Original Article

Characteristics and provision of care of patients with the acute respiratory distress syndrome: descriptive findings from the DACAPO cohort baseline and comparison with international findings

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Background: Little is known about the characteristics and real world life circumstances of ARDS (acute respiratory distress syndrome) patient populations. This knowledge is essential for transferring evidence-based therapy into routine healthcare. The aim of this study was to report socio-demographic and clinical characteristics in an unselected population of ARDS patients and to compare these results to findings from other large ARDS cohorts.

Methods: A German based cross-sectional observational study was carried out. A total of 700 ARDS patients were recruited in 59 study sites between September 2014 and January 2016. Socio-demographic, disease and care related variables were recorded. Additionally, characteristics of other large ARDS cohorts identified by a systematic literature search were extracted into evidence tables.

Results: Median age of ARDS patients was 58 years, 69% were male. Sixty percent had no employment, predominantly due to retirement. Seventy-one percent lived with a partner. The main cause of ARDS was a pulmonary 'direct' origin (79%). The distribution of severity was as follows: mild (14%), moderate (48%), severe (38%). Overall ICU mortality was calculated to be 34%. The observed prevalence of critical events (hypoxemia, hypoglycemia, re-intubation) was 47%. Supportive measures during ICU-treatment were applied to 60% of the patients. Other ARDS cohorts revealed a high heterogeneity in reported concomitant diseases, but sepsis and pneumonia were most frequently reported. Mean age ranged from 54 to 71 years and most patients were male. Other socio-demographic factors have been almost neglected.

Conclusions: The proportion of patients suffering of mild ARDS was lower compared to the only study identified, which also applied the Berlin definition. The frequency of critical events during ICU treatment was high and the implementation of evidence-based therapy (prone positioning, neuro-muscular blockers) was limited. More evidence on socio-demographic characteristics and further studies applying the current diagnostic criteria are desirable.

Keywords: Acute respiratory distress syndrome (ARDS); intensive care units (ICUs); lung; rescue measures

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Introduction

The acute respiratory distress syndrome (ARDS) is a life-threatening condition characterized by either direct or indirect damage to the lung parenchyma causing critical hypoxemia and potentially hypercapnia and resulting in mechanical ventilation (1). In the year 2011 the Berlin-Definition revised and modified the American-European Consensus (AECC) diagnostic criteria of ARDS and acute lung injury (ALI) (2) that had been applied until that point. As a consequence the distinction between ARDS and ALI was removed and ARDS was classified in mild, moderate, and severe stages depending on the ratio of partial pressure arterial oxygen PaO_2 and fraction of inspired oxygen FiO_2 (PaO_2/FIO_2-ratio) (3). Even though a broad range of interventions to manage ARDS in intensive care was investigated and partly recommended in recent years, evidence that all these measures can substantially decrease mortality is still limited (4). Most of the evidence stems from high quality randomized controlled trials (RCTs) that include highly selected populations in strictly defined clinical settings. Data from such RCTs are urgently needed, but external validity is often limited. Therefore, transferring evidence from high quality RCTs into routine healthcare is problematic and effects found in RCTs will likely not be reproduced. Data collected in everyday life and/or everyday routine care are called *real world data (RWD)* (5) and are important to understand the complexities of ARDS outside the clinical trials setting. RWD obtained by observational study designs allow to investigate exposures, which are impossible to manipulate experimentally due to tight integration with the studied patients or ethical concerns. In this context some lifestyle risk factors such as cigarette smoke exposure or alcohol abuse (6), socio-demographic factors such as race and gender (7), and clinical comorbidity (8) have been investigated in rather small cohorts of ARDS patients. Larger cohorts allow to describe the clinical epidemiology of ARDS and to analyse associations between patient characteristics or care related factors and outcome measures. In this context, a closer look reveals a high degree of variability between different cohorts/samples. Some studies display major differences regarding to incidence and mortality (9). One reason for this variability might be that most European countries like the United Kingdom (10) or Germany (11) show considerable differences in the management of ARDS or other critical illnesses due the non-central clinical governance of health care provision.

Generally, there is a lack of descriptive socio-demographic and health care related data based on large and representative ARDS cohorts/samples. Therefore, we used data from the first 700 ARDS-patients enrolled in the DACAPO-Cohort [DACAPO: Surviving ARDS: The influence of quality of care and individual patient characteristics on health related quality of life and return to work in survivors of the ARDS] (12) for a descriptive analysis of socio-demographic and clinical characteristics as well as care-related factors of ARDS patients during intensive care unit (ICU) treatment. Our second aim was to compare the characteristics of the DACAPO cohort with findings of other large, multi-centric cohort studies.

Methods

Design and setting

Data were obtained from a large Germany-wide prospective cohort study [DACAPO study (12), ClinicalTrials.gov Identifier: NCT02637011]. Briefly, the DACAPO study investigates the influence of quality of care and individual patient characteristics on health-related quality of life (HRQoL) and return to work in survivors of ARDS. The data presented in this paper were collected once during

ICU treatment, the design of the study is thus cross-sectional. In order to represent the entire spectrum of intensive health care service, ICUs with different medical specialization were invited all over Germany to participate in the DACAPO-study. Finally, 59 ICUs of 415 German hospitals with at least one department for intensive care (13) contributed eligible patients to the DACAPO cohort.

Eligibility and identification of cases

Inclusion criteria for patient enrolment were the presence of an ARDS according to the Berlin definition (3) and being 18 years of age or older. No exclusion criteria were applied.

ARDS was diagnosed by the medical team of the respective study site. In order to minimize sources of selection and information bias the responsible physicians and study nurses of the participating ICUs underwent a training regarding to the diagnostic criteria of ARDS Berlin definition, the assessment and the documentation of the medical and socio-demographic characteristics of interest.

Because of the consecutive inclusion of the participating ICUs, the period of patient recruitment varied between the study sites. Overall, 700 patients were enrolled in 59 study sites from September 2014 to January 2016. Data of these first 700 patients of the DACAPO-cohort were analysed for the purpose of this study.

Measures and data collection

We present descriptive data on the following variables of interest:

(I) General characteristics of participating study sites (e.g., level of care, university hospital) and their recruitment activities are reported;

(II) Socio-demographic characteristics of patients include sex, age, educational and professional level, current employment and living situation. This information was provided by patients, patients' caregivers or legal guardians;

Clinical parameters comprise cause and severity of ARDS, diagnosis and therapeutic aim at admission as well as the presence of selected comorbidities. The Sequential Organ Failure Assessment score (SOFA) (14) and the Simplified Acute Physiology Score II (SAPS II) (15) were used to assess severity of illness at admission. Both scores were calculated according to the published algorithms (14,15). Additionally, the length of stay at ICU until death or discharge, the occurrence of critical events [hypoxemia (SpO_2 <85% for at least 5 min), hypoglycemia (defined as blood glucose measurement <70 mg/dL), accidental extubation, re-intubation] was assessed. In the clinical intensive care setting, an arterial SpO_2 <85%, corresponding to a PaO_2 ≤50 mmHg with a time span of a few minutes, is accepted as a valuable marker for hypoxemia (16,17). The advocated measures in these situations are the control of artificial airways and ventilator function/modes/settings, the suction of endotracheal secretions, the acute use of open lung approaches, and/or acute imaging diagnostics (Chest X-ray, ultrasound). In addition the use of supportive measures [tracheotomy, NO-inhalation, extracorporeal membrane oxygenation (ECMO), prone positioning, neuromuscular blockers] was recorded.

All clinical parameters were prospectively assessed and entered in electronic case report forms (eCRFs) by trained physicians or study personnel at individual study sites.

Statistics

Total scores were calculated only for patients without missing data on the item level. Descriptive statistics were calculated. Dichotomous or categorical parameters are presented in frequencies and percentages. Median (Md) and interquartile range (IQR) were calculated for continuous variables. All analyses were computed using IBM SPSS Statistics (version 21).

Systematic literature search

Additionally, we performed a systematic electronic search for observational studies of ARDS patients. We included only multi centre (more than one study site) studies with observational study design (cohort, case control, cross-sectional) and cohorts/samples larger than 200 patients in developed countries which were published from 01/01/2000 to 01/02/2016. To ensure high external validity of the reported findings, only cohorts/samples of ARDS patients without any exclusion criteria were selected. The retrieval of studies was performed in PubMed using the combined filter and Medical Subject Headings (MeSH) term: ((((“Respiratory Distress Syndrome, Adult”[MeSH Major Topic] AND (“2000/01/01”[PDAT] : “3000”[PDAT])) AND (“english”[Language] OR “german”[Language])) NOT animal[Filter]) AND “epidemiologic studies”[MeSH Terms]) NOT all child[Filter]. In a first step, the records were screened by two pairs of raters on the basis of title and abstract independently. Finally, the remaining records

Table 1 Characteristics of 59 participating ICUs

Characteristics	59 ICUs[a]
Center of the German ARDS Network, N (%)	38 (64.4)
ICU's of University hospitals, N (%)	30 (50.8)
Maximum level of care[b], N (%)	35 (59.3)
Duration of recruitment (weeks), Md [IQR]	55 [42–61]

[a], with at least one patient included in this paper; [b], maximum level of care refers to hospitals with highly differentiated medical-technical equipment. ICU, intensive care unit; ARDS, acute respiratory distress syndrome; Md, median; IQR, interquartile range.

were appraised in detail by reading the full-text paper. Discrepancies were discussed between raters until consensus was achieved. All relevant characteristics of ARDS patients and medical care reported in the papers were extracted into evidence tables.

Results

Findings in the DACAPO-cohort

Thirty-eight (64%) of the 59 participating ICUs were centres of the German ARDS Network (18) and 30 ICUs of university hospitals participated (*Table 1*). As intended by the strategy which was applied to select the participating study sites, these comprised ICUs with different specializations (e.g., surgery/operative, anesthesia, internal medicine) and of various sizes and were heterogeneous regarding level of care.

Socio-demographic characteristics are presented in *Table 2*. Two-thirds of the patients were male and median age was 58 (IQR =46.0–69.0) years. 16% of patients had a high schooling level qualifying for university entrance and 12% had no professional qualification. About a quarter of the sample (27%) were in full-time employment, the predominant reason for unemployment was retirement (71%). 61 % were married/in a civil partnership and 71% lived with a partner. Important medical characteristics at ICU admission are displayed in *Table 3*. SAPS-II- (Md =46; IQR =36.0–58.0) and SOFA-scores (Md =9; IQR =7.0–11.0) represent a certain cohort of critically ill patients. Especially cardiovascular and renal dysfunctions led to elevated SOFA item scores. The most frequent comorbidities included cancer and alcohol disorder. About one third (29%) of patients were obese (body mass index ≥30 kg/m^2).

The main cause of ARDS was of pulmonary 'direct' origin (79 %) (*Table 4*). The degree of severity of ARDS was unequally distributed in our sample, with nearly half of the cases classified as moderate, while 'mild' ARDS was only present in 14% of cases. At the time of diagnosis the median oxygenation level (PaO_2/FiO_2) was 101.5 (IQR =70.7–160.0). In one-third of patients (33%), ARDS had been diagnosed in referring hospital/ICU, before transfer to one of the participating ICUs. The percentage of 'severe' ARDS tended to be higher in the cohort of transferred patients (46% *vs.* 38% in the entire cohort). The leading diagnosis at ICU-admission was 'respiratory disease', while 'trauma' (8%), 'gastrointestinal/abdominal disease' (6%) or 'post-surgery' were rarely noted as main diagnoses. ICU mortality was 34%.

The occurrence of critical events and use of supportive measures are presented in *Table 5*. At least one critical event occurred in nearly half of the patients. Hypoxemic episodes were registered in 27% of patients, and 21% developed at least one hypoglycemic situation. A re-intubation was performed in 17%. The distribution of the use of supportive measures was as follows: less than half of ARDS patients received prone positioning (45%) and only a minority received neuromuscular blockers (11%). Overall, 425 out of 700 patients (61%) received at least one evidence-based rescue measure.

Findings in other large ARDS-cohorts

A total of 11 studies met the eligibility criteria applied to the studies found by the systematic literature search. Data extracted from these studies is shown in *Table S1*.

Not all cohorts/samples were independent. We identified an overlap of included patients in at least three studies (19-21).

A Taiwanese registry-based (National Health Insurance Research Database) study included more than 40,000 ARDS patients (22). Overall, the sample sizes of the studies detected by literature search ranged from 255 to 40,876. Three out of the 11 studies went beyond a national multi centre approach and included different international (23,24) or European (25) study sites.

Most of the large published cohorts/samples applied AECC diagnostic criteria. Only the most recent study (23) used the Berlin definition of ARDS.

Studies reported almost exclusively disease related factors. Socio-demographic and care related variables remained largely neglected. Exceptions were age (measures of central tendency ranged from 54 to 71 years) and sex (surplus of women in only one cohort). Mortality ranged

Table 2 Socio-demographic characteristics of 700 patients with ARDS

Socio-demographic characteristics	N	n (%) or Md (IQR)
Sex	700	
Female		215 (30.7)
Male		485 (69.3)
Age (years)	699	58.0 (46.0–69.0)
Educational level	682	
No school leaving certificate		13 (1.9)
Not yet a school leaving certificate		6 (0.9)
Schooling <10 years		
Secondary school leaving certificate		256 (37.5)
Schooling =10 years		
Intermediate school leaving certificate		202 (29.6)
Schooling >10 years		
University entrance level		106 (15.5)
Unknown		99 (14.5)
Professional level	681	
Still in professional training		12 (1.8)
No professional qualification		79 (11.6)
Professional qualification		425 (62.4)
University degree		57 (8.4)
Other degree		14 (2.1)
Unknown		94 (13.8)
Current employment	684	
Full-time employed		184 (26.9)
Part-time employed		24 (3.5)
Occasionally or unregularly employed		17 (2.5)
Unemployed		407 (59.5)
Unknown		52 (7.6)
Reason for unemployment	406	
Retired		290 (71.4)
Housewife/husband		27 (6.7)
Seeking for employment		34 (8.4)
None of them		51(12.6)
Unknown		4 (1.0)
Nationality	687	
German		641 (93.3)
Other		42 (6.1)
Unknown		4 (0.6)
Marital status	686	
Married/registered partnership		415 (60.5)
Not married		157 (22.9)
Widowed		44 (6.4)
Divorced/separation of registered partnership		50 (7.3)
Unknown		20 (2.9)
Living with a partner	687	
Yes		487 (70.9)
No		186 (27.1)
Unknown		14 (2.0)
Number of persons in the household	641	2.0 (2.0-3.0)
Residence	688	
With permanent residence		678 (98.5)
Homeless		6 (0.9)
Unknown		4 (0.6)
Health insurance	679	
Statutory		584 (86.0)
Private		63 (9.3)
Other[a]		15 (2.2)
Unknown		17 (2.5)

Data was provided by patients' caregivers/legal guardians. Numbers do not add up to N=700 due to missing values. [a], including non-German health insurances, other compensation, no health insurance. ARDS, acute respiratory distress syndrome; Md, median; IQR, interquartile range.

Table 3 General medical characteristics of 700 patients with ARDS

Medical characteristics	N	n (%) or Md (IQR)
SAPS-II[a] score	485	46.0 (36.0–58.0)
SOFA score[b]	390	9 [7–11]
Respiratory	659	3 [3–4]
Coagulation	675	0 (0–2)
Liver	655	0 (0–1)
Cardiovascular	647	3 [3–4]
Central nervous system	459	0 (0–0)
Renal	647	1 (0–2)
Oxygenation[b] PaO_2/FiO_2 ratio	657	101.5 (70.7–160.0)
Selected comorbidities[c] (multiple answers)	408	
Active cancer therapy		68 (16.7)
Malignancy with distant metastases		24 (5.9)
Hematological malignancy		29 (7.1)
Chronic heart failure (NYHA-IV)		15 (3.7)
AIDS		5 (1.2)
Cirrhosis of the liver		30 (7.3)
Physician diagnosed alcohol disorder		48 (11.8)
None of them		313 (76.7)
BMI	679	26.6 (24.2–31.0)
Obesity[d]	679	197 (29.0)

ARDS, acute respiratory distress syndrome; Md, median; IQR, interquartile range; SAPS-II score, Simplified Acute Physiology Score II; SOFA score, Sequential Organ Failure Assessment; BMI, body mass index; ECMO, extracorporeal membrane oxygenation; NYHA-IV, New York Heart Association stage IV; AIDS, acquired immune deficiency syndrome. [a], as assessed at admission at the ICU; [b], as assessed at time of the diagnosis of ARDS; [c], according to the SAPS-III score; [d], BMI ≥30 kg/m^2.

from 33% (26) to 60% (24). SAPS II, APACHE (Acute Physiology and Chronic Health Evaluation) II &III and SOFA were commonly used measures for general morbidity. There was also no clear approach in reporting additional diseases. Some of the studies reported comorbidity others are limited to causes or risk factors of ARDS. Regardless of operationalization, sepsis was the most frequently recorded disease, closely followed by pneumonia.

Discussion

We aimed at providing a comprehensive description of 700 ARDS patients from the DACAPO cohort baseline, in order to add to the body of RWD on ARDS. We found that seventy percent of ARDS patients were male and that median age was 58 years. The majority of patients lived in a 2-person-household with partnership. These socio-demographic data suggest that the sample is likely reflective of the general population of this age in Germany, except for sex distribution (13). The latter observation is completely in accordance to other cohorts of ARDS patients listed in *Table S1* and emphasizes the role of male sex as risk factor for heart and lung diseases in general and ARDS in particular. The finding of a high proportion of elderly patients is highly relevant, since old patients surviving a critical illness are at high risk for long-term physical and cognitive impairment (27) requiring prolonged care of the families and of the medical system (28). It must be determined in further health care studies, whether elderly patients receive adequate care after survival of ARDS.

Table 4 Characteristics relating to ARDS and its treatment of 700 patients with ARDS

Disease and treatment related characteristics	N	n (%) or Md (IQR)
Cause of ARDS	692	
Pulmonary		547 (79.0)
Extrapulmonary		127 (18.4)
Not specified		18 (2.6)
Severity of ARDS[a]	700	
Mild		99 (14.1)
Moderate		333 (47.6)
Severe		268 (38.3)
Transferred from other hospital to participating ICU	692	
No		461 (66.6)
Yes		231 (33.4)
Characteristics of transferred patients[b]	231	
Sex (female)		82 (35.5)
Age (years)		53.0 (42.0-63.0)
Severe ARDS		121 (45.8)
Therapeutic aim at admission	463	
Curative		447 (96.5)
Palliative and/or limitation of therapy		14 (3.0)
Unknown		2 (0.4)
Diagnosis at admission	613	
Respiratory disease		348 (56.8)
Sepsis/infection		72 (11.7)
Trauma		47 (7.7)
Gastrointestinal/abdominal disease		36 (5.9)
Post surgery		32 (5.2)
Neurological disease/neurosurgical intervention		27 (4.4)
Shock/reanimation		15 (2.4)
Cardiac disease		15 (2.4)
Kidney failure		3 (0.5)
Multiple organ failure		3 (0.5)
Metabolic/endocrinological disease		3 (0.5)
Intoxication		1 (0.2)
Other		11 (1.8)
Mortality	700	
Death during ICU		235 (33.6)
Discharged alive		465 (66.4)
Length of stay until death/discharge (days)	677	21 [13–34]

[a], according to the Berlin definition; [b], patients who have been transferred did not statistically significant differ from patients who had not been transferred regarding sex, age and severity of ARDS (χ^2-tests for sex and severity of ARDS; *t*-test for age). ICU, intensive care unit; ARDS, acute respiratory distress syndrome; Md, median; IQR, interquartile range.

Table 5 Occurrence of critical events and use of supportive measures in 700 patients with ARDS

Critical events and supportive measures	N	n (%)
Occurrence of critical events (multiple answers)		
Hypoxia[a]	670	180 (26.9)
Hypoglycaemia[b]	676	139 (20.6)
Unintended extubation	683	15 (2.2)
Re-intubation	682	115 (16.9)
Any of the above	684	320 (46.8)
Use of supportive measures (multiple answers)		
Tracheotomy	684	363 (53.1)
NO-inhalation	675	80 (11.9)
ECMO	691	216 (31.3)
Prone positioning	683	308 (45.1)
Neuro-muscular blockers	675	70 (10.4)
Prone positioning and/or neuro-muscular blockers and/or ecmo	692	425 (61.4)

ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation. [a], defined as a registration of SpO_2 <85% for at least 5 minutes; [b], defined as blood glucose measurement <70 mg/dL.

In terms of severity, moderate ARDS was most frequently recorded, while mild ARDS was only reported in 14% of the patients. This observation is in line with the generally low oxygenation levels (PaO_2/FiO_2) of the DACAPO cohort and in contrast to the only cohort composed of ARDS patients diagnosed on the basis of the Berlin definition criteria (23). In this study the proportion of patients with mild ARDS was more than twofold higher (30%). Potentially, during routine clinical care the mild form of ARDS is under-diagnosed and overlooked even in university hospitals and/or hospitals providing a maximum level of care which participated in our study. Taking a closer look at the recorded concomitant illnesses, especially cancer and respiratory diseases are frequent in our patient sample. Because of a highly heterogeneous selection of concomitant diseases reported in the literature, a direct comparison of these results with findings of the existing scientific reports is very difficult. Some studies report causes or risk factors of ARDS while others present comorbidities with varying pooling. An obvious difference between the present data and results of other studies lies in the lower prevalence of sepsis (12%). One possible explanation for this could be the explicit recording of one main diagnosis at admission to ICU in the DACAPO study, whereas other studies recorded multiple diseases. Overall, pulmonary/respiratory diseases including pneumonia seem to be one of the most important cause or risk factors of ARDS, both in the large cohorts described in the literature and in the DACAPO-cohort. In addition the present data highlight the high prevalence of malignant cancer (active cancer therapy, malignancy with metastases, hematological malignancy) in patient with ARDS. Only one of the selected studies did address such an important comorbidity (25). Since the diagnosis 'cancer' influences intensive care markedly (29) and has certain consequences on the long-term care of surviving ARDS-patients, the high number of cancer patients in the cohort by Vincent *et al.* (25) and in the present cohort has an impact for the health care system and should be re-evaluated in large cohorts.

The cause of ARDS was assessed as pulmonary or 'direct' in 79% of patients. Although criticized by some authors (30), the differential assessment of the pathogenesis of ARDS (direct versus indirect) seems to be confirmed by recent biological findings which underline separate injurious pathways of pulmonary and non-pulmonary lung damage (31).

The high proportion of patients in which critical events (hypoglycemia, re-intubation, accidental extubation) (47%) occurred is surprising, considering that most participating study centres were ICUs of university hospitals or of hospitals with a maximum level of care. We found no ARDS

specific data regarding the occurrence of critical events, but a prospective cohort study in an academic tertiary-care ICU revealed a proportion of patients with at least one critical adverse event of 19% (32). Furthermore the occurrence of such events was associated with longer duration of hospitalization. In a more recent study from the Mayo Clinic, USA, the effects of adverse events during ICU treatment were analyzed retrospectively in 828 acutely ill hospitalized patients with sepsis, shock, or pneumonia or undergoing high-risk surgery between 2001 and 2010 (32). All analyzed patients were at risk for or had developed ARDS. One adverse event increased the length of stay in the ICU by 2.4 (0.6–4.2) days. Beside the high proportion of patients with more severe ARDS, the latter finding could be an explanation for the extended length of ICU stay of the DACAPO-cohort (Md =21 days) compared to the cohort described by Bellani *et al.* (23) (Md =10 days). We conclude that the high occurrence of critical events in the management of ARDS patients is still a field in which patient safety initiatives, clinical care and medical education pathways need a better integration. Important elements for these initiatives include improving the reliability and standardization of processes of care, reducing unnecessary variation and complexity, and encouraging team working (33).

Finally, we recorded the use of evidence based supportive rescue measures in the treatment of ARDS-patients. Prone positioning and neuro-muscular blockers were only used in the minority of patients, although prone positioning is highly recommended in moderate-severe ARDS due to evidence from RCTs and meta analysis (34,35) . In addition a recent RCT demonstrated benefit of neuromuscular blockade in severe ARDS (36), but further studies are needed to investigate neuromuscular blockade as routine measure. ECMO was applied in 31% of patients, reflecting the increasing interest in and use of this technique in European countries. ECMO is recommended by a recent published consensus in critical hypoxemia despite optimized therapy (PaO_2/FIO_2 <70 for ≥3 hours) (37). In 2015 a survey was performed at German ARDS centres to determine the current treatment strategies in ARDS patients (11). It revealed that in accordance with our findings neuro-muscular blockers were periodically administered by 32%, and prone positioning was used by 60% of the centres. Thus, there is considerable scope for improving bedside implementation of evidence-based pathways in the management of ARDS in German ICUs.

The comparatively low mortality (34%) in our study is likely linked to the ARDS diagnosis criteria. While most studies applied the obsolete AECC criteria of ARDS which comprise only moderate and severe forms, the Berlin definition also includes mild ARDS. A comparison with the only cohort (23) that applied the Berlin definition criteria as we did reveals an almost perfect match of mortality rate. But inference has to be drawn considering the differences in the distributions of ARDS severity between these two cohorts.

Strengths of our study include the high number of enrolled ARDS patients without the application of any exclusion criteria form multiple sites all over Germany, the comprehensive assessment of socio-demographic and care-related data, the use of validated clinical severity scores, data collection by a standardized electronic data management system, and extensive quality assurance regarding missing and erroneous data. Our study also has some limitations: (I) we did not perform a registry-based study which is characterized by inclusion of all consecutively diagnosed ARDS cases. In Germany no institution or health-care regulation for an ARDS-registry exists, perhaps the present study might be a stimulation to found such a systematic registration; (II) there is a strong representation of hospitals belonging to the German ARDS network (specialized in the management of ARDS), potentially limiting external validity of our results; (III) generally, comparisons between data from older studies conducted in the 'pre-Berlin-definition-era' and data from our and other current studies using the Berlin-definition are problematic, since different diagnostic criteria are applied. Therefore, the investigated patient populations are not completely congruent and any conclusions must be drawn with caution.

Conclusions

Taking together, we conclude from our *real world* observational study that the characteristics of ARDS patients from the DACAPO cohort baseline are similar to other large ARDS-cohorts regarding age and sex distribution. The ICU-mortality is consistent with the mortality recorded by the only other study that applied the current Berlin definition of ARDS. Mild ARDS was underrepresented in our study, the reason being that it seems to be frequently overlooked in everyday routine care. Future studies should carefully consider this potential source of selection bias. Additionally the present study revealed a high occurrence of critical events during intensive care treatment. The implementation of evidence-based medicine (prone positioning and neuro-muscular blockers) seems to be still limited, pointing towards

opportunities for improving current care. The lack of other large observational studies investigating socio-demographic characteristics of ARDS patients beyond age and sex is striking. We call for more research efforts to go beyond the description of medical characteristics and additionally focus on socio-demographic characteristics and life circumstances as well as comorbidities of patients suffering from ARDS, applying the Berlin definition in the first place.

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Footnote

Conflicts of Interest: S Kluge is member of the advisory board

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Supplementary

Table S1 Characteristics of large (N>200) observational studies of ARDS patients and description of patients' medical and socio-demographic characteristics

Author	Study design and recruitment					Patients' medical characteristics				Patients' socio-demographic characteristics	
	Study design	Date, duration and country of recruitment	Number of study sites	Sample/cohort size	ARDS-criteria	Causes/risk factors/comorbidity	Severity of ARDS	Severity of illness: SAPS/Apache/LIS/SOFA	ICU-mortality	Age (years)	Gender (female)
Hughes *et al.* [2003] (38)	Prospective observational	05/1999–12/1999, Great Britain	26 ICUs	N=367	AECC	Sepsis (40.8%); respiratory infection (29.9%); acute pancreatitis (8.5%); multiple trauma (4.1%); pulmonary aspiration (4.4%); other (12.3%); pulmonary (47.4%); extrapulmonary (52.6%)	n/a	SAPS II: M=42.4 (95% CI =40.8–44.1); Apache II M=22.3 (95% CI =21.6–23.1)	53.1%	M=56.8 (95% CI =55.1–58.5)	n/a
Brunn-Buisson [2004] (39)	Prospective observational	02/1999–03/1999, 10 European countries	78 ICUs	N=463 (ALI and ARDS patients)	AECC	Respiratory failure (45.5%); cardiac failure (34.7%); liver failure (12.8%); renal failure (13.3%); hematological disease (8.4%); immunoincompetence (12.9)	ALI (13.4%); ARDS (64.4%)	SAPS II: Md =41 (IQR =31–51)	45.8%	M=54.7; SD =18.4	36.1%
Ferguson *et al.* [2005] (24)	Prospective observational	1998, international (20 countries)	361 ICUs	N=467	AECC	Barotrauma (6.4%); pneumonia (45.6%); sepsis (51.2%); shock (51.8%); hepatic failure (10.9%); renal failure (37.0%); coagulopathy (24.8%); respiratory acidosis (12.0%); metabolic acidosis (16.1%)	n/a	SAPS II: M=46.9, SD =16.5	60.2%	M=55.0, SD =17.2	36.6%
Rubenfeld *et al.* [2005] (40)	Prospective observational	04/1999–07/2000, USA	21 hospitals	ALI: N=1,113; (ARDS: N=828)	AECC	n/a	n/a	n/a	ALI: 38.5% (95% CI =34.9–42.2). ARDS: 41.1% (95% CI =36.7–45.4)	n/a	n/a
Vincent *et al.* [2010] (25)	Prospective observational	May 1 to May 15, 2002, Europe	198 ICUs	N=393 (ALI- and ARDS-patients)	AECC	Cancer (12.5%); hematologic cancer (5.3%); diabetes (5.3%); liver cirrhosis (3.1%); AIDS (1.5%)	ALI (15.0%); ARDS (85.0%)	Early onset of ALI/ARDS (N=254): SAPS II: Md =47 (IQR: 37–62). SOFA: Md =8 (IQR: 5–11). Late onset of ALI/ARDS (N=139): SAPS II: Md =40 (IQR: 31–53); LIS: M=2.9, SD =0.6; Apache II: M=21.6, SD =5.9; SOFA: Md =7 (IQR: 4–9).	38.9%	Early onset of ALI/ARDS (N=254): Md =62 (IQR: 46-73). Late onset of ALI/ARDS (n=139): MD =62 (IQR: 46-73)	28%
Li *et al.* [2011][$] (26)	Population-based, retrospective cohort study (trend analysis)	2001–2008, USA	2 hospitals	N=751	AECC	Charlson comorbidity index: Md =18–41	n/a	Apache III: Md =64–85	33–48%	Md =69–71	15–36%
Villar *et al.* [2011][#] (19)	Prospective observational	11/2008–10/2009, Spain	17 hospitals	N=255	AECC	Pneumonia (42.3%); sepsis (31.4%); trauma (9.4%); aspiration (8.2%); pancreatitis (4.7%); overdose/poisoning (1.6%); others (2.3%)	n/a		42.7%	Md =58 (IQR: 41–73)	41.3%
Villar *et al.* [2013][#](21)	Prospective cohort (two cohorts)	Derivation cohort: 05/2004–10/2005; validation cohort: September 2008–December 2009, Spain	Derivation cohort: 15 ICUs. Validation cohort: 17 hospitals	Derivation cohort: N=170. Validation cohort: N=282	AECC	Derivation cohort: pulmonary (54.7%); non-pulmonary (45.3%); sepsis (28.8%); bacterial pneumonia (27.0%); multiple trauma (17.6%); aspiration pneumonia (16.5%); others (10.0%). Validation cohort: pulmonary (50.7%); non-pulmonary (49.3%); sepsis (32.3%); bacterial pneumonia (33.7%); multiple trauma (11.7%); aspiration pneumonia (10.3%); others (12.0%);	n/a	Derivation cohort: APACHE II: M=20, SD =8; LIS: M=2.74, SD =0.72. Validation cohort: APACHE II: M=21, SD =6; LIS: M=2.86, SD =0.62	42%	Derivation cohort: M=54 (IQR: 35–66). Validation cohort: M=56 (IQR: 40–73)	n/a
Chen *et al.* [2015] (22)	Population-wide claims data analysis	1997–2011, Taiwan	n/a	N=40,876	ICD-9-CM codes 518.82, 518.5	Pneumonia (49.7%); sepsis (33.2%); trauma (29.9%); acute pancreatitis (1.9%)	n/a	n/a	(Hospital-mortality 57.8%)	M=66	32.1%
Villar *et al.* [2015][#](20)	Prospective observational	2004–2005 and 2008–2010, Spain	27 hospitals	N=478	AECC; additional PEEP ≥5	Pneumonia (26.8%); sepsis (30.1%); trauma (16.7%); aspiration pneumonia (12.5%); others (3.8%)	n/a	APACHE II: M=21, SD =7; LIS: M=2.9, SD =0.7	(Hospital mortality 42.2%)	Md =55 (IQR: 40–70)	n/a
Bellani *et al.* [2016] (23)	Prospective observational	Four weeks during winter 2014, worldwide	459 ICUs	N=3,022 (all ARDS patients); N=2,377 (ARDS patients, who received invasive ventilation and had ARDS on day 1 or 2 after onset of acute hypoxic respiratory failure)	Berlin-Definition	For the sample n=3,022: pneumonia (59.4%); extrapulmonary sepsis (16.0%); aspiration (14.2%); non-cardiogenic shock (7.5%); trauma (4.2%); blood transfusion (3.9%); pulmonary contusion (3.2%); inhalation (2.3%); drug overdose (1.9%); pulmonary vasculitis (1.4%); burn (0.3%); drowning (0.1%); other risk factor (2.7%); no risk factor (8.3%); COPD (21.7%); diabetes (21.7%); immunoincompetence (12.1%); chronic cardiac failure (10.4%); chronic renal failure (10.1%); active neoplasm (8.5%); hematological disease (4.7%)	For the sample (N=2,377): mild (30.0%), moderate (46.5%), severe (23.4%)	For the sample (N=2,377): SOFA: M=10.1 (95% CI =9.9–10.2)	For the sample N=3,022: 34.0%. For the sample N=2,377: 35.3%	For the sample (N=3,022): M=61.5 (95% CI =60.9–62.1). For the sample (N=2,377): Md =61 (IQR: 61–62)	28.0%

M, mean; SD, standard deviation; Md, median; IQR, interquartile range; 95% CI, 95% confidence interval; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment Score; APACHE, Acute Physiology and Chronic Health Evaluation Score; LIS, Lung Injury Score; n/a, not available. #, there is some overlap between the cohorts reported in Villar 2015, 2013, 2011; $, patient characteristics were reported stratified according to year of recruitment. Ranges of reported medians are given in this table.

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