ORIGINAL ARTICLE

# Determinants of Quality of Life and Return to Work Following Acute Respiratory Distress Syndrome

## A Systematic Review

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## SUMMARY

Background: Acute respiratory distress syndrome (ARDS) in adults is a consequence of lung damage caused by either pulmonary or extrapulmonary disease. Survivors often suffer from an impaired health-related quality of life (HRQoL), mental and physical impairments, and persistent inability to work.

Methods: In this systematic review of the literature, we consider the determinants of HRQoL and return to work (RtW). 24 observational studies showing a statistical association between one or more determinants and HRQoL or RtW were included. Because of the heterogeneity of these studies, no statistical aggregation of the individual effect estimates was carried out; instead, the results are summarized descriptively.

Results: Psychopathological manifestations, in particular, are associated with impaired quality of life. In contrast, many care- and disease-related determinants had only small, non-significant effects on HRQoL and RtW. The one-second capacity was found in all studies to be positively associated with the HRQoL. ARDS induced by sepsis seems to be a risk factor for a lower HRQoL in comparison to ARDS of other causes. A synthesis of the evidence is impeded both by the high level of heterogeneity of studies and by the high risk of selection bias in all studies.

Conclusion: The identification of determinants of impaired quality of life after ARDS is essential for the assessment of clinically relevant interventions. In multiple studies, major significant effects were only observed when determinants the content of which was closely related to the scales of the HRQoL instruments were measured at the same time as the HRQoL.

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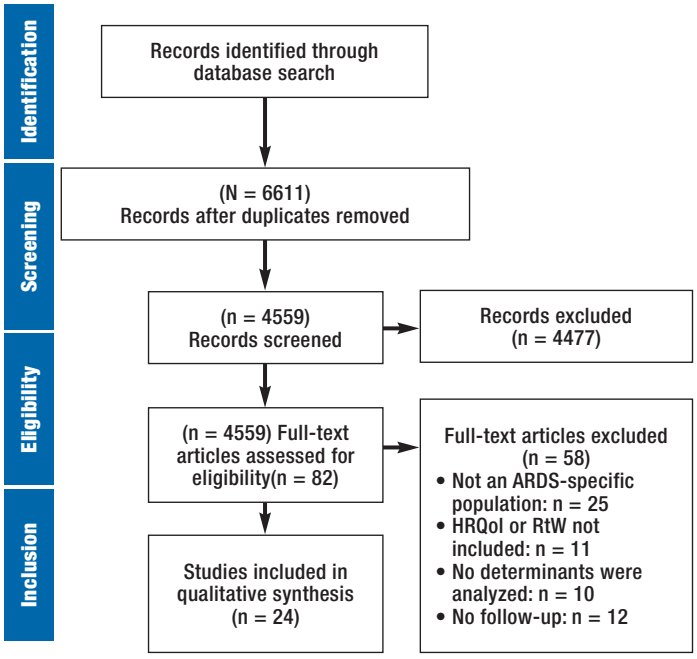
Acute respiratory distress syndrome (ARDS) in adults results in a life-threatening damage of the lung. The most important risk factor for ARDS is pneumonia, followed by sepsis and aspiration (1). The extent of injury and the resulting hypoxemia usually make mechanical ventilation necessary. The ARDS criteria established in 1994 by the American-European Consensus Conference (AECC) were long used as the standard for ARDS diagnosis (2). In 2011, the AECC criteria were revised by the Berlin Definition (3), which includes the criterion "acute onset" (<7 days) in addition to the presence of bilateral infiltrates that cannot be attributed exclusively to left-sided cardiac insufficiency. Classification of severity (mild, moderate, or severe) is based on the oxygenation index according to Horowitz.

With a prevalence of approximately 10% of all patients treated in an intensive care unit (ICU), and an in-hospital mortality of 35–46% (depending on severity), ARDS represents a major challenge for intensive medical care (1). An overall decrease in ARDS mortality could be achieved continuously until the 1990s (4). However, survivors of ARDS also suffer from persistent physical and psychological morbidity. For instance, the point prevalence of depressive symptoms (33%) or of generalized anxiety disorder (40%) is strongly increased in survivors two years after ARDS (5). An increased risk of post-traumatic stress disorder (PTSD) is present in 29% of ARDS patients (6). Further, a prospective cohort study showed that five years after the disease, the health-related quality of life (HRQoL) of survivors of ARDS was reduced by about one standard deviation as compared to a matched control population (7). Finally, a systematic review from 2006 (8) found that HRQoL of survivors of ARDS was significantly reduced in nearly all domain-specific pooled scores of the 36-item Short-Form Health Survey (SF-36) (9) as compared to population norms.

In addition to HRQoL, return to work (RtW) is an endpoint for survivors of ARDS, which is a good operationalization—indeed, better than clinical

FIGURE 1




**Flow diagram** of the study selection processes (according to the PRISMA Statement) ARDS, acute respiratory distress syndrome; HRQoL, health-related quality of life; RtW, return to work

parameters—for overcoming morbidity. In a German cohort of ARDS survivors, only 64% had returned to their previous work five years after ARDS (10).

Recognizing the factors associated with quality of life or RtW would help to identify risk groups and, notably, would serve as a starting point for intervention measures that could increase the success of treatment. Here, we provide, to our knowledge, the first systematic review of determinants of HRQoL and/or RtW in survivors of ARDS.

## Methods

### Protocol and registration

The presentation of this systematic review is based on the recommendations of the Preferred Reporting Items for Systematic Reviews (PRISMA) (e1). The protocol was registered in the International Prospective Register of Systematic Reviews PROSPERO (CRD42014014335) (e2).

### Inclusion criteria

To ensure the highest possible external validity of the results found in the studies, only observational studies were included. Interventional studies, which often have highly selected populations, were excluded.

The examined population had to consist of survivors of ARDS or acute lung injury (ALI) (as defined by Berlin or AECC; deviating diagnostic criteria were accepted if described).

Statistical associations between determinants, and HRQoL and/or RtW, in survivors of ARDS or ALI had to be reported.

### Information sources and searches

Searches of Cochrane Systematic Reviews, MEDLINE, PSYNDEX, PsycINFO, Embase, Science Citation Index Expanded, and Social Science Citation Index Expanded were conducted without date limitations, from the beginning of each database until 13 August 2014. A comprehensive, highly sensitive research strategy was developed by SB, FDS, and HK. The search strategy and documentation were based on latest recommendations (e3, e4).

### Study selection

For study selection, the authors formed working pairs, each of which consisted of a clinical practitioner (SB, KTH) and a psychologist (SuB, FDS). Each pair then made a pre-selection based on titles and abstracts in a first step. The original articles to be included were then selected in a second step based on the full text.

### Data collection

The following characteristics were extracted from the selected original articles by the first author (FDS):

- General information about the study (authors, year of publication, country, period of data collection, study design)
- Description of the sample/cohort (inclusion and exclusion criteria, with particular emphasis on the underlying diagnostic criteria of ARDS/ALI, sex, and age)
- Operationalization of the outcomes of HRQoL and RtW

Additionally, the effect sizes and significance of the investigated determinants were recorded whenever this had been documented or could be calculated from the indicated statistical values.

### Risk of bias of individual studies

Since this systematic review was meant to include the full range of observational study designs, no instrument was suitable for determining a risk of bias applicable to all types of studies. Thus, an instrument was developed by three authors (FDS, SuB, and CA), based on the Newcastle-Ottawa Scale, for cohort and case-control studies (e5) (*eBox*). Using this instrument, each study was evaluated independently by two persons with regard to risk of selection and information bias.

### Synthesis of results

Because of the heterogeneity of the studies (in study design, timing of measurements, determinants, and outcomes), the synthesis of results is a descriptive summary rather than a meta-analysis.

## Results

The electronic search revealed 4559 studies. After the screening process, 24 studies met the inclusion criteria

(*Figure 1*). The size of the investigated cohorts/samples ranged from N = 15 to N = 152. Cross-sectional study designs (19 studies) outweighed designs with prospective (13 studies) and retrospective (2 studies) data collection approaches. In the majority of studies, HRQoL / RtW and determinants were obtained both prospectively and cross-sectionally.

Studies with follow-ups varied both in number (from one to four) and timing of follow-ups (*Table, Figure 2*). Statistical associations between determinants and HRQoL were reported in 23 of the 24 studies. Determinants for RtW were analyzed in six studies. HRQoL was recorded via six generic and two disease-specific instruments (*Table*). The risk of information bias is low due to the use of validated measurement instruments in almost all studies. In contrast, all studies have an unclear or high risk of selection bias.

#### Determinants of HRQoL

Overviews of the determinants investigated are given in *eTables 1* and *2*. In the category of sociodemographic determinants, only age seems to be associated with a reduced quality of life after surviving ARDS (7, 11, 12). The physical health component summary score of SF-36, for which a higher value indicates a higher quality of life (13), showed a strong negative correlation with age (ρ [rho] = –0.52).

The highest number of determinants was found among the disease-related characteristics. Results of pulmonary function testing were especially frequently examined at the same time as HRQoL and RtW. Among the different spirometric values and across studies, the Forced Expiratory Volume in 1 second (FEV1) is significantly positively associated with HRQoL (ρ = 0.16 to ρ = 0.46) (14–16). However, a high forced vital capacity (FVC) shows no significant correlation with HRQoL or RtW (12, 14–17). The effect sizes for the various quality of life instruments and their different domains range between ρ = –0.004 and ρ = 0.58.

In three studies, various aspects of morbidity during ARDS (based on Acute Physiology and Chronic Health Evaluation II, APACHE II; Lung Injury Score, LIS; Charlson–Deyo comorbidity score; extent of extrapulmonary organ failure) were examined as predictors of later HRQoL (12, 18, 19). Only low scores in LIS proved to be a significant determinant for reduced HRQoL measured using a dimension of the Sickness Impact Profile (SIP) modified for lung function (12, 20). A few studies examined the etiology of ARDS in more depth (14, 18, 19, 21). In the SF-36 domains, sepsis-induced ARDS, as compared to trauma-induced ARDS, was associated with small to moderate negative effects in the SF-36 domains as compared to trauma-induced ARDS (21). Larger effect sizes (Cohen's *d* = 0.57–0.65) resulted when the St. George's Respiratory Questionnaire (SGRQ) was used to determine quality of life (21).

The duration of medical care as a care-related determinant was examined in more detail in seven studies (10, 13, 15, 19, 21–23). The total duration of treatment in both the ICU and the hospital (ρ = –0.34 to ρ = –0.45) (21, 22), as well as the duration of mechanical ventilation (ρ = –0.44 to ρ = 0.13) (10, 13, 15, 19, 21, 22) and extracorporeal membrane oxygenation (ECMO) (23), correlate negatively with some SF-36 domains. Of the supportive measures for ARDS treatment during the acute phase, ECMO was shown to have negative effects of up to medium strength (Cohen's *d* = 0.62) on the physical health component summary score of SF-36 (10, 24).

For the psychosocial determinants, the presence of depressive symptoms showed strong negative correlations, especially with the mental health component summary score of SF-36 (ρ = –0.64 to ρ = –0.94) (22, 25, 26). Symptoms of PTSD (6, 10, 27) and anxiety disorder (22, 28) also show strong negative associations with HRQoL. Likewise, cognitive deficits in the domains of memory, attention, and executive functions appear to be associated with the reduction of some domains of SF-36 and SIP (22, 29, 30). Finally, effect sizes of Cohen's *d* = 0.45 are observed for the physical role functioning of the SF-36 (22).

#### Determinants of return to work (RtW)

Of the care-related determinants, neither the duration of ICU treatment and total hospital stay (10) nor treatment with ECMO (10, 17, 24, 31) showed significant effects on RtW, although patients treated with ECMO have a twice-as-high chance of long-term incapacity for work as those not treated with ECMO (17). Survivors of ARDS with moderate to severe depressive symptoms have a 0.2-fold lower chance of return to work after two years (25). Aside from this, no significant effects were observed for disease-related (12) or sociodemographic (10) characteristics on RtW. For these variables, no effect sizes could be extracted from the original articles.

## Discussion

While previous review articles have compiled evidence for a decreased quality of life in survivors of ARDS (8, 32), the explicit aim of this review was to provide a summary of the research on the determinants of HRQoL and RtW in ARDS survivors. Importantly, being able to identify determinants provides the opportunity to intervene during the disease phase and to reduce the incidence of physical and psychological impairments.

Evidence taken from the studies analyzed here is limited, due to the strong heterogeneity of these studies and their often low methodological quality (because of selection bias and insufficient statistical analyses). Nonetheless, for generic quality of life instruments, larger effects only exist when there is a narrow contextual relation (and probably also a close temporal link) between the investigated determinant and the quality of life instrument. Thus, no study shows that the initial disease severity predicts later HRQoL. Similarly, there is a lack of significant correlations between HRQoL

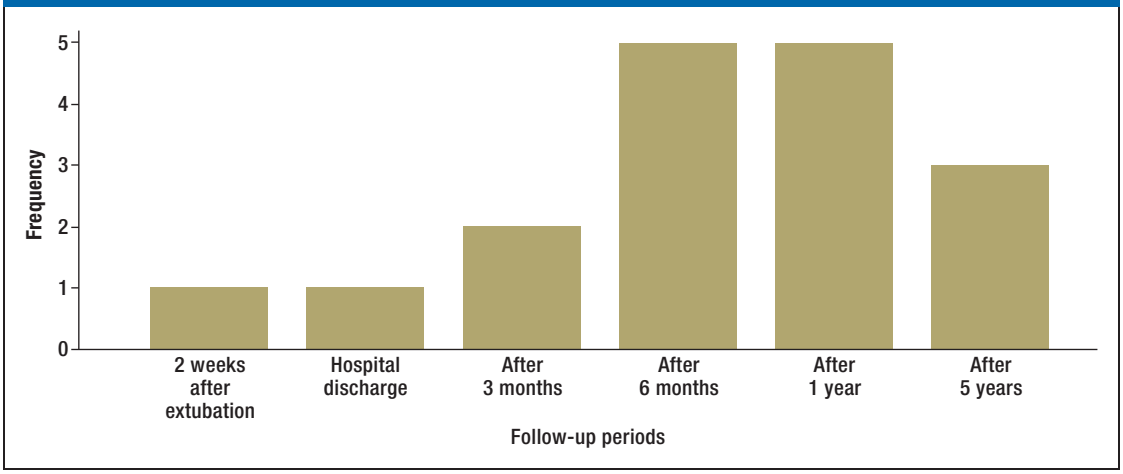
**TABLE**

Characteristics of the 24 studies included in the review

| First author (year) (ref.) | Type of data collection | Country/ region | ARDS criteria | HRQoL instrument | N (survivors) | Age |
|---|---|---|---|---|---|---|
| Adhikari et al. (2011) (26) | Cross-sectional | Canada | AECC | SF-36 | 48 | Md = 48<br>IQR = 39–61 |
| Adhikari et al. (2009) (25) | Cross-sectional | Canada | AECC | – | 71 | Md = 42<br>IQR = 35–56 |
| Angus et al. (2001) (18) | Prospective | USA | AECC | QWB | 104 | M = 44.7<br>SD = 15.0 |
| Briegel et al. (2013) (10) | Prospective/ cross-sectional | Germany | AECC | SF-36 | 125 | – |
| Hopkins et al. (2004) (22) | Prospective/ cross-sectional | USA | „ARDS survivors“ | SF-36 | 73 | M = 45.8<br>SD = 16.4 |
| Davidson et al. (1999) (21) | Prospective matched | USA | AECC | SF-36<br>SGRQ | 77 | Md = 40.6 |
| Deja et al. (2006) (6) | Cross-sectional | Germany | „Severe ARDS“ | SF-36 | 65 | M = 39<br>SD = 15 |
| Herridge et al. (2011) (7) | Prospective/ cross-sectional | Canada | AECC | SF-36 | 64 | Md = 44 |
| Kapfhammer et al. (2004) (27) | Cross-sectional | Germany | AECC | SF-36 | 46 | Md = 36.5 |
| Kim et al. (2004) (15) | Prospective/ cross-sectional | USA | AECC | CRQ, SQLI | 29 | – |
| Masclans et al. (2011) (14) | Prospective/ cross-sectional | Spain | AECC | NHP | 38 | Md = 50<br>IQR = 34–55 |
| Li et al. (2006) (16) | Cross-sectional | Hong Kong | AEEC<br>„ARDS caused by SARS“ | SF-36 | 36 | M = 42.0<br>SD = 12.1 |
| Linden et al. (2009) (11) | Cross-sectional | Sweden | „Severe ARDS and ECMO“ | SGRQ | 15 | M = 40 |
| Luyt et al. (2012) (24) | Prospective | France | „H1N1-associated ARDS“ | SF-36 | 37 | ECMO Md = 35.5<br>IQR = 30–39<br>no ECMO<br>Md = 42<br>IQR = 32.75–51.25 |
| McHugh et al. (1994) (12) | Prospective/ cross-sectional | USA | AECC | SIP | 37 | M = 41 |
| Mikkelsen et al. (2009) (30) | Cross-sectional | USA | ARDS as self-reported | SF-36, SIP | 79 | M = 43.3<br>SD = 12.7 |
| Rothenhausler et al. (2001) (29) | Cross-sectional | Germany | AECC | SF-36 | 46 | M = 41.5<br>SD = 14.7 |
| Schelling et al. (2000) (19) | Prospective/ cross-sectional | Germany | AECC | SF-36 | 50 | Md = 34.5 |
| Schelling et al. (1998) (17) | Prospective/ retrospective | Germany | AECC | SF-36 | 66 | Md = 36 |
| Schmidt et al. (2013) (23) | Prospective | France | ARDS and ECMO | SF-36, SGRQ | 67 | – |
| Stevenson et al. (2013) (28) | Cross-sectional | USA | AECC<br>ALI patients | EQ-5D, SF-36 | 152 | Md = 49<br>IQR = 40–57 |
| Stoll et al. (1998) (31) | Prospective matched | Germany | AECC | SF-36 | 28 | ECMO<br>Md = 34<br>no ECMO<br>Md = 38 |
| Weinert et al. (1997) (13) | Retrospective/ cross-sectional | USA | AECC<br>ALI patients | SF-36 | 24 | M = 40<br>SD = 12 |
| Wilcox et al. (2013) (40) | Cross-sectional | Canada | AECC | SF-36 | 24 | – |

AECC, American-European Consensus Conference; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CRQ, Chronic Respiratory Questionnaire; ECMO, extracorporeal membrane oxygenation; EQ-5D, EuroQol Five Dimensions Questionnaire; HRQoL, health-related quality of life; IQR, interquartile range; M, mean; Md, median; NHP, Nottingham Health Profile; QWB, quality of well-being; SARS, severe acute respiratory syndrome; SD, standard deviation; SF-36, 36-Item Short-Form Health Survey; SGRQ, St George's Respiratory Questionnaire; SIP, Sickness Impact Profile; SQLI, Spitzer's Quality of Life Index

**FIGURE 2**




**Distribution of the follow-up periods** in the studies with fixed survey time points (11 studies). If a study reported several follow-up periods, all were included in this Figure. Studies with varying follow-up periods across the participants (13 studies) were not considered.

and/or RtW, and care-related determinants, for almost every investigated supportive measure (including nitric oxide [NO] inhalation, corticosteroid delivery, and renal replacement therapy). The only exception is ECMO therapy, which shows a significant negative correlation with some SF-36 domains. The reason for this seemingly harmful effect of ECMO is most likely due to the lack of statistical adjustment for disease severity. In this context, it should be noted that the inclusion of confounding variables in statistical models, which is necessary for observational studies, was missing from almost all studies.

In contrast, significant associations with large effect sizes are reported for operationalizations of mental and physical morbidity, which are closely related to some scales of the HRQoL instruments and which were measured in a cross-sectional design together with the outcome. In particular, many studies report that physical morbidity, psychopathological symptomatology, or cognitive deficits after ICU treatment have adverse effects on HRQoL or RtW. For instance, strong correlations have been shown between the results of the 6-minute walk test or some spirometric values and the physical function domains of the SF-36. The same is true for the presence of a psychopathological symptomatology and the mental health component summary score of the SF-36.

In order to judge the importance of these results for survivors of ARDS, the high prevalence of persistent physical and psychological morbidity following an ICU stay must be considered additionally (33). In this context, the term 'post-intensive care syndrome' (PICS) has been coined to refer to new or worsening impairments that can be physical (pulmonary, neuromuscular, physical function), cognitive (executive functions, memory, attention, visuospatial processing), and mental (anxiety disorders, PTSD, and depression) (34). Therefore, there is a need for interventions that go beyond the established rehabilitation measures—with the aim of positively influencing HRQoL and RtW, both directly and indirectly.

ICU follow-up clinics represent a complex intervention, even though evidence is insufficient. These clinics are medical institutions specially designed for the diagnosis and management of common impairments following ICU treatment (35).

A further intervention that is currently being discussed in the literature is the use of ICU diaries, which has shown to be effective in reducing psychopathological symptoms in some studies (36, 37). ICU diaries are chronological, daily records of the patient's ICU stay. They are usually filled in by the nursing staff, but relatives and friends can also comment on their visits to the patient. These diaries aim to help the patient fill in memory gaps about the ICU treatment and thus come to terms with their experiences.

Finally, several randomized controlled trials (RCTs) have highlighted the positive effects of early mobilization of patients during ICU stay (38). However, these findings are limited by the fact that the strongest significant effects were reported only for short-term outcomes at the time of hospital discharge (e.g., 6-minute walk test [39]). To date, no significant effects have been shown for long-term outcomes at 12 months post-ICU discharge (38).

### Limitations

The studies examined here are highly heterogeneous due to their use of different tools—generic and disease-specific—for HRQoL assessment, the use of different measurement time points for the outcomes of interest, and the high level of variations in diagnostic criteria for acute lung failure. In addition, the high risk of a selection bias found in all studies leads to a loss of internal and external validity.

## Summary

Survival of acute lung failure is often associated with pronounced psychological and physical sequelea. Determinants of the development of such damage, which impairs the quality of life, have not yet been sufficiently investigated. Future research should focus on identifying predictors by using appropriate statistical analyses, which would enable risk groups to be identified and would allow targeted interventions to improve quality of life and facilitate RtW. Since the effects of the HRQoL measurement of determinants that are temporally distant are often small, sample size calculation should be based on a formula that takes into account relevant effect sizes.

The negative association between physical and psychological morbidity and HRQoL in survivors of ARDS shows that new effective interventions are needed to improve health after ICU treatment. Currently promising approaches include introducing mobilization during intensive care, keeping ICU diaries, and establishing ICU follow-up clinics.


### KEY MESSAGES

- Patients who survive ARDS often have a reduced health-related quality of life (HRQoL) and show more psychopathological symptoms (depression, post-traumatic stress disorder, anxiety disorders).
- Return to work (RtW) has been an endpoint in only a few studies.
- Significant associations with HRQoL were shown in various studies only for determinants that had a narrow content and temporal relation to the scales of the HRQoL instruments. This applies in particular to some values of the pulmonary function testing (spirometry) and to the presence of psychiatric symptoms.
- Future research should focus on methodologically adequate investigation of determinants that enable the identification of risk groups or concrete preventive measures in terms of intervention options during the acute treatment phase.


**Conflict of interest statement**

Prof. Bein is a member of the Medical Advisory Board of Novalung (XENIOS AG), Heilbronn, for which he received attendance and speaking fees.
The other authors declare that no conflict of interest exists.

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Supplementary material:
For eReferences please refer to:
www.aerzteblatt-international.de/ref0717

eBox, eTables:
www.aerzteblatt-international.de/17m103

## Erratum

The article entitled "Regional Differences in the Prevalence of Cardiovascular Disease—Results from the German Health Update (GEDA) from 2009–2012" by Dornquast et al in issue 42 of Deutsches Ärzteblatt (21 October 2016) contains two numerical errors. In the methods section, the authors reported the response rates of the included GEDA studies. The values of 23.9% and 34.5% for GEDA 2012 and 2009 are incorrect. The correct proportions are 22.1% (GEDA 2012) and 29.1% (GEDA 2009). ***MWR***

Supplementary material to:

# Determinants of Quality of Life and Return to Work Following Acute Respiratory Distress Syndrome

## A Systematic Review

by Frank Dodoo-Schittko, Susanne Brandstetter, Sebastian Blecha, Kathrin Thomann-Hackner, Magdalena Brandl, Helge Knüttel, Thomas Bein, and Christian Apfelbacher

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**eBOX**

## Instrument for assessing the risk of selection and information bias of the studies included in a systematic review

### Selection bias

Description of the study population:

Sufficient specifications about the inclusion and exclusion criteria. This includes:

1. Clear definition of acute respiratory distress syndrome (ARDS): Berlin Definition or American-European Consensus Conference (AECC) definition; alternatively, criteria used for progression, oxygenation, and imaging should be specified;
2. Further inclusion and exclusion criteria, or a statement that clarifies that no further inclusion/exclusion criteria were considered (for instance: "The study included all patients which fulfilled the diagnostic criteria for ARDS according to the Berlin definition.").

„Inclusion and/or exclusion criteria were used for patient recruitment" should be chosen only if the conditions in 1. and 2. were met.

Categories:

- Inclusion and/or exclusion criteria were used for patient recruitment
- No inclusion and/or exclusion criteria were used for patient recruitment
- Unclear

Sampling method

Did all patients in the population have the same chance of entering the cohort/sample, or were the examined clusters (e.g. ICUs) randomly selected and was there a complete enumeration ? These issues always refer to the (first) time of inclusion of patients, which can be the time of ICU admission for a prospective study, or the inclusion of survivors for a longitudinal study. For each case, it must be determined whether sampling was random at that time.

For example, if inclusion started at ARDS diagnosis, yet the statements are only given for follow-up of survivors from this sample at 6 months, the category „unclear" must be selected. The same applies to the absence of specifications about the total population for which the studied cohort/sample should be representative.

Categories:

- The entire cohort/sample was drawn randomly from the population of interest
- The entire cohort/sample was not drawn randomly from the population of interest
- Unclear

Loss to follow-up in the cohort

In the case of a longitudinal study with several (>2) follow-ups, assessment of adequacy should only consider and evaluate the last follow-up. Furthermore, deceased patients should not be considered lost to follow-up. Thus, the number of deaths must be deducted from the total loss to follow-up. If this number is not documented, the 80%–rule still applies.

Categories:

- No follow-up
- Complete follow-up (for all recorded people)
- Loss to follow-up unlikely to cause bias (follow-up rate ≥ 80%)
- Follow-up rate <80%
- No statements about loss to follow-up

### Information bias

Classification of exposure

Categories:

- Secure records (e.g. records related to medical treatment, imaging, laboratory findings). This includes psychiatric diagnoses, which are performed by a doctor
- Validated psychometric instruments: all instruments with satisfactory objectivity, reliability, and validity, or instruments which were satisfactorily evaluated on the basis of probabilistic test theory
- Structured interview: systematic interview (questions and their sequence are fixed, with a mostly closed response format)
- Written self-reports: any unsystematic written documentation

Classification of outcomes

Categories:

- Secure records (e.g. records related to medical treatment, imaging, laboratory findings). This includes psychiatric diagnoses performed by a doctor
- Validated psychometric instruments: all instruments with satisfactory objectivity, reliability, and validity, or instruments which were satisfactorily evaluated on the basis of probabilistic test theory
- Structured interview: systematic interview (questions and their sequence are fixed, with a mostly closed response format)
- Written self-reports: any unsystematic written documentation

**eTABLE 1**

Determinants of health-related quality of life (HRQoL) described in the literature. Studies marked with an * show a significant association of a determinant from the corresponding. Effect sizes are given when they were either reported or could be calculated from the reported data.

| Determinants of HRQoL | Study (Reference) | Effect size |
|---|---|---|
| Disease-related | | |
| General morbidity measures | | |
| APACHE II | Angus et al. (2001) (18)<br>Schelling et al. (2000) (19) | – |
| Charlson–Deyo Comorbidity Score | Angus et al. (2001) (18) | – |
| Karnofsky Performance Status Scale | Weinert et al. (1997) (13) | SF-36 PCS: ρ = -0.75<br>SF-36 MCS: ρ = -0.61 |
| | Angus et al. (2001)* (18) | QWB: ρ = -0.27 |
| 6-min walk test | Masclan et al. (2011) (14) | – |
| | Herridge et al. (2011)* (7) | – |
| | Li et al. (2006)* (16) | SF-36: ρ = 0.52 to ρ = 0.75 |
| ARDS etiology | Angus et al. (2001) (18) | – |
| | Kim et al. (2004) (15) | – |
| | Masclans et al. (2011) (14) | – |
| | Davidson et al. (1999)* (21) | SF-36: Cohen's d = 0.27 to d = 0.65<br>SGRQ: Cohen's *d* = 0.65<br>(patients with sepsis had worse mean scores in all domains of SF-36 and SGRQ) |
| | Schelling et al. (2000) (19) | – |
| Extent of lung damage | Wilcox et al. (2013) (40) | SF-36-PCS: ρ = -0.10<br>SF-36-MCS: ρ = -0.31 |
| | McHugh et al. (1994)* (12) | – |
| | Masclans et al. (2011) (14) | – |
| | Schelling et al. (2000)* (19) | – |
| Results of lung function testing | | – |
| Diffusion capacity for CO | Kim et al. (2004) (15) | SQLI: ρ = -0.02 |
| | McHugh et al. (1994) (12) | SIP: ρ = -0.44 to ρ = -0.46 |
| | Li et al. (2006)* (16) | SF-36: ρ = 0.18 to ρ = 0.53 |
| | Schelling et al. (2000) (19) | – |
| FEV1 (forced expiratory volume in 1 second) | Masclans et al. (2011)* (14) | NHP: ρ = -0.36 |
| | Kim et al. (2004) (15) | SQLI: ρ = 0.16 |
| | Li et al. (2006)* (16) | SF-36: ρ = 0.19 to ρ = 0.46 |
| FVC (forced vital capacity) | Masclans et al. (2011)* (14) | NHP: ρ = -0.36 |
| | Kim et al. (2004) (15) | SQLI: ρ = -0.004 |
| | McHugh et al. (1994) (12) | – |
| | Li et al. (2006)* (16) | SF-36: ρ = 0.32 to ρ = 0.59 |
| | Schelling et al. (2000) (19) | – |
| FEV1/FVC | Schelling et al. (2000) (19) | – |
| Total lung capacity (TLC) | Schelling et al. (2000) (19) | – |
| | Kim et al. (2004) (15) | SQLI: ρ = 0.08 |
| | Li et al. (2006)* (16) | SF-36 PF: ρ = 0.14 to ρ = 0.36 |
| Residual lung volume | Li et al. (2006) (16) | SF-36: ρ = -0.21 to ρ = 0.04 |
| CO transfer coefficient | Li et al. (2006) (16) | SF-36: ρ = -0.23 to ρ = 0.1 |

| Determinants of HRQoL | Study (Reference) | Effect size |
|---|---|---|
| Maximum oxygen uptake | Kim et al. (2004)* (15) | SQLI: ρ = 0.44 |
| Care-related | | |
| Duration of intubation/ventilation | Hopkins et al. (2004)* (22) | SF-36 PCS: ρ = –0.36<br>SF-36 MCS: ρ = –0.41 |
| | Schelling et al.(2000)* (19) | SF-36 PCS: ρ = –0.44<br>SF-36 MCS: ρ = 0.13 |
| | Davidson et al.(1999)* (21) | – |
| | Kim et al. (2004) (15) | SQLI: ρ = 0.01 |
| | Weinert et al. (1997) (13) | SF-36 PCS: ρ = –0.30<br>SF-36 MCS: ρ = –0.25 |
| Duration of hospitalization | Hopkins et al. (2004)* (22) | SF-36 PF: ρ = –0.35<br>SF-36 PRF: ρ = –0.45 |
| | Davidson et al. (1999)* (21) | SF-36 PF: Cohen's *d* = 0.71 |
| Duration of ICU treatment | Hopkins et al. (2004)* (22) | SF-36 PF: ρ = –0.34<br>SF-36 PRF: ρ = –0.43 |
| | Kim et al. (2004) (15) | SQLI: ρ = –0.03 |
| Duration of ECMO treatment | Schmidt et al. (2013)* (23) | – |
| ECMO | Briegel et al. (2013) (10) | – |
| | Stoll et al. (1998)* (31) | – |
| | Luyt et al. (2012) (24) | SF-36-PCS: Cohen's *d* = 0.25<br>SF-36-MCS: Cohen's *d* = 0.06<br>(both scores showed better means for patients treated with ECMO) |
| Prone positioning | Masclans et al. (2011) (14) | – |
| Nitric oxide (NO) inhalation | Masclans et al. (2011) (14) | – |
| Administration of steroids | Masclans et al. (2011) (14) | – |
| Use of renal replacement therapy | Masclans et al. (2011) (14) | – |
| Psychosocial | | |
| Depression | Adhikari et al. (2011)* (26) | SF-36 MCS: ρ = –0.68<br>SF-36 MH: ρ = –0.82<br>SF-36 EF: ρ = –0.64 |
| | Hopkins et al. (2004)* (22) | SF-36: ρ = –0.29 to ρ = –0.76 |
| | Weinert et al. (1997) (13) | SF-36 PCS: ρ = –0.17<br>SF-36 MCS: ρ = –0.94 |
| Post-traumatic stress disorder (PTSD) | Deja et al. (2006)* (6) | – |
| | Briegel et al. (2013)* (10) | SF-36 PCS: Cohen's *d* = 0.64<br>SF-36 MCS: Cohen's *d* = 0.76<br>(survivors with PTSD had worse mean scores) |
| | Kapfhammer et al. (2004)* (27) | – |
| | Schelling et al. (1998)* (17) | – |
| Anxiety disorder | Hopkins et al. (2004)* (22) | SF-36: ρ = –0.30 to –0.59 |
| | Stevenson et al. (2013)* (28) | SF-36 PCS: ρ = –0.18<br>SF-36 MCS: ρ = –0.73<br>EQ-5D VAS: ρ = –0.34 |
| Cognition | Rothenhausler et al. (2001)* (29) | – |
| | Mikkelsen et al. (2009)* (30) | – |

| Determinants of HRQoL | Study (Reference) | Effect size |
|---|---|---|
| | Hopkins et al. (2004)* (22) | SF-36: Cohen's $d < 0.01$ to $d = 0.45$ (survivors with cognitive deficits had worse mean scores in all SF-36 domains) |
| Sociodemographic | | |
| Age | Angus et al. (2001) (18) | – |
| | Weinert et al. (1997) (13) | SF-36 PCS: ρ = –0.52<br>SF-36 MCS: ρ = 0.07 |
| | Linden et al. (2009)* (11) | – |
| | Herridge et al. ( 2011)* (7) | – |
| | McHugh et al. (1994)* (12) | – |
| Sex | Angus et al. (2001) (18) | – |
| | McHugh et al. (1994) (12) | – |
| Other | | |
| Time elapsed since disease onset / follow-up period | Weinert et al. (1997) (13) | SF-36 PCS: ρ = 0.29<br>SF-36 MCS: ρ = 0.37 |
| | Briegel et al. (2013) (10) | SF-36: Cohen's $d = 0.04$ to $d = 0.38$ (with the exception of general health perceptions, all SF-36 domains showed better values for patients in the decade 1995–2005 as compared to the decade 1985–1994). |
| | Hopkins et al. (2004)* (22) | – |
| | Masclans et al. (2011) (14) | NHP: ρ = 0.68 |
| | Adhikiri et al. (2009) (25) | – |
| | Schmidt et al. (2013) (23) | – |

APACHE, Acute Physiology And Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; EF, emotional role functioning; EQ-5D VAS, EuroQol Five Dimensions Questionnaire visual analog scale; NHP, Nottingham Health Profile; MSC, mental health component summary score; MH, mental health; PF, physical functioning; PRF, physical role functioning; PSC, physical health component summary score; QWB, Quality of well-being; SF-36, 36-Item Short-Form Health Survey; SGRQ, St George's Respiratory Questionnaire; SIP, Sickness Impact Profile; SQLI, Spitzer's Quality of Life Index

**eTABLE 2**

Determinants of return to work (RtW) described in the literature. Studies marked with an * show a significant association between a determinant from the corresponding category with the respective outcome. Effect sizes are given when they were either reported or could be calculated from the reported data.

| Determinants of RtW | Study | Effect size |
|---|---|---|
| **Disease-related** | | |
| Extent of lung damage | McHugh et al. (1994) (12) | – |
| Results of lung function testing | | – |
| Diffusion capacity for CO | McHugh et al. (1994) (12) | – |
| FVC (forced vital capacity) | McHugh et al. (1994) (12) | – |
| **Care-related** | | |
| Duration of intubation/ventilation | Briegel et al. (2013) (10) | – |
| Duration of ICU treatment | Briegel et al. (2013) (10) | – |
| ECMO | Briegel et al. (2013) (10) | – |
| | Luyt et al. (2012) (24) | – |
| | Stoll et al. (1998) (31) | – |
| | Schelling et al. (1998) (17) | OR = 2.0<br>Long-term incapacity for work<br>Category: ECMO<br>Reference category: non-ECMO |
| **Psychosocial** | | |
| Depression | Adhikari et al. (2009)* (25) | OR = 0.20<br>Return to work<br>Category: moderate to severe depressive symptoms; reference category: minimal to mild depressive symptoms |
| **Sociodemographic** | | |
| Age | Briegel et al. (2013) (10) | – |
| | McHugh et al. (1994) (12) | – |
| Sex | Briegel et al. (2013) (10) | – |
| **Other** | | |
| Time between disease / follow-up period | Briegel et al. (2013) (10) | – |

ECMO, extracorporeal membrane oxygenation; OR, odds ratio