

SUPPLEMENT

Understanding Causes of Death in Patients with Acute Respiratory Distress Syndrome: A Narrative Analysis and Review

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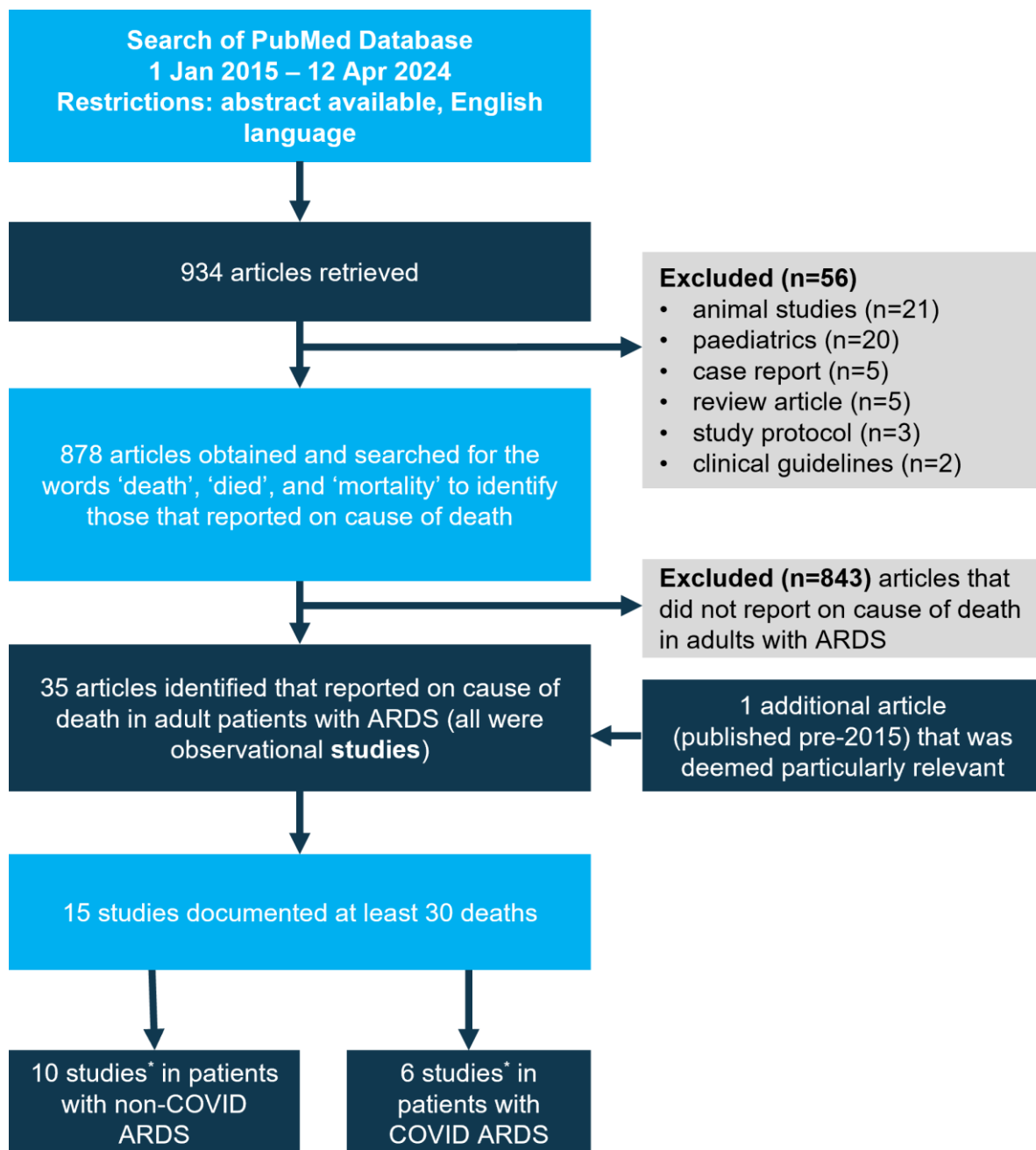
eMethods – Search strings

Primary search

("acute respiratory distress syndrome" [title] OR "ARDS" [title]) AND ("death" [title] OR "deaths" [title] OR "mortality" [title] OR "survival" [title] OR "non-survivors" [title] OR "non-survival" [title] OR "prognosis" [title] OR "clinical course" [title] OR "management" [title] OR "intensive care" [title] OR "outcome" [title] OR "outcomes" [title]) NOT "case report" NOT "pediatrics" [title] NOT "paediatrics" [title] NOT "pediatric" [title] NOT "paediatric" [title] NOT "Review" [PT]

Additional search

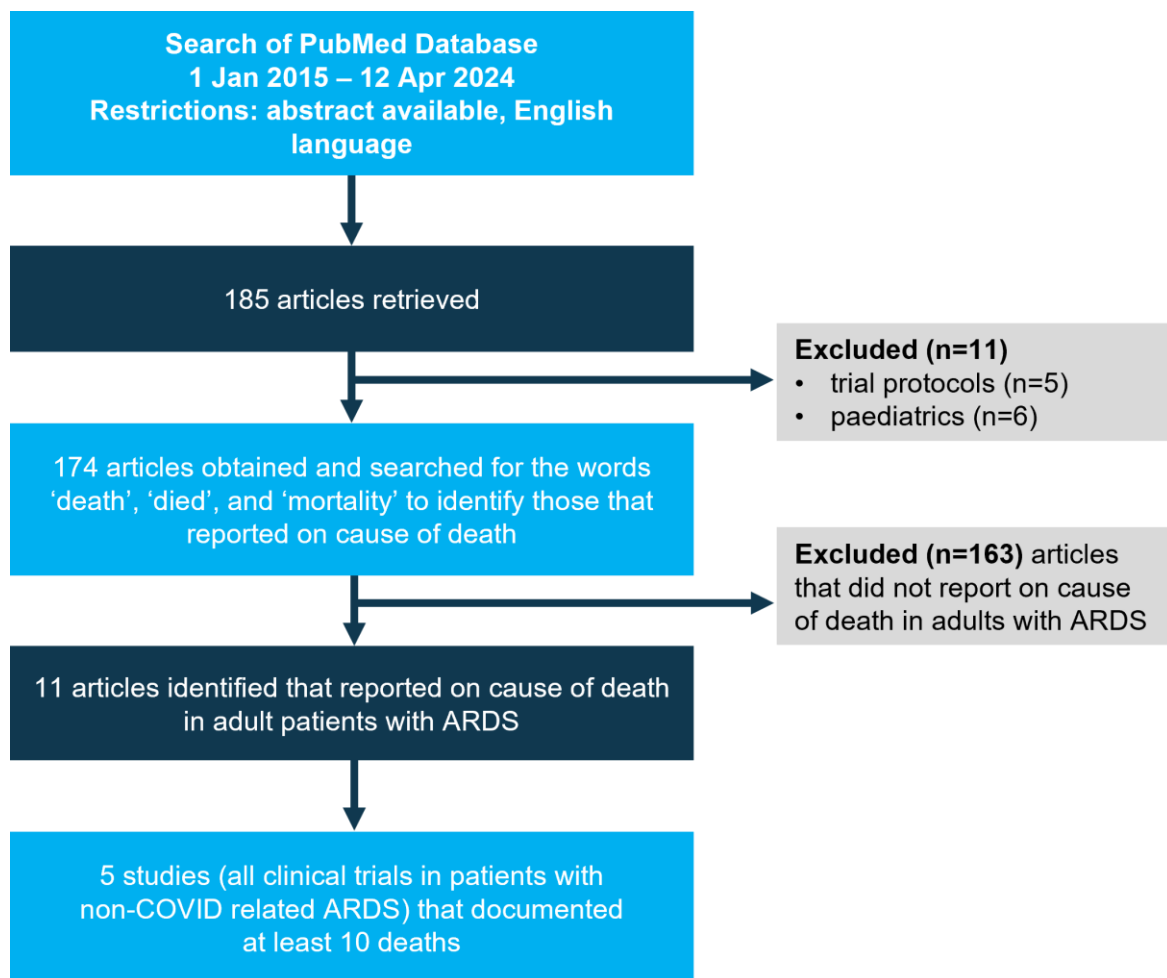
("acute respiratory distress syndrome" [title] OR "ARDS" [title]) AND ("trial" [title])



eFigure 1a. Identification of articles included in the review from the initial broad search.

*One study reported on cause of death among patients with non-COVID ARDS and separately among patients with COVID ARDS

ARDS, acute respiratory distress syndrome



eFigure 1b. Identification of articles included in the review from the search targeted to capture ARDS clinical trials.

ARDS, acute respiratory distress syndrome

eTable 1. Reported cause of death in patients with non-COVID ARDS (observational studies reporting on at least 100 deaths).

| Reported cause of death | | | | | | | | | | | | | | | | | | |
|---|-------------------|-----------------|--------------------------|-----|----------------------|---------|-------------|---|-----------------------------------|---------------------|--------------|------------|-------------|----------|----------|-----|-------------|--------------------------------|
| Author(s); year; study period | Deaths / patients | Data collection | Pre-specified categories | MOF | Refractory hypoxemia | Sepsis* | Brian death | Withdrawal of life support / end of life decision | Limitation of therapeutic efforts | Mesenteric ischemia | CNS disorder | Pulmonary‡ | Neurologic‡ | Cardiac‡ | Hepatic‡ | GI‡ | Hemorrhage‡ | Other§ |
| Laffey et al. 2017, LUNG SAFE; International 2014 | 964 / 2813 | Prospective | ✓ | NC | NC | NC | NC | NC | NC | NC | NC | 42% | 11% | 37% | 5% | NC | 1% | 3% renal failure 1% unknown |
| Villar et al, 2018; Spain; NR | 302 / 778 | Prospective | ✓ | 49% | 23% | 17% | 5% | NC | 4% | NC | NC | NC | NC | NC | NC | NC | NC | 2% |
| Gacouin et al; 2020; France; Oct 2009–Mar 2020 | 197 / 572 | Prospective | ✓ | 50% | 16% | NC | NC | 6% | NC | 6% | 8% | NC | NC | NC | NC | NC | NC | 15% |

| Reported cause of death | | | | | | | | | | | | | | | | | | |
|--|-------------------|-----------------|--------------------------|-----|----------------------|---------|-------------|---|-----------------------------------|---------------------|--------------|------------|-------------|----------|----------|-----|-------------|--------|
| Author(s); year; study period | Deaths / patients | Data collection | Pre-specified categories | MOF | Refractory hypoxemia | Sepsis* | Brian death | Withdrawal of life support / end of life decision | Limitation of therapeutic efforts | Mesenteric ischemia | CNS disorder | Pulmonary† | Neurologic‡ | Cardiac‡ | Hepatic‡ | GI‡ | Hemorrhage‡ | Other§ |
| Ketcham <i>et al</i> , 2020; US; 2016–2017 | 127 / NR | Retrospective | ✓ | NC | NC | 29% | NC | NC | NC | NC | NC | 28% | 17% | 10% | 6% | 4% | 4% | 2% |

*Includes septic shock.

†In individuals aged ≥18 year.

‡Organ system that most directly contributed to death or withdrawal of life support.

§In Villar *et al*, 2% had patients had either ventricular arrhythmia (n=1), hemorrhagic shock (n=2), cardiogenic shock (n=2), or anaphylactic shock (n=1). In Gacouin *et al*, ‘other’ was not further specified.

^{||}This was not considered as a pre-specified mutually exclusive category for cause of death; however, the authors reported that 87% of patients who died had life support withdrawn.

ARDS, acute respiratory distress syndrome; CNS, central nervous system; GI, gastrointestinal; MOF, multiple organ failure; NC, not considered (i.e. not a category in studies that had pre-specified categories); NR not reported; US, United States

eTable 2. Reported cause of death among patients with non-COVID ARDS (observational studies reporting on 30 to <100 deaths; n=6).

| Author(s); year; study period | Deaths / patients | Data collection | Pre-specified categories | Reported cause of death | | | | | | | | | | | | | | | | | | |
|--|----------------------|-----------------|--------------------------|-------------------------|-----------|-----------------|--------------|----------------------|---------------------------------|---------------------|--------------------|------------|---------------|---------------|-----------------------|------------|-------------|-------------|----------------------------|--------|--------------------|--------|
| | | | | MOF | MOF/shock | MOF with sepsis | Septic shock | Refractory hypoxemia | Refractory respiratory acidosis | Respiratory failure | Respiratory system | CNS cause | Cardiac cause | Hepatic cause | GI cause | Hemorrhage | Renal cause | Head injury | Withdrawal of life support | Trauma | Infectious disease | Other* |
| Stapleton et al, 2005; US; 1998 | 30 / 205 | Prospective | ✓ | NC | NC | 30% | NC | NC | NC | 13% | NC | 29% | 8% | 7% | 3% | 4% | 5% | NC | NC | NC | NC | NC |
| Maamar et al, 2023; France; Oct 2009–Dec 2022 | 32/ 106 [†] | Prospective | ✓ | 57%[‡] | NC | NC | NC | 17% | NC | NC | NC | 10% | NC | NC | 7%[§] | NC | NC | NC | 10% | NC | NC | NC |
| Wu et al, 2017; Taiwan; 2007–2016 | 53 / 106 | Retrospective | ✗ | NR | NR | 89% | NR | NR | NR | NR | NR | NR | NR | NR | NR | 6% | NR | NR | NR | NR | NR | NR |

| Author(s); year; study period | Deaths / patients | Data collection | Pre-specified categories | Reported cause of death | | | | | | | | | | | | | | | | | | |
|---|-------------------|-----------------|--------------------------|-------------------------|-----------|-----------------|--------------|----------------------|---------------------------------|---------------------|--------------------|-----------|---------------|---------------|----------|------------|-------------|-------------|----------------------------|--------|--------------------|--------|
| | | | | MOF | MOF/shock | MOF with sepsis | Septic shock | Refractory hypoxemia | Refractory respiratory acidosis | Respiratory failure | Respiratory system | CNS cause | Cardiac cause | Hepatic cause | GI cause | Hemorrhage | Renal cause | Head injury | Withdrawal of life support | Trauma | Infectious disease | Other* |
| Al-Thani et al, 2022; Qatar; Jan 2014– Jan 2020 | 35 / 85 | Retrospective | * | 26% | NR | NR | 14% | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | 57% | NR | NR | NR | NR |
| Gerard et al, 2018; Belgium; Jan 2007– Jan 2017 | 30 / 51 | Prospective | * | NR | 40% | NR | NR | 17% | 20% | NR | NR | NR | NR | NR | NR | NR | NR | NR | 13% | NR | NR | 10% |
| Riviello et al, 2016; Rwanda; Feb 2014– Apr 2014 | 38 / 42 | Prospective | * | NR | NR | NR | NR | NR | NR | NR | 11% | NR | NR | NR | 16% | NR | NR | NR | NR | 32% | 18% | 10% |

*In Gerard *et al*, ‘other’ was not further specified. In Riviello *et al*, cause of death was recorded as cancer in 8%, pregnancy/postpartum in 5%, cardiovascular disease in 5%, and unknown in 5%. In Al-Thani *et al*, 3% had cardiac arrest recorded as cause of death. †Influenza ARDS. ‡Infection-related MOF. §Mesenteric ischaemia. CNS, central nervous system; GI, gastrointestinal; MOF, multiple organ failure; NC, not considered (i.e. not a category in studies that had pre-specified categories); NR, not reported

eTable 3. Details on individual observational reporting on causes of death among patients with non-COVID ARDS) studies (n=10).

| Author(s), year, country, study period | Patients with ARDS | Demographics | Setting | ARDS definition | Causes of death |
|--|--|--|---|--|---|
| Laffey <i>et al</i>, 2017 International (50 countries across 6 continents) 4 consecutive weeks in winter 2014 | 2813 patients with ARDS who received invasive/non-invasive ventilation | Mean age 61.3 years (SD 16.8) 38% female | 459 ICUs | Berlin | N=not reported (deaths) <ul style="list-style-type: none"> • Respiratory failure: 41.6% • Cardiovascular failure: 37.1% • Neurologic failure: 10.9% • Hepatic failure: 5.3% • Coagulation failure: 1.2% • Unknown: 0.9% • No significant geographical variations were observed |
| Villar <i>et al</i>, 2018 Spain Not reported | 778 adults with moderate-to-severe ARDS treated with MV Cause of ARDS: <ul style="list-style-type: none"> • Pneumonia: 39% • Sepsis: 31% • Aspiration: 11% • Trauma: 11% • Acute pancreatitis: 5% • Other: 4% | Mean age 55 years (SD±17); 31% female | Three independent, national, multi-centre observational cohorts that enrolled patients from a network of ICUs | AECC criteria on PEEP ≥5cm H ₂ O and the Berlin criteria for moderate/severe ARDS | N=302 deaths <ul style="list-style-type: none"> • MOF: 49% • Refractory hypoxaemia due to non-resolving ARDS: 23% • Irreversible septic shock: 17% • Brain death: 5% • Limitation of therapeutic efforts: 4% • Other: 2% (1 ventricular arrhythmia, 2 haemorrhagic shock, 2 cardiogenic shock, 1 anaphylactic shock) |
| Gacouin <i>et al</i>, 2020 France Oct 2009–Mar 2020 | 572 adults with ARDS Cause of ARDS was influenza virus alone in 13% and non-influenza alone in 87% | Whole cohort, median age 58 years (IQR, 47–68) | Single ICU | AECC | N=197 deaths <ul style="list-style-type: none"> • Primary infection-related MOF (50% n=98) • Refractory hypoxaemia (16% n=31) • Mesenteric ischaemia (6% n=12) • Central nervous system disorder (8% n=16) • End-of-life decision (6% n=11) • Other (15% n=29) |

| Author(s), year, country, study period | Patients with ARDS | Demographics | Setting | ARDS definition | Causes of death |
|---|---|--|--|---|---|
| Ketchum et al, 2020 US 2016–2017 | 127 adults hospitalised with AHRF ($\text{PaO}_2/\text{FiO}_2 \leq 300$) and ARDS, and receiving invasive MV for >12 hours, who died during hospitalization ARDS risk factors present: <ul style="list-style-type: none"> • Shock (non-cardiogenic): 78% • Transfusion: 46% • Sepsis (non-pulmonary): 43% • Pneumonia: 52% • Aspiration: 22% • Other*: 51% • None: 2% <i>*Included major trauma (9%), major surgery (7%), pulmonary contusion (3%), pancreatitis (2%), major burn (1%), inhalation injury (1%), vasculitis (<1%).</i> | Median age 62 years (IQR, 51–71) 43% female | Single tertiary centre <u>ICU setting</u> <ul style="list-style-type: none"> • Medical: 72% • Cardiac: 3% • Surgical: 18% • Trauma/burn: 6% • Neurologic: 1% | Berlin | Primary cause of death (organ system that most directly contributed to death or withdrawal of life support; assessed in the 72 hours before death); N=127 deaths <ul style="list-style-type: none"> • Sepsis: 29% • Pulmonary: 28% • Neurologic: 17% • Cardiac: 10% • Hepatic: 6% • Gastrointestinal: 4% • Haemorrhage: 4% • Renal: 1% • Haematologic: 1% • Withdrawal of life support: 87% |
| Stapleton et al, 2005 US 1998 | 205 patients with ARDS | Median age 48 years (range 1–86 years) 66% female | Single centre | $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 150 , or ≤ 200 while receiving positive end-expiratory pressure $\geq 5\text{cm H}_2\text{O}$; opacities on chest radiography involving at least 50% of three or four quadrants; pulmonary capillary wedge pressure 18 | N=76 deaths <ul style="list-style-type: none"> • MOF with sepsis: 30% • Central nervous system cause: 29% • Respiratory failure: 13% • Cardiac cause: 8% • Hepatic cause: 7% • Gastrointestinal cause: 3% • Haemorrhage: 4% • Haematologic: 1% • Renal cause: 5% |

| Author(s), year, country, study period | Patients with ARDS | Demographics | Setting | ARDS definition | Causes of death |
|--|---|---|---------------|--|--|
| | | | | mmHg or no other clinical evidence of left atrial hypertension; and no other obvious explanation for these findings. | |
| Maamar et al, 2023 France Oct 2009–Feb 2022 | 106 patients with influenza-ARDS | Median age 59.0 years (IQR,49.0–65.7) 39% female | Single ICU | Berlin | N=32 deaths <ul style="list-style-type: none"> • Primary infection-related MOF: 57% • Refractory hypoxemia: 17% • Mesenteric ischemia: 7% • Central nervous system disorder: 10% • End-of-life decision: 10% |
| Wu et al, 2017 Taiwan 2007–2016 | 106 non-trauma patients who received vvECMO for ARDS Causes of ARDS were categorised into 4 groups: <ul style="list-style-type: none"> • Bacterial pneumonia: 37% (n=41; three were fungal pneumonia, and the top three found bacteria were <i>Staphylococcus aureus</i>, <i>Pseudomonas aeruginosa</i>, and <i>Acinetobacter baumannii</i>) • Viral pneumonia: 21% (n=24; all influenza type A) • Aspiration pneumonitis: 3% (n=3) | Mean age 53 years (SD±15) years 33% female | Single centre | Not reported | N=56 deaths (35 while on ECMO) <ul style="list-style-type: none"> • Death while on vv-ECMO due to haemorrhagic complications (11%, n=6); included intracranial hemorrhages (n=2), intra-abdominal or retroperitoneal hemorrhages (n=1), and gastrointestinal tract hemorrhages (n=4) • MOF syndrome with sepsis (89%; n=50) Among the 56 deaths: <ul style="list-style-type: none"> • 39% had bacterial pneumonia has cause of ARDS • 23% had viral pneumonia has cause of ARDS • 0% had aspiration pneumonitis has cause of ARDS |

| Author(s), year, country, study period | Patients with ARDS | Demographics | Setting | ARDS definition | Causes of death |
|---|---|--|--|--|---|
| | <ul style="list-style-type: none"> Others: 3% (n=38); included pneumonia without identifiable pathogens (n=24); pulmonary hemorrhage caused by autoimmune vasculitis (n=2); pneumonia after near-drowning (n=1); and pulmonary edema due to acute on chronic renal failure (n=4), acute pancreatitis (n=3), or after percutaneous interventions (n=4; 3 for cardiac lesions and 1 for cerebral aneurysm) | | | | <ul style="list-style-type: none"> 32% had 'other' acute respiratory diagnoses |
| Riviello <i>et al</i>, 2016 Rwanda Feb 2014–Apr 2014 | 42 patients (age >15 years) with ARDS Cause of ARDS: <ul style="list-style-type: none"> Infection: 44% (majority being pulmonary) Trauma: 29% Surgery: 25% | Median age 37 years (IQR, 26–49) 46% female | Single centre | Berlin (modified; without a requirement for PEEP, hypoxia cutoff defined by $SpO_2/FIO_2 \leq 315$, and use of either lung ultrasound or chest radiograph for determination of bilateral opacities) | N=38 deaths <ul style="list-style-type: none"> Trauma: 32% (n=12) Infectious diseases: 18% (n=7) Gastrointestinal system: 16% (n=6) Respiratory system: 11% (n=4) Neoplasms: 8% (n=3) Cardiovascular: 5% (n=2) Pregnancy/peripartum: 5% (n=2) Unknown: 5% (n=2) |
| Al-Thani <i>et al</i>, 2022 Qatar Jan 2014– Jan 2020 | 85 patients with trauma who developed ARDS Cause of ARDS=trauma | Mean age 34.3 years (SD±14.9) years 8% female | Level I trauma facility, single centre | Berlin | N=35 deaths <ul style="list-style-type: none"> Head injury: 57.1% MOF: 25.7% Septic shock: 14.3% Cardiac arrest: 2.9% |

| Author(s), year, country, study period | Patients with ARDS | Demographics | Setting | ARDS definition | Causes of death |
|---|---|---|--------------------------|-----------------|---|
| Gerard <i>et al</i>, 2018 Belgium Jan 2007– Jan 2017 | 51 patients with an ICD-9 code 518.82 ‘clinical modification suggesting ARDS’ in the discharge diagnosis notes, along with a procedure code for Open Lung Biopsy or Exploratory thoracotomy | Median age 66.9 (IQR 52–76) 45% female | Mixed ICU; single centre | Berlin | N=30 deaths <ul style="list-style-type: none"> • Shock/MOF: 40% • Refractory hypoxemia: 17% • Refractory respiratory acidosis: 20% • Withdrawal of life support: 13% • Other: 10% |

AECC, American-European Consensus Criteria; AHRF, acute hypoxemic respiratory failure; ARDS, acute respiratory distress syndrome; FiO₂, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; ICD, International Classification of Diseases; MOF, multiple organ failure; MV, mechanical ventilation; PaO₂, partial pressure of oxygen; PEEP, positive end-expiratory pressure; SD, standard deviation; SpO₂, oxygen saturation; vvECMO, venovenous extra corporeal membrane oxygenation

eTable 4. Details on individual observational studies reporting on causes of death among patients with COVID ARDS) (n=6).

| Author(s), year, country, study period | Patients with ARDS | Demographics | Setting | ARDS definition | Causes of death |
|--|--|--|----------------------|-----------------|--|
| Estenssoro <i>et al</i> , 2021 Argentina Mar 2020–Oct 2020 | 1909 patients with COVID-19 receiving invasive MV ARDS developed in 1672 (87.6%) patients | Median age 62 years (IQR, 52–70) 32% female | Multicentre; 63 ICUs | Berlin | <p>Primary cause of death (N=1079)</p> <ul style="list-style-type: none"> • Refractory hypoxaemia: 43% (n=462; among these 174 had septic shock identified as secondary cause of death; and 139 had multiple organ dysfunction syndrome identified as tertiary cause of death) • Septic shock: 31% (n=337) • Multiple organ dysfunction syndrome: 18% (n=190) • Acute myocardial infarction: 1% (n=16) • Acute heart failure: 1% (n=12) • Stroke: 1% (n=8) • Do-not-resuscitate: 1% (n=6) • Pulmonary thromboembolism: 0% (n=1) • Other: 4% (n=48) <p>Secondary concomitant cause of death (N=486)</p> <ul style="list-style-type: none"> • Septic shock: 36% (n=175) • Multiple organ dysfunction syndrome: 47% (n=229) • Acute myocardial infarction: 1% (n=4) • Acute heart failure: 2% (n=8) • Stroke: 1% (n=6) • Do-not-resuscitate: 8% (n=37) • Other: 5% (n=26) <p>Tertiary concomitant cause of death (N=486)</p> <ul style="list-style-type: none"> • Multiple organ dysfunction syndrome: 68% (n=80) • Acute myocardial infarction: 1% (n=1) • Acute heart failure: 1% (n=1) • Do-not-resuscitate: 17% (n=20) • Other: 9% (n=10) |

| Author(s), year, country, study period | Patients with ARDS | Demographics | Setting | ARDS definition | Causes of death |
|--|---|---|--|-----------------|--|
| Estenssoro <i>et al</i>, 2022 Argentina Mar 2020–Oct 2020 | 1525 patients with COVID-19 ARDS receiving invasive MV | Mean age 61 years (± 13) 31% female | Multicentre; 63 ICUs | Berlin | N=894 deaths Refractory hypoxaemia was the main cause of death: 47% (n=420) |
| Maamar <i>et al</i>, 2023 France Oct 2009–Feb 2022 | 244 patients with COVID-19 ARDS | Median age 63.5 years (IQR, 54.0–71.2) 33 female | Single ICU | Berlin | N=37 deaths <ul style="list-style-type: none"> • Primary infection-related MOF: 23% • Refractory hypoxemia: 50% • Mesenteric ischemia: 10% • Central nervous system disorder: 7% • End-of-life decision: 7% |
| Raasveld <i>et al</i>, 2022 International Mar 2020–Dec 2020 | 193 patients with COVID-19 ARDS receiving VV-ECMO | Median age 53 years) IQR, 48–60) 22% female | Multicentre; 15 ICUs | Not reported | N=67 (35% of patients) Irreversible respiratory failure during ECMO resulting in palliation: 88% (n=59) |
| Pestaña <i>et al</i>, 2022 Spain Mar–Apr 2020 | 141 adults with COVID-19 ARDS | Median age 61 years (IQR 57–67) 23% female | Single centre ICU | Not reported | N=52 deaths <ul style="list-style-type: none"> • Refractory respiratory failure and persistent hypoxaemia ($\text{PaO}_2/\text{FiO}_2 < 100$): 65% (n=34), with 85% of these (29/34) having presented during mechanical ventilation with a restrictive pattern of respiratory mechanics • Pulmonary embolism (diagnosed by CT scan or clinical signs of right ventricular failure by echocardiogram): 14% • Septic shock: 33% • Haemorrhage/neurological disorders: 20% Some patients had a combination of ≥ 2 of these diagnoses |
| Daviet <i>et al</i>, 2021 France Mar–Nov 2020 | 76 patients with severe COVID-19 ARDS and supported with ECMO | Median age 61 years (IQR, 54–65) | Single centre constituted of 5 different ICU units | Not reported | N=37 deaths (at 90-days) <ul style="list-style-type: none"> • Septic shock: 35% • Haemorrhagic shock: 32% • Irretractable respiratory failure: 16% • Cardiogenic shock: 3% • Stroke: 5% • MOF: 8% |

ARDS, acute respiratory distress syndrome; CT, computed tomography; ECMO, extra corporeal membrane oxygenation; FiO₂, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; MOF, multiple organ failure; MV, mechanical ventilation; PaO₂, partial pressure of oxygen

eTable 5. Categories used to record death in observational studies where this was pre-specified.

| Author(s); year; study period | Country, study year/ period | Patients | Deaths | Prospective/ retrospective recording of cause of death | Pre-specified categories |
|---|-----------------------------|----------|--------|--|--|
| Studies among patients with non-COVID ARDS | | | | | |
| Laffey et al 2017 ¹⁶ | International 2014 | 2813 | 964 | Prospective | Section completed at ICU death (death form) If patient did not survive: What was the most important factor leading to ICU Death (Check one) <ul style="list-style-type: none"> • respiratory failure • cardiovascular failure (i.e. Unresponsive shock) • renal failure • hepatic failure • coagulation failure • neurologic failure |
| Villar et al, 2018 ¹³ | Spain NR | 778 | 302 | Prospective | Physicians instructed to report the primary cause of death within the following categories: <ul style="list-style-type: none"> • refractory hypoxemia due to unresolved ARDS • multi-system organ failure • irreversible shock • brain death • limitation of therapeutic efforts for end-of-life • Others |
| Gacouin et al; 2020 ¹⁴ | France Oct 2009–Mar 2020 | 572 | 197 | Prospective | Categorized into the following groups: <ul style="list-style-type: none"> • primary infection-related MOF • refractory hypoxemia • mesenteric ischemia • central nervous system disorder • end-of-life decision • others |
| Ketcham et al, 2020 ¹⁵ | US 2016–2017 | NR | 127 | Retrospective | The following tick lists were applied: <i>“Please choose the organ system with IRREVERSIBLE dysfunction that most directly contributed to the patient’s death”</i> <ul style="list-style-type: none"> • septic shock • pulmonary • cardiac • central nervous system |

| Author(s); year; study period | Country, study year/ period | Patients | Deaths | Prospective/ retrospective recording of cause of death | Pre-specified categories |
|-------------------------------|-----------------------------|----------|--------|--|---|
| Maamar <i>et al</i> , 2023 | France Oct 2009–Feb 2022 | 106 | 32 | Prospective | <ul style="list-style-type: none"> • hematologic • hemorrhagic • hepatic • gastrointestinal <p>renal “AND, please choose the organ system with SEVERE dysfunction that most directly contributed to the patient’s death”</p> <ul style="list-style-type: none"> • septic shock • pulmonary • cardiac • central nervous system • hematologic • hemorrhagic • hepatic • gastrointestinal • renal <p>Categorized into the following groups:</p> <ul style="list-style-type: none"> • primary infection-related MOF • refractory hypoxemia • mesenteric ischemia • central nervous system disorder • end-of-life decision |
| Stapleton <i>et al</i> , 2005 | US 1998 | 205 | 30 | Prospective | <p>Three of the authors (investigators) reviewed patients medical charts. A death was categorized as due to the presenting injury/illness or progression of the ARDS risk factor if it was associated with conditions that preceded ARDS onset.</p> <p>Rigorous inspection of temporal relationships of laboratory data, hemodynamic and respiratory parameters, and nursing and physician notes was used to identify one of nine causes of death:</p> <ul style="list-style-type: none"> • MOF with sepsis • respiratory • cardiac, • central nervous system • hematologic |

| Author(s); year; study period | Country, study year/ period | Patients | Deaths | Prospective/ retrospective recording of cause of death | Pre-specified categories |
|---|--------------------------------|----------|--------|--|--|
| | | | | | <ul style="list-style-type: none"> • hemorrhage • hepatic • gastrointestinal • renal |
| Studies among patients with covid-related ARDS | | | | | |
| Estenssoro <i>et al</i> , 2021 | Argentina Mar 2020–Oct 2020 | 1909 | 1079 | Prospective | <p>Causes of death were selected from a list of nine predetermined possibilities:</p> <ul style="list-style-type: none"> • refractory hypoxemia • septic shock • multiple organ dysfunction syndrome • acute myocardial infarction • acute heart failure • stroke • do-not resuscitate order • pulmonary thromboembolism • other <p>Note: “<i>more than one cause of death could be considered</i>”</p> |
| Estenssoro <i>et al</i> , 2022 | Argentina Mar 2020–Oct 2020 | 1525 | 894 | Prospective | <p>Causes of death were selected from a list of nine predetermined possibilities:</p> <ul style="list-style-type: none"> - refractory hypoxemia - septic shock - multiple organ dysfunction syndrome - acute myocardial infarction - acute heart failure - stroke - do-not resuscitate order - pulmonary thromboembolism - other <p>Note: “<i>more than one cause of death could be considered</i>”</p> |
| Pestaña <i>et al</i> , 2022 | Spain | 141 | 52 | Retrospective | <p>Four clinical diagnoses were defined to assess the causes of death:</p> <ul style="list-style-type: none"> • refractory respiratory failure |

| Author(s); year; study period | Country, study year/ period | Patients | Deaths | Prospective/ retrospective recording of cause of death | Pre-specified categories |
|-------------------------------|---|----------|--------|--|---|
| Maamar <i>et al</i> , 2023 | France Mar–Apr 2020 Oct 2009–Feb 2022 | 244 | 37 | Prospective | <ul style="list-style-type: none"> • pulmonary embolism (diagnosed by CT scan or clinical signs of right ventricular failure by echocardiography) • septic shock • other (hemorrhage, neurological disorders) Categorized into the following groups: <ul style="list-style-type: none"> • primary infection-related MOF • refractory hypoxemia • mesenteric ischemia • central nervous system disorder • end-of-life decision |

CT, computed tomography; MOF, multiple organ failure; US, United States

eTable 6. Reported cause of death in clinical trials of patients with ARDS (all were non-COVID-related ARDS, n=5).

| Author(s), year, country, study period | Patients with ARDS | Setting | ARDS definition | Recording of death | Reported causes of death |
|--|--|--|-----------------|--------------------|---|
| Constantin et al, 2019 France Jun 2014– Feb 2017 | 420 patients with moderate-severe ARDS randomized to personalized MV strategy or control (non-personalized standard of care) 196 patients in the personalized arm and 204 patients in the control arm were included in the analysis | Multicentre (20 ICUs) | Berlin | Not specified | <p>All ARDS deaths (N=107)</p> <ul style="list-style-type: none"> • Death directly related to ARDS: 34% (n=36) • Related to underlying disease: 64% (n=68) • Unknown: 3% (n=3) <p>Focal ARDS (26 deaths)</p> <ul style="list-style-type: none"> • Death directly related to ARDS: 35% (n=9) • Related to underlying disease: 62% (n=16) • Unknown: 4% (n=1) <p>Non-focal ARDS (81 deaths)</p> <ul style="list-style-type: none"> • Death directly related to ARDS: 33% (n=27) • Related to underlying disease: 64% (n=52) • Unknown: 2% (n=2) |
| Villar et al, 2020 Spain Mar 2013– Dec 2018 | 277 patients with moderate-to-severe ARDS receiving MV and randomized to i.v. dexamethasone plus conventional treatment (n=139) or control (continued routine intensive care=138) | Multicentre (17 ICUs across Spain) | AECC/ Berlin | Not specified | <p>ICU deaths (N=69)</p> <ul style="list-style-type: none"> • MOF: 51% (n=35) • Irreversible shock: 16% (n=11) • Refractory hypoxemia: 16% (n=11) • Brain death: 6% (n=4) • Limitation of therapeutic efforts: 7% (n=5) • Others: 4% (n=3) |
| Mahmoud et al, 2020 Egypt Mar 2016– Jan 2018 | 60 patients aged 21–60 years with severe ARDS nonresponsive to recruitment maneuver, prone position and neuromuscular block, randomized to nebulized heparin (n=20), nebulized streptokinase (n=20) or conservative management (n=20) | Single centre | Berlin | Not specified | <p>Deaths (N=39)</p> <p>Death in heparin group (N=14 deaths) “Mortalities were due to MOF secondary to sepsis”</p> <p>Deaths in streptokinase group (N=7)</p> <ul style="list-style-type: none"> • MOF due to sepsis (n=5) • Acute massive MI (n=1) • massive bilateral pulmonary embolism (n=1) <p>Deaths in control group (N=18) No details reported</p> |

| Author(s), year, country, study period | Patients with ARDS | Setting | ARDS definition | Recording of death | Reported causes of death |
|--|--|--------------------------|-----------------|--------------------|---|
| Bellingan et al, 2022 UK and US Mar 2016– Sep 2018 | 36 patients with moderate-to-severe ARDS randomized to multipotent adult progenitor cells (n=26; 3 subcohorts of n=3, n=3 and n=20) or placebo (n=10) Cause of ARDS <ul style="list-style-type: none"> • Pneumonia: 56% (n=20) • Pneumonia/sepsis: 19% (n=7) • Sepsis: 11% (n=4) • Aspiration: 8% (n=3) • Other: n=6% (n=2) | Multicentre (12 centres) | Berlin | Not specified | Deaths (N=14) Reported causes of death included respiratory and multiple organ failure, sepsis, pneumonia, aspiration, pulmonary hemorrhage, and intestinal ischemia |
| McAuley et al, 2017 UK Feb 2011– Feb 2014 | 60 patients with ARDS receiving MV randomized to receive keratinocyte growth factor (n=29) or placebo (n=31) | Muticentre (two ICUs) | AECC | Not specified | Deaths (N=12) <ul style="list-style-type: none"> • Sepsis and MOF: 17% (n=2) • MOF (n=1) • Obstructive hydrocephalus and sepsis (n=1) • Hypoxic brain injury (n=1) • Cerebral hematoma (n=1) • Myocardial infarction and ruptured aortic aneurysm and metastatic pancreatic cancer diagnosed during ICU admission (n=1) • Systemic fungal infection (n=1) • Chronic obstructive pulmonary disorder and hypercapnic respiratory failure (n=1) • Chronic obstructive pulmonary disorder and hypercapnic respiratory failure (n=1) • Ruptured aortic aneurysm with MOF (n=1) • MOF and pulmonary hemorrhage and pneumocystis pneumonia (n=1) |

AECC, American-European Consensus Conference; ARDS, acute respiratory distress syndrome; ECMO, extra corporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; i.v. intravenous; MI, myocardial infarction; MOF, multiple organ failure; MV, mechanical ventilation; RCT, randomized controlled trial; SD, standard deviation

eTable 7. Reported cause of death in patients with COVID-ARDS (observational studies, n=6).

| Reported cause of death | | | | | | | | | | | | | | | | | |
|---|-------------------|-----------------|--------------------------|-------------------------|-------------------------------------|----------------------|-----------------------------------|---|--------------|--------------------|-----------|---------------------|-----------|-------------------|-------------------|---|--------------------------|
| Author(s); year; study period | Deaths / patients | Data collection | Pre-specified categories | MOF | Multiple organ dysfunction syndrome | Refractory hypoxemia | Irreversible respiratory failure* | Refractory respiratory failure and persistent | Septic shock | Pulmonary embolism | Acute MI | Acute heart failure | Stroke | Cardiogenic shock | Hemorrhagic shock | Do not resuscitate/end of life decision | Other [†] |
| Estenssoro et al, 2021 [‡] ; Argentina; Mar 2020– Oct 2020* | 1079 / 1909 | Prospective | ✓ | NC | 18% | 43% | NC | NC | 31% | <1% | 1% | 1% | 1% | NC | NC | 1% | 4% |
| Estenssoro et al, 2022 ; Argentina; Mar 2020– Oct 2020 | 894 / 1525 | Prospective | ✓ | NC | NC | 47% | NC | NC | NC | NC | NC | NC | NC | NC | NC | NC | NC |
| Maamar et al, 2023 ; France; Oct 2009– Dec 2022 | 37/ 244 | Prospective | ✓ | 23% [§] | NC | 50% | NC | NC | NC | NC | NC | NC | NC | NC | NC | 7% | 17% |

| Reported cause of death | | | | | | | | | | | | | | | | | |
|--|-------------------|-----------------|--------------------------|-----------|-------------------------------------|----------------------|-----------------------------------|---|--------------|--------------------|----------|---------------------|-----------|-------------------|-------------------|---|------------|
| Author(s); year; study period | Deaths / patients | Data collection | Pre-specified categories | MOF | Multiple organ dysfunction syndrome | Refractory hypoxemia | Irreversible respiratory failure* | Refractory respiratory failure and persistent † | Septic shock | Pulmonary embolism | Acute MI | Acute heart failure | Stroke | Cardiogenic shock | Hemorrhagic shock | Do not resuscitate/end of life decision | Other ‡ |
| Raasveld <i>et al</i>, 2022; International; Mar 2020–Dec 2020 | 67 / 193 | Retrospective | ✗ | NR | NR | NR | 88% | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Pestaña <i>et al</i>, 2022; Spain; Mar–Apr 2020 | 52/141 | Retrospective | ✓ | NC | NC | NC | NC | 65% | 33% | 14% | NC | NC | NC | NC | NC | NC | 20% |
| Daviet <i>et al</i>, 2021; France; Mar–Nov 2020 | 37/76 | Ambispective | ✗ | 8% | NR | NR | 16% | NR | 35% | NR | NR | NR | 5% | 3% | 32% | NR | NR |

Note: In Pestaña *et al*, some patients had a combination of at least two diagnoses as cause of death. *This study also reported on secondary and tertiary concomitant cause of death (the percentages shown in the table are for the primary cause of death). †Defined as PaO₂/FiO₂ <100. ‡Infection-related MOF. ‡10% mesenteric ischaemia, and 7% central nervous system disorder. ‡In Estenssoro *et al*, ‘other’ was not further specified. In Pestaña *et al*, ‘other’ referred to hemorrhage or neurological disorders. FiO₂, fraction of inspired oxygen; MI, myocardial infarction; MOF, multiple organ failure; NC, not considered (i.e. not a category in studies that had pre-specified categories); NR, not reported; PaO₂, partial pressure of oxygen