Short-Term Survival of Acute Respiratory Distress Syndrome Patients at a Single Tertiary Referral Centre in Indonesia

Zulkifli Amin, Hasna Afifah, Chrispian O. Mamudi

Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Corresponding Author:
Zulkifli Amin, MD., PhD., FCCP, FINASIM. Division of Respirology and Critical Care Internal Medicine, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl Diponegoro No. 71, Jakarta 10430, Indonesia. email: zulkifliamin52@gmail.com.

ABSTRAK

Tujuan: *mengetahui kesintasan jangka pendek dalam 28 hari pada pasien acute respiratory distress syndrome (ARDS).* ***Metode:*** *studi retrospektif dilakukan di rumah sakit pusat rujukan tersier di Jakarta, Indonesia. Pada studi ini, digunakan data rekam medis yang diambil selama 10 bulan, yaitu Oktober 2015 hingga Agustus 2016. Keluaran primer studi ini adalah kesintasan jangka pendek selama 28 hari terhitung sejak pasien didiagnosis sebagai ARDS. Hasil yang didapatkan kemudian dianalisis menggunakan Kaplan-Meier dan analisis multivariat Cox regresi.* ***Hasil:*** *studi ini mendapatkan 101 pasien ARDS dalam periode 10 bulan. Kesintasan keseluruhan selama 28 hari adalah 47.5% dan nilai median adalah 10 hari (95% CI 2.47 – 17.52). Kesintasan pada pasien ARDS cenderung menurun signifikan pada minggu pertama setelah didiagnosis ARDS. Hal itu menunjukkan mortalitas tertinggi terjadi pada minggu pertama. Skor APACHE II >20 menunjukkan HR 2.45 (95% CI 1.40-4.28) dan derajat ARDS moderat-berat menunjukkan HR 2.27 (95% CI 1.25-4.12).* ***Kesimpulan:*** *kesintasan jangka pendek di negara berkembang seperti Indonesia masih rendah dan manajemen yang optimal pada awal dari minggu pertama pada pasien ARDS akan memperbaiki tingkat kesintasan.*

Kata kunci: *sindrom distres pernapasan akut, kesintasan, negara berkembang*

ABSTRACT

Aim: *to identify the 28-day short-term survival rate in patients with acute respiratory distress syndrome (ARDS).* ***Methods:*** *this is a retrospective cohort study conducted at a tertiary referral hospital in Jakarta, Indonesia. We conducted the study for 10 months and data was extracted from medical records between October 2015 and August 2016. The primary end point of the study was 28-day short-term survival rate using the initial date of ARDS diagnosis as the index time. Overall survival rate was analyzed using Kaplan-Meier test and multivariate Cox regression analysis.* ***Results:*** *there were 101 ARDS subjects during 10 months of study. The overall rate of 28-day survival was 47.5% and the median time of survival was 10 days (95% CI 2.47–17.52). The survival rate in ARDS patients was reduced significantly at the first week after the diagnosis of ARDS was made, which indicated that the highest mortality occured in the first week. Subjects with APACHE II score of >20 had a hazard ratio (HR) of 2.45 (95% CI 1.40-4.28) and those with moderate-severe of ARDS had HR of 2.27 (95% CI 1.25-4.12).* ***Conclusion:*** *the short-term survival rate of ARDS in developing countries including Indonesia is still low and early management with optimal treatment provided within the first week may improve the survival rate.*

Keywords: *ARDS, survival, developing countries.*

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is an intense inflammation of lung that may lead to life-threatening condition. Patients are usually treated with supportive ventilation.[1-3] ARDS has been well studied by many developed countries,[4-6] and mortality has been reduced to up to 30%. Nevertheless, the survival rate remains moderate to low in developing countries including Indonesia. It may be due to some major problems such as limited access to hospitals, lack of facilities and ARDS is under-diagnosed by most clinicians.

Early identification based on the knowledge of short-term survival rate of ARDS may help clinicans in acute care setting to predict earlier prognosis and provide help for appropriate and prompt treatment. Clinicians should be more aware about the best time to provide supportive care or perform careful observation for ARDS patients, particularly the underdiagnosed case. Our data is limited on this issue.[7] Therefore, the burden of ARDS remains underreported in Indonesia.

Moreover, most published studies in Asian developing countries still use the old criteria of AECC (American-European Consensus Conference) definition, which would now be obsolete. To our knowledge, our study is the first study using new criteria of Berlin definition in Indonesia. We hope that our study could be a trigger to improve the management of ARDS and may provide an insight about the burden of ARDS and consequently; therefore, any deterioration can be prevented earlier.

METHODS

Study Design and Population

A retrospective cohort study was conducted at Cipto Mangunkusumo General Hospital, a national referral hospital in Jakarta, Indonesia. We enrolled all adult patients aged 18 years and older who were admitted to the hospital with a diagnosis of ARDS as documented on their medical records. The study was conducted in 10 months, i.e. between October 2015 and August 2016.

Diagnosis of ARDS was defined using the criteria of Berlin definition. The definition of ARDS in Berlin criteria was characterized by the following key components: there was acute onset over 1 week or less following any identified clinical event; de novo respiratory symptoms or worsening of previous respiratory symptoms; bilateral opacities detected on chest X-ray or CT, which may not be fully explained by pleural effusions; respiratory failure, which must not be fully explained by cardiac failure or fluid overload. The ARDS was categorized as being mild (200 mmHg <PaO2/FiO2 ≤300 mmHg with PEEP ≥5 cmH2O), moderate (100 mmHg <PaO2/FiO2 ≤200 mmHg with PEEP ≥5 cmH2O), and severe (PaO2/FiO2 ≤100 mmHg with PEEP ≥5 cmH2O).[8]

Primary and Secondary Endpoints

The primary endpoint of our study was the 28-day short-term survival rate using the initial date of hospital admission as the index time. Secondary endpoint included factors (APACHE II score, severity) that might affect the survival. Those variables were classified as dichotomous variables. Our study has been approved by Ethic Committe of Faculty of Medicine University of Indonesia, registration number: 998/UN2.F1/ETIK/2015. Informed consent to the sujects was not requested since our study was observational and we followed the routine practice in our setting.

Sample Size

Short-term survival rate as the primary end point of our study was used to calculate sample size. We used the survival rate obtained from a previous large-scale study conducted by Bellani G, et al[6] as a baseline. The study included 50 countries over 5 continents and the 28-day survival rate showed by that study was 60.4%.[6] The confidence level was set at 95% and the precision of predicted survival rate was set at 15% in 28 days since there might be different survival rate between developed and developing countries. The minimum sample size, which should be obtained in our study was 91 patients. A 10% drop-out rate was anticipated; thus, a minimum sample size of 101 subjects was determined.

Statistical Analysis

We used SPSS 20.0 (Chicago, USA) to analyse the data. Dichotomous variables were presented as number or percentage. The overall survival was analyzed using Kaplan Meier test and the date of first hospital admission day was determined as the index date. We presented the result of overall survival rate in percentage, the median time of survival in days and the specific time when most patients had faster deterioration. We also performed mulivariate Cox regression analysis to examine survival time with variables included in the model and the results were reported with their corresponding hazard ratio and 95% CI. We considered p-value of less than 0.05 as significantly different.

RESULTS

There were 101 subjects participated in our study. Important clinical characteristics related to ARDS were shown **Table 1**. Mean age was 52.7±17.2 years. Out of 101 subjects, 45 (45.5%) subjects aged less than 60 years and 55 (54.4%) subjects aged over 60 years. There was a slight male dominance. Approximately 83% patients had ARDS risk factors such as extrapulmonary sepsis and pneumonia. As many as 63.4% patients had APACHE II score of less than 20 and the rest had score of more than 20.

Survival Rate

The overall 28-day survival was 47.5% and median time of survival was 10 days (95% CI 2.47–17.52). The survival rate was more likely to have a significant drop in the first week compared to the following weeks. Almost 50% patients died in the first week. It indicated that the highest mortality in ARDS patients occured in the first week.

The survival of ARDS patient with mild, moderate, and severe grade were 63.6%, 38.9%, and 28.6%, respectively. The median of survival time for mild, moderate and severe were 21, 5, and 3 days.

Table 1. Main characteristics of patients with ARDS

Parameters	n (%)	Survivors, n (%)	Non-survivors, n (%)
Age			
- ≥60 years old	55 (54.4)	25 (45.4)	30 (55.6)
- <60 years old	46 (45.6)	23 (50)	23 (50)
Gender			
- Male	48 (47.5)	26 (54.2)	22 (45.8)
- Female	53 (52.5)	22 (41.5)	31 (58.5)
APACHE II			
- <20	66 (65.3)	37 (56.1)	29 (43.9)
- >20	35 (34.7)	11 (31.4)	24 (68.6)
Severity			
- Mild	44 (43.5)	28 (63.6)	16 (36.4)
- Moderate	36 (35.7)	14 (38.9)	22 (61.1)
- Severe	21 (20.8)	6 (28.6)	15 (71.4)
Gas exchange, first day of ARDS			
- PaO_2/FiO_2 ratio [(median min-max)], mmHg		221 (41-612)	142 (53-624)
- $PaCO_2$ [(median min-max)], mmHg		31.4 (17.3-77.10)	32.6 (1-73)
- pH [(median min-max)]		7.43 (7.14-7.61)	7.43(7.03-7.61)

Table 2. Cox regression analysis of ARDS patients

Variables	Hazard ratio	95% CI	p-value
APACHE II	2.45	1.40-4.28	.002
Severity	2.27	1.25-4.12	.007
mild vs moderate-severe			

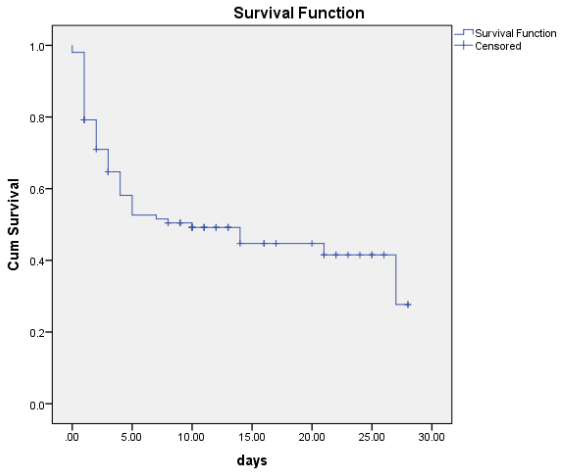

Figure 1. The overall 28-day survival rate since the first diagnosis of ARDS.

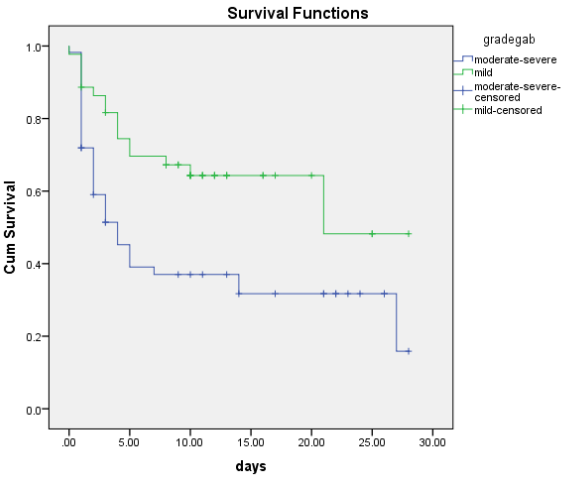

Figure 2. Kaplan-Meier survival analysis of 28-day survival rate according to severity of ARDS. The survival was lower for those with moderate-severe ARDS compared to those with mild ARDS (p = 0.004, log-rank test).

DISCUSSION

The survival rate of ARDS patients remains low and varies widely. Most studies have reported that the mortality rate ranges from 30 to 60%.[9,24] The overall survival of ARDS patients in the lung-protective ventilation era has shown an increasing trend.

A recent large-scale study conducted by Bellani et al,[6] which was performed in 50 countries across 5 continents, showed that the survival rate has reached 60.4% (95% CI 58,7-62,2). Mansur A et al[10] showed that the 28-day survival rate among ARDS caucasian patients is over 65%; furthermore, the survival rate in mild-moderate grade patients is even higher, which is more than 85%.

However, there are limited studies conducted in Asia on survival of ARDS, especially in developing countries. A previous small-sized study conducted in a single tertiary care center in Pakistan showed that the 28-day of survival rate is 44%.[11] A large retrospective study in Taiwan between 1997 and 2011 showed that the overall in-hospital mortality rate was 57.8% and the rate was decreased from 59.7% to 47.5% in 2011 (p<0.001).[12] In our study, the survival rate is similar to most studies conducted in Asia, especially in lower-middle-income countries. (**Table 3**)

Compared to the mortality rate of ARDS patients in a high- or upper-middle-income countries such Singapore, China and Japan, the mortality rate is higher in the lower-middle income countries.[13] A study conducted by Lew T et al in Singapore showed that mortality at 28 days for their entire cohort was 10.1% and for ICU death, the rate was 37%. A Japanese study by Endo S et al showed that the 30-day mortality rate of acute lung injury (ALI) and ARDS were 21.6% and 20.5%, respectively.[14] Moreover, the hospital mortality rate in Iceland decreased by 1% per year, i.e. from 50% in 1988-1992 to 33% in 2006-2010.[15] ARDS mortality rate is still high in many developing countries where the facilities for intensive care and assisted ventilation are not widely available. There is a need to provide intensive care that is accessible and affordable to patients.

A study conducted in Singapore by Lew et al[13] also showed that the in-hospital mortality rate is the lowest (33.5%) in young patients (age 18-29 years) and the highest (68.2%) in the elderly patients (>80 years, p<0.001). Patients who died during hospitalization are older and

Table 3. Comparison the mortality/survival rate of ARDS from various studies among developing countries in Asia

Studies	Countries	Mortality/survival rate	Criteria
Hartini, et al[7]	Indonesia	Study in a tertiary care hospital, the overall mortality rate of mechanically ventilated patients was 65.7%.	AECC
Sharif N, et al[11]	Pakistan	Study in a single tertiary care center, the 28-day survival rate was 44%.	AECC
George T, et al[16]	India	Study in a rural-urban hospital, the overall mortality rate was 36.6%. Patients were dominated with younger age and tropical infection.	AECC
Varghese GM, et al[22]	India	Study in a university teaching hospital, the overall mortality rate of ARDS patients with scrub typhus was 67.9%	Not mentioned
Bhadade RR, et al[23]	India	Study in a tertiary care hospital, the overall mortality was 57%. Patients were dominated with younger age and tropical infection.	AECC
Singh G, et al[24]	India	Study in a tertiary care hospital, the overall mortality in those with ARDS admitted to surgical intensive care unit was 41.8%.	AECC

predominantly male. Moreover, there is a lower mortality rate of ARDS patients at younger age (36%) as shown by a study conducted in India.[16] In our study, almost 50% of our patients are <60 years old and the mortality rate is similar between young and elderly patients. Some studies have shown that the age distribution of ARDS patients are variable. A small sample study in a rural area of India shows that the mortality among ARDS patients are 36.4% and it is possibly due to different baseline characteristics compared to other studies as the study included younger age of subjects and tropical disease.[16] However, several Asian studies have demonstrated that most subjects are at younger age and elderly age is usually associated with the increased risk of death.[11,12,14,16,17]

As we have known, the mortality rate in patients with ARDS is similar for both genders, either male or female, and many studies have reported various results.[12,18,19] Further investigations should be conducted by assesing the sex hormone level or sex-specific gene polymorphism in Asian races related to ARDS risk.

Mortality rate is found to be higher with greater ARDS severity.[6,10] The Berlin definition has a better classification to predict mortality compared to the old definition of AECC. Major studies including our findings have been consistent with the Berlin classification. Moreover, lower APACHE II scores and higher baseline ratio of PaO_2 to fraction of inspired oxygen are associated with earlier recovery.[11,13,15,16] Our findings are also consistent with the results of previous studies. APACHE II score still can serve as the 'gold standar' to predict the deterioration in ARDS. However, many parameters should be included in the score and applying the score every 24-48 hours is not practical to many settings in the middle-income countries. A new score with fewer parameters, but having similar capacity as APACHE II score is urgently needed, especially in our country.

Many studies have also shown that the highest mortality among ARDS patients is found within the first week after the diagnosis of ARDS is made.[10,16,20] However, a study conducted in Singapore reveals that the highest mortality among SARS-associated ARDS patients is found after the patients spending 7 days in ICU due to late complications.[11]

Different etiologies of ARDS may affect the survival rate found in those studies. Classifying the etiologies would be useful to provide information whether a certain etiology can contribute to a higher risk of ARDS deterioration. Some measures may prevent the development of ARDS including prompt resuscitation within 6 hours, early administration of effective antimicrobials and appropriate control of source of infection.[21]

Optimal management and careful observation in ARDS patients within the first week of their hospitalization would prevent further deterioration and ultimately, it can decrease the

mortality rate and complications. A previous study conducted by Sharif N et al showed that high APACHE II score, sepsis, multiorgan failure, refractory shock, and refractory hypoxemia are the leading causes of death in ARDS patients.[11] Results of our study are consistent with their findings regarding the fact that the APACHE II score did affect the mortality rate and in our study, our subjects were also predominated by sepsis and pneumonia.

We admit that there are some limitations of our study since it was a retrospective design with a single center setting.

Nevertheless, our focus is on the overall survival rate among ARDS patients found in our setting and our study is the first study reporting the actual condition in Indonesia. Further studies are required and preferably to be performed in multicenter settings with a higher power of study. Classifying ARDS based on the specific etiology and conducting a large-scale epidemiological study may be beneficial to raise the awareness of this devastating clinical syndrome in developing world.

CONCLUSION

Our study demonstrates that the short-term survival rate of ARDS is 47.5%. There is equal distribution of age, gender and sepsis among survivors and non survivors. High APACHE II score and severe grade are associated with high mortality. Earlier optimal management provided in the first week may increase the survival rate of ARDS patiens.

The overall survival rate of ARDS patients in the era of lung-protective ventilation has been improved over time either in high- or low-middle income countries. However, lower survival rate is found in lower-middle income countries. It may be related to disparity in facilities and resource, which causes the identification of ARDS cases and management of ARDS treatment to less optimal than high-income countries since in those countries, ARDS guideline have been routinely applied.

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