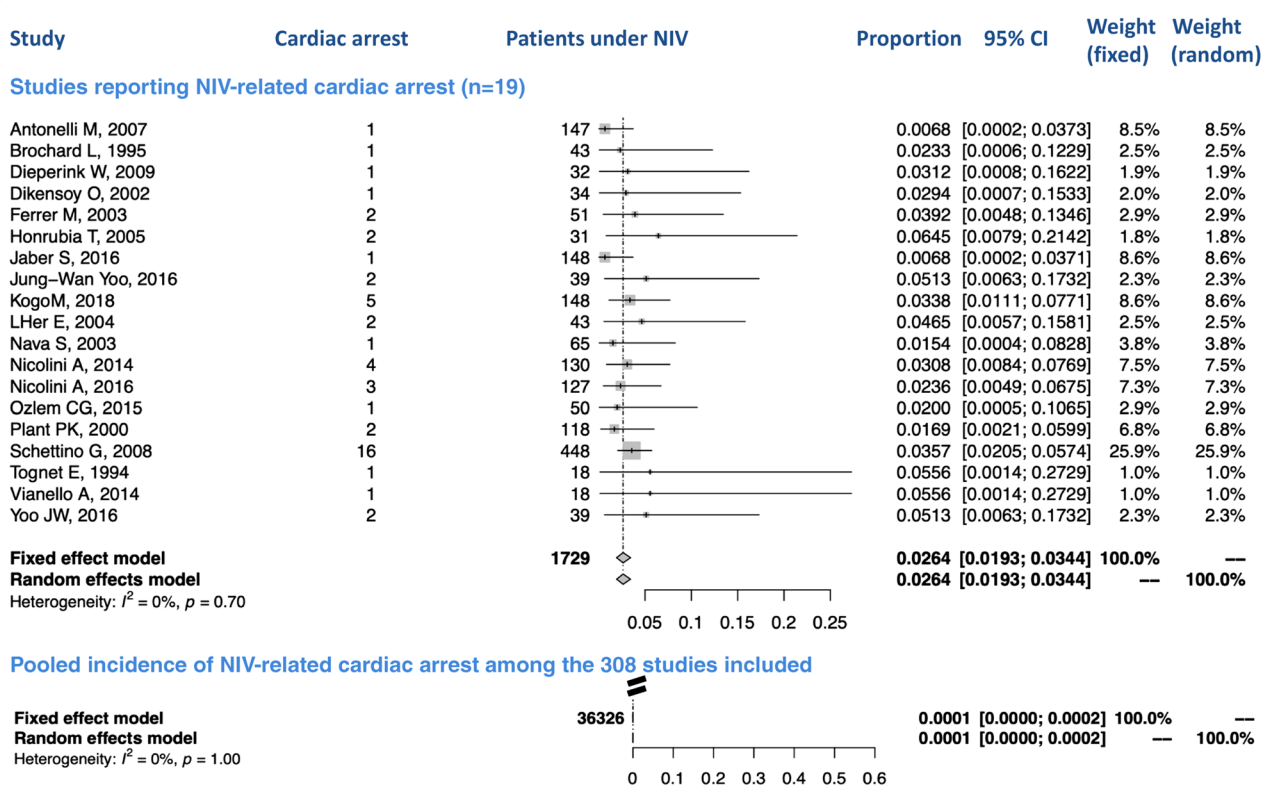


**Fig. 2** Forest plot of the pooled incidence of NIV-related cardiac arrest for acute respiratory failure treatment among 19 studies reporting NIV-related cardiac arrest with calculation of pooled incidence among the 308 studies assessed. Among the 1729 patients under NIV with assessed NIV-related cardiac arrests, 49 cardiac arrests were reported. The pooled incidence among all the studies included (reporting and not reporting cardiac arrests) was 0.01% (95% CI 0.00–0.02, $I^2$ = 0% (0–15%)). The pooled incidence among the 19 studies reporting cardiac arrests was 2.6% (95% CI 1.9–3.4, $I^2$ = 0% (0–49%)). *NIV* non-invasive ventilation

### Pooled incidence of other severe complications related to NIV and hospital mortality (Fig. 3)

The absolute number of severe complications related to NIV and hospital mortality is reported in Fig. 3. NIV failure pooled incidence was 11.1% (95% CI 9.0–13.3, $I^2$ = 97%) (Supplementary Fig. S3). Hospital mortality pooled incidence was 6% (95% CI 4.4–7.9, $I^2$ = 98%) (Supplementary Fig. S4).

The pooled incidences of other reported severe complications related to NIV (respiratory arrest, severe collapse, pneumothorax, pneumonia related to NIV, gastric insufflation, agitation, encephalopathy) are reported in Supplementary Figs. S5 to S11.

The pooled incidences of NIV-related cardiac arrest according to the year of study publication (from 1981 to 2020) and the study design (RCTs versus non-RCTs) are presented in Fig. 4A, and the pooled incidences of NIV failure and hospital mortality in Fig. 4B and C, respectively. The time effect and study design effect were not significant.

## Discussion

In this systematic review and meta-analysis reporting for the first time the pooled incidence of NIV-related cardiac arrest, at least one cardiac arrest occurred in one patient per 10,000 under NIV for ARF. NIV-related cardiac arrest was recorded in 49 out of 1729 patients (pooled incidence of 0.01% (95% CI 0.00–0.02), 10 per 100,000 procedures). NIV-related cardiac arrest occurrence was strongly related to NIV failure.

Our results suggest that the numbers of cardiac arrests reported vary by year and are probably underestimated. There is a well-known bias of under-reporting of adverse effects in observational studies [27], confirmed in the current systematic review, meta-analysis and meta-regression. It is worth noting that this bias is also present in RCTs, particularly concerning the secondary outcomes [28] and side adverse events [29], which are often under-reported. This suggests that even in RCTs, NIV-related cardiac arrest incidence was underestimated.

NIV is recommended as the first-line treatment of the early phase of ARF in selected patients. RCTs showed that the use of NIV in ARF with COPD, acute cardiogenic

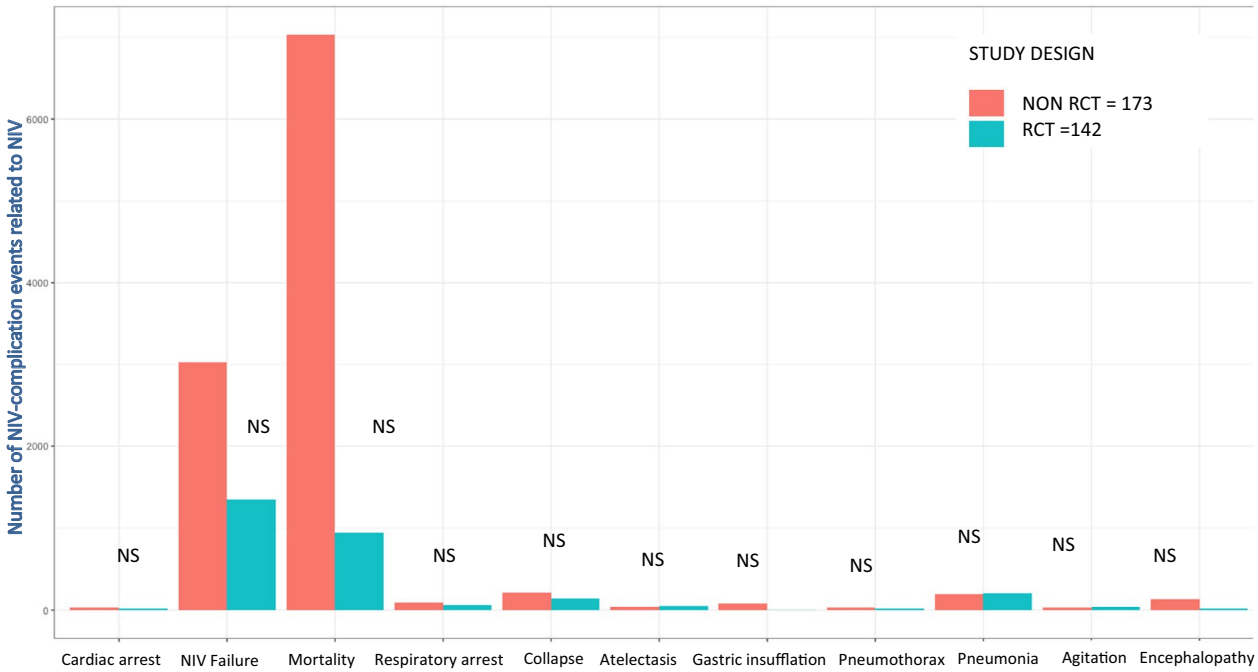


**Fig. 3** Number of NIV complication events related to NIV and hospital mortality in RCTs ($n = 138$) and non-RCTs ($n = 170$). This histogram shows the number of events of severe complications related to NIV according to the study design (two groups: RCTs, $n = 138$ in color blue and non-RCTs, $n = 170$ in color red). The cardiac arrest absolute number was 15 (31%) and 34 (69%) for RCTs and non-RCTs, respectively, the NIV failure absolute number was 1346 (31%) and 3025 (69%) for RCTs and non-RCTs, respectively, and the hospital mortality absolute number was 946 (12%) and 7027 (88%) for RCTs and non-RCTs, respectively. No statistical differences were found between the two groups for all complications. *RCT* randomized controlled trial, *Non-RCT* non-randomized controlled trial, *NIV* non-invasive ventilation, *NS* non-significant

(See figure on next page.)

**Fig. 4** Pooled incidence by year for 1000 patients with NIV-related cardiac arrest, NIV failure and hospital mortality over time (from 1981 to 2020) in RCTs ($n = 138$) and non-RCTs ($n = 170$). **A** Pooled incidence by year with 10,000 patients with NIV-related cardiac arrest over time (from 1981 to 2020) in RCTs ($n = 138$) and non-RCTs ($n = 170$). This spaghetti plot shows the number of events expressed in the pooled incidence of NIV-related cardiac arrest according to study design (two groups: RCTs in color blue and non-RCTs in color red) for each year from 1981 to 2020, for 1000 patients under NIV. With the package "metafor", we used the inverse method to calculate each pooled incidence for NIV-related cardiac arrest for each year in the two groups RCTs versus non-RCTs. Then we plotted the data with the package "Ggplot2" and the function "ggparcoord" to add the line between each point representing the pooled incidence. The study effect (RCTs versus non-RCTs) and time effect were not significant. *RCT* randomized controlled trial, *non-RCT* non-randomized controlled trial, *NIV* non-invasive ventilation. **B** Pooled incidence by year for 1000 patients with NIV failure over time (from 1981 to 2020) in RCTs ($n = 138$) and non-RCTs ($n = 170$). This spaghetti plot shows the number of events expressed in the pooled incidence of NIV failure according to study design (two groups: RCTs in color blue and non-RCTs in color red) for each year from 1981 to 2020, for 1000 patients under NIV. With the package "metafor", we used the inverse method to calculate each pooled incidence for NIV failure for each year in the two groups RCT versus non-RCTs. Then we plotted the data with the package "Ggplot2" and the function "ggparcoord" to add the line between each point representing the pooled incidence. The study effect (RCTs versus non-RCTs) and time effect were not significant. *RCT* randomized controlled trial, *non-RCT* non-randomized controlled trial, *NIV* non-invasive ventilation, *NS* non-significant. **C** Pooled incidence by year for 1000 patients with hospital mortality over time (from 1981 to 2020) in RCTs ($n = 138$) and non-RCTs ($n = 170$). This spaghetti plot shows the number of events expressed in the pooled incidence of hospital mortality according to study design (two groups: RCTs in color blue and non-RCTs in color red) for each year from 1981 to 2020, for 1000 patients under NIV. With the package "metafor", we used the inverse method to calculate each pooled incidence for mortality for each year in the two groups RCTs versus non-RCTs. Then we plotted the data with the package "Ggplot2" and the function "ggparcoord" to add the line between each point representing the pooled incidence. The study effect (RCTs versus non-RCTs) and time effect were not significant. *RCT* randomized controlled trial, *non-RCT* non-randomized controlled trial, *NIV* non-invasive ventilation, *NS* non-significant

pulmonary edema and after abdominal surgery resulted in a better prognosis [1, 3, 30]. After many studies performed in the 1990s and 2000s showing a decrease in mortality rate with NIV use, several studies [31, 32] reported in 2015 that NIV was independently associated with increased mortality in acute hypoxemic ARF patients, compared with high-flow nasal oxygen (HFNO). In ARF in COVID-19 patients, an initial strategy of CPAP

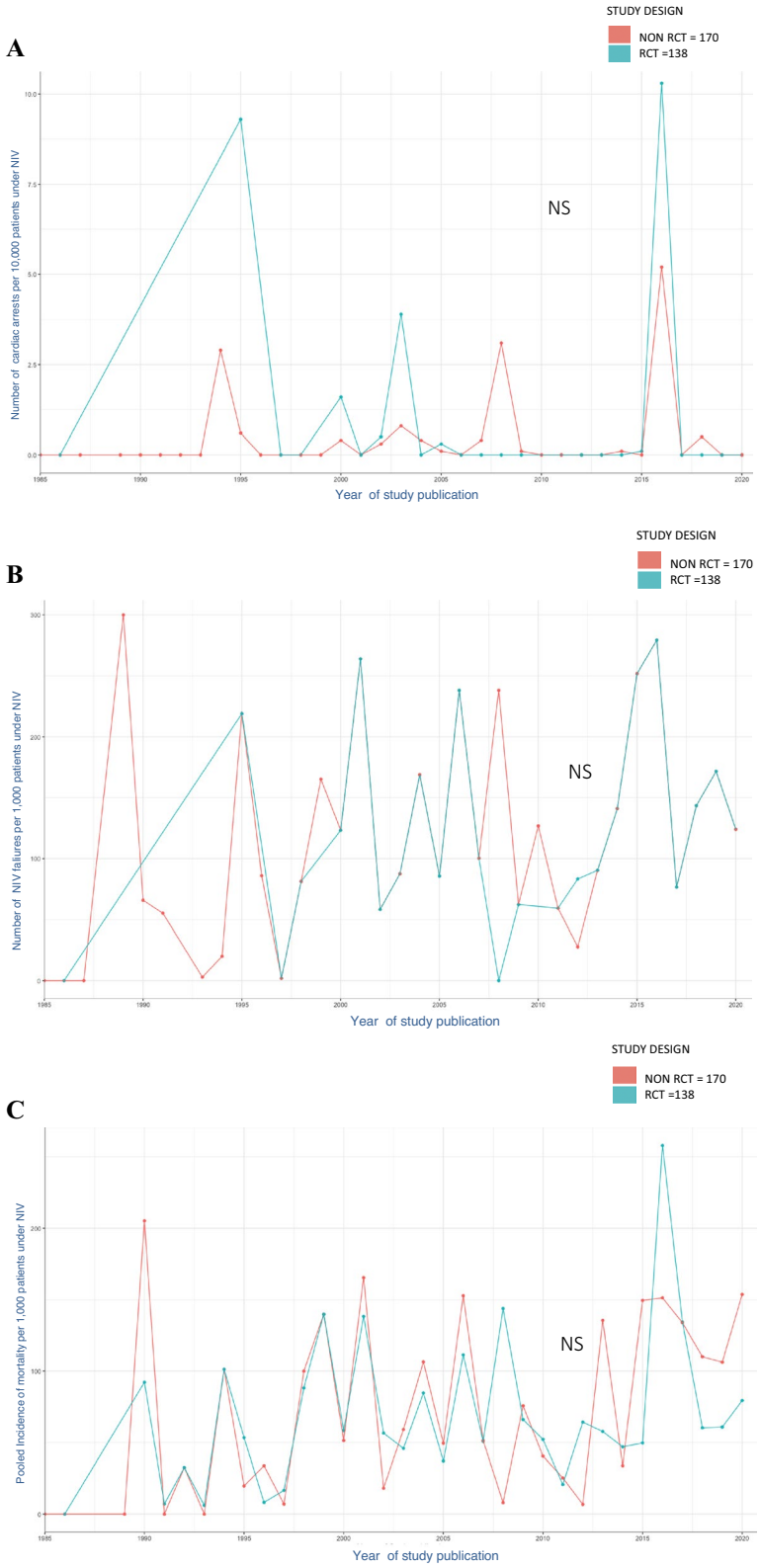


Fig. 4 (See legend on previous page.)

significantly reduced the risk of tracheal intubation or mortality compared with conventional oxygen therapy [8]. In the specific population of immunocompromised patients, a dedicated RCT [33] and a large prospective multinational cohort study [34] reported no benefit and no harm from NIV in immunocompromised patients. Patient selection [35] is therefore one of the major determinants of NIV failure. In the current systematic review and meta-analysis, we did not find any significant differences in the rate of NIV-related cardiac arrest according to the indication for NIV. However, we found that the studies performed before 2010 reported a higher incidence of NIV-related cardiac arrest.

NIV failure has been associated with an increased risk of intubation-related complications [36]. In this systematic review, studies reporting cardiac arrest were associated with higher rates of NIV failure. NIV interface selection might be one of the major determinants of NIV failure. NIV with a helmet, compared with a traditional face mask, was associated with reduced hospital mortality and intubation requirement in randomized controlled studies, in COVID-19 and non-COVID-19 patients [9, 11]. In the current meta-analysis, even if the pooled incidence of NIV-related cardiac arrest was lower in the helmet group, no significant difference was found between NIV interfaces. This lack of significance could be due to a lack of power. Surprising findings include the non-significant association of NIV-related cardiac arrest and the impact factor of studies. Moreover, no significant difference was seen between RCTs and non-RCTs (Figs. 3 and 4).

Other severe complications related to NIV were reported in the current systematic review, meta-analysis and meta-regression. However, under-reporting is likely to be even higher than in NIV-related cardiac arrests, given the low pooled incidence of respiratory arrests, severe collapse or other severe complications. However, even under-reported, the cumulated pooled incidence of all the complications raises major questions about the benefit-risk ratio of performing NIV. In this setting, the training of the team is of crucial importance. NIV performed outside of a trained team, including nurses and physicians, is often associated with more complications. One could hypothesize that team training is associated with less NIV failure and less NIV-related cardiac arrest [4]. Moreover, when the benefit of NIV is not proven, the risks potentially associated with NIV must be considered by the bedside physician.

Following the results of the current study, the perspectives are wide. First, life-threatening side effects of therapeutics performed in the ICU setting should be reported. This applies to NIV but also to other treatments such as HFNO, intubation, mechanical ventilation, etc. Second, NIV-related cardiac arrests exist, and preventing their occurrence better in the future is challenging for the bedside clinician. Even if it was not possible in the current study to assess the relationship between delayed intubation and the pooled incidence of NIV-related cardiac arrest, the risks of delaying intubation must be underlined and might have been associated with NIV-related cardiac arrest. Indeed, when intubation is delayed in ICU patients, mortality is consistently increased in many studies [37]. One of the first studies showing the risks of delayed intubation was the study of Esteban et al. [38]. In 227 patients from 37 centers, NIV use was associated with increased mortality [38]. It is worth noting that the interval between the onset of respiratory failure and reintubation was significantly longer in the NIV group than in the standard-therapy group. Similar results were found with the use of HFNO [39]. Kang et al. [39] showed that failure of HFNO might cause delayed intubation and worse clinical outcomes in patients with ARF. The choice of NIV interface and patient selection should be also carefully thought through by physicians. Third, modern monitoring parameters, especially in the ward, could help to decrease NIV-related complications.

Some limitations exist for this systematic review and meta-analysis. We conducted the meta-analysis at the study level; therefore, variables at the patient level were not available for this analysis. Thus, we could not establish additional potential risk factors possibly associated with the pooled incidence of NIV-related cardiac arrest, such as severity of patient illness, experience of the team and operator or delay in performing intubation. However, using meta-regression, we found that the study period and NIV failure rate were associated with the occurrence of reported cardiac arrests. Second, the use of meta-analytic techniques to pool published summary data is associated with the possibility of missing studies, the heterogeneity of included studies, and the use of aggregated patient data, which can restrict ability to check for uniform definitions of outcome variables. Concerns exist when incidence rates are pooled, because so much depends on the sample. The bias of under-reporting cannot be corrected, and as discussed earlier, the real incidence of NIV-related cardiac arrest is probably higher. Moreover, exclusion of the cardiac arrests occurring in the setting of the decision to withdraw life-sustaining treatment or do-not-resuscitate orders probably resulted in an underestimation of the incidence of cardiac arrest. Third, it is worth noting that the study was focused on the treatment of ARF, and not on prevention. The pooled incidence reported cannot be extrapolated to NIV performed to prevent ARF. Fourth, the causal link between NIV failure and cardiac arrest is not certain. We can suppose that NIV failure was the cause of cardiac

arrest; however, causality cannot be confirmed given the inclusion of retrospective studies. We cannot rule out that in some cases, cardiac arrest leads to endotracheal intubation and therefore NIV failure. Fifth, we were not able to assess cumulative incidence over number of days of applied NIV as these data were not available in most studies. Sixth, as data on sedation use during NIV were scarce, we were not able to assess the relationship between sedation use and cardiac arrest incidence.

Large prospective studies are necessary to better assess the incidence of NIV-related cardiac arrest and its risk factors, to better select the patients likely to receive NIV safely. It is already known that NIV failure and ICU mortality depend on the indications for NIV [10]. However, no large prospective multicenter international study has focused on the incidence, risk factors and strategies to prevent NIV-related cardiac arrest.

## Conclusion

Cardiac arrest related to NIV occurred in one patient per 10,000 under NIV for ARF treatment. NIV-related cardiac arrest was correlated with NIV failure. Our results suggest that cardiac arrest and other severe complications are not reported equally throughout study periods, and are probably underestimated. An important area of future inquiry will be the implementation of large prospective multicenter international studies to identify the risk factors associated with NIV-related cardiac arrest.

**Supplementary Information**
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**Author contributions**
AR, ADJ and SJ contributed to the conception and design of the study, to the analysis and interpretation of data, to drafting the submitted article, and provided final approval of the version to be published. AR, ADJ and EV contributed to data acquisition, drafting the submitted article, and provided final approval of the version to be published. AR, ADJ, NM and SJ contributed to data analysis, drafting the submitted article, and provided final approval of the version to be published. AR, ADJ, EV, NM, EA and SJ contributed to data interpretation, drafting the submitted article, and provided final approval of the version to be published. All authors provided agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Data sharing**
Research data will be made available to the scientific community, immediately on publication, with as few restrictions as possible. All requests should be submitted to the corresponding author who will review with the other investigators for consideration. A data use agreement will be required before the release of participant data and institutional review board approval as appropriate.

**Declarations**

**Conflicts of interest**
SJ reports receiving consulting fees from Drager, Medtronic, Fresenius, Baxter, Mindray and Fisher & Paykel. ADJ reports receiving consulting fees from Drager, Medtronic and Fisher & Paykel. EA has received fees from Gilead Sciences, Alexion, Astellas, MSD and Drager. No potential conflicts of interest relevant to this article were reported for the other authors.

**Ethics committee approval**
The study was registered in PROSPERO (CRD42019132801).

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