ORIGINAL ARTICLE

Severe acute respiratory distress syndrome induced by influenza compared with other viral infections and effects of intravenous immunoglobulin infusion therapy in Vietnamese children

Shoji Kawachi[1,2,3], Thuy Thi Bich Phung[4], Liem Thanh Nguyen[4], Hiroyuki Nunoi[5], and Kazuo Suzuki[1,6]

[1]Department of Immunology, National Institute of Infectious Diseases, Tokyo, Japan
[2]Department of Anesthesiology and Intensive Care, National Center for Global Health and Medicine, Tokyo, Japan
[3]Department of Anesthesiology and Intensive Care, Tomakomai City Hospital, Hokkaido, Japan
[4]National Hospital of Pediatrics, Hanoi, Vietnam
[5]Division of Pediatrics, Department of Reproductive and Developmental Medicine, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan
[6]Asia International Institute of Infectious Diseases Control, and Graduate School of Medicine, Teikyo University, Tokyo, Japan

Correspondence:
Shoji Kawachi, M.D., Ph.D.
Vice President,
Tomakomai City Hospital, Hokkaido, Japan
1-5-20 Shimizu-cho, Tomakomai, Hokkaido 053-8567, Japan
TEL: +81-144-33-3131, FAX: +81-144-34-7511
E-mail: skawachi@niid.go.jp

Received June 1, 2016; **Revised** June 24, 2016;
Accepted June 27, 2016

Abstract

Acute respiratory distress syndrome (ARDS) associated with A(H5N1) avian influenza virus infection develops severe ARDS, and also other types of influenza among children. It is an urgent mission to elucidate the mechanism of influenza-associated ARDS and to develop a therapeutic strategy. For this purpose, we have been co-operating the prospective study for severe ARDS with National Hospital of Pediatrics–Hanoi (NHP-Hanoi) from October 2007. During 2007/10 to 2013/03, 102 patients were diagnosed as severe ARDS matched in the criteria of prospective study. Among them, influenza viruses were detected from tracheal lavage fluid and/or nasopharyngeal aspirate (NPA/TLF) samples with PCR in 8 cases; A(H5N1), A(H1N1)pdm09, A(H3N2). These 8 cases and 9 cases of severe ARDS with A(H5N1) infection before 2007/10 were considered as influenza group together. During 2007/10 to 2013/03, other viruses were detected in 22 severe ARDS cases (not-influenza group): CMV, HRV, ADV, RSV and Measles. When the clinical data were analyzed in 17 influenza group and 22 not-influenza group respectively, significant differences were observed in pH and $PaCO_2$ in arterial blood gas analysis (ABGA) and also AST/ALT values, white blood cells and platelets counts in the serum. Survival probability analysis showed the significant differences between the groups (p=0.0023 by log-lank test, p=0.0013 by Wilcoxon test) resulting longer survival days in not-influenza group. In addition, intravenous immunoglobulin infusion (IVIG) treatment showed difference in survival profile of patients especially in influenza-associated ARDS, suggesting that the IVIG therapy may be effective against severe ARDS with pneumonia. Our results will provide the crucial clinical information.

Keywords: acute respiratory distress syndrome (ARDS); children; Influenza viral infection; IVIG therapy; survival probability

Abbreviations used

ADV: adenovirus, ARDS: acute respiratory distress syndrome, AST: aspartate amino transferase, ALT: alanine transaminase, CMV: cytomegalovirus, CRP: C-reactive protein, HRV: human rhinovirus, IVIG: intravenous immunoglobulin infusion, LDH: lactate dehydrogenase, MOH: ministry of health, PICU: pediatric intensive care unit, PLT: platelet, PT: prothrombin time, RBC: red blood cell, RSV: respiratory syncytial virus, TLF/NPA: tracheal lavage fluid and/or nasopharyngeal aspirate samples, WBC: white blood cell

Introduction

The pediatric acute respiratory distress syndrome (ARDS) remains one of the most important severe diseases in pediatric intensive care, which still has high mortality rate in nowadays. ARDS is a prime example of a disease that affects both children and adults, although ARDS occurs with less frequency in children than in adults[1)] and the risk factors and pathophysiology of ARDS are similar in both adults and children[2)]. The most common trigger of ARDS is infectious disease, most commonly in the lower respiratory tract, that is pneumonia[3,4)]. However, the severity of ARDS is sometimes different according to the kinds of infections. Avian influenza A(H5N1) viral pneumonia is one of the typical infectious diseases which induces severe ARDS with low survivability[5)]. The primary influenza viral pneumonia, which occurs in avian A(H5N1) influenza, often leads the patients to severe ARDS. On the other hands, the main complication of seasonal influenza virus infection is upper airway infection, which sometimes occurs together with, or is followed by, bacterial pneumonia and ARDS. In Vietnam, there might be some ARDS trigger of viral infections, which rarely exist in the other area, such as avian influenza

A(H5N1) pneumonia. Thus the surveillance prospective and retrospective study has been planed and held with pediatric intensive care unit (PICU) in National Hospital of Pediatrics, Hanoi (NHP-Hanoi, Vietnam).

We here showed the difference of the mortality between severe ARDS induced by influenza and other viral infection, and the efficacy of high dose γ globulin infusion (IVIG) treatment for the severe ARDS as anti-inflammatory therapy.

Materials and Methods

Data source and study design

Prospective study: After permission of Ethical Committee in NHP-Hanoi (ref. no. NHP-RICH-07-001, 2007/9/30) and MOH-Vietnam (Ministry of Health, Vietnam), the study had started in pediatric intensive care unit (PICU) of NHP-Hanoi from 1st October 2007 until the end of March 2013. Written informed consent was obtained from the parents of each patient, according to the study protocol. The entry criteria of the patients in the prospective study are as follows; 1. The patients who admitted the PICU-NHP with ARDS under intra-pulmonary reason (pneumonia), and needed mechanical ventilation. 2. The patients aged over one month. 3. The P/F ratio (PaO_2/FIO_2 ratio) ≤ 100 mmHg in arterial blood gas analysis during the stay in the PICU. ARDS was diagnosed according to American European Consensus Conference (AECC) criteria (1994). The AECC ALI and ARDS criteria are used most commonly to diagnose ALI and ARDS in adults and children, utilizing four clinical parameters: a) acute onset; b) severe arterial hypoxemia resistant to oxygen therapy alone (PaO_2/FIO_2 ratio ≤200 mmHg (≤26.6 kPa) for ARDS and PaO_2/FIO_2 ratio ≤300 mmHg (≤40 kPa) for ALI); c) diffuse pulmonary inflammation (bilateral infiltrates on chest radiograph); and d) no evidence of left atrial hypertension[6]. Because our study had been conducted since 2007 and the study protocol had made in 2006, we do not use the Berlin Definition as ARDS definition in our study[7]. However, we use 'severe ARDS' as 'ARDS with P/F ratio under 100 (the Berlin Definition)' in this manuscript. Serum, and TLF/NPA samples were collected on admission to PICU-NHP from each patient. Arterial blood gas analysis, cell blood counts and several kinds of chemical serum parameters were examined on admission of PICU. All patients were tracheal intubated and mechanical respiratory support was performed basically with the National Institutes of Health ARDS Clinical Trials Network (ARDS Net) ventilator management protocol for adults (http://www.ardsnet.org/) as a PaO_2 target of 55 to 80 mmHg (7.3 to 10.7 kPa) (SpO_2 target 88%-95%) according to the AECC strategy (1998)[8].

This study was designed as observational study (not interventional study), thus treatments for the patents were decided as same as possible among the patients with Vietnam side clinicians. Therefore, primary endpoint of the study was the time of discharge from PICU in alive without artificial respiratory support or in dead. We followed all patients up to the Hospital discharge, and confirmed that all survived patients had discharged from hospital healthy without respiratory failure.

Retrospective study for avian A (H5N1) influenza: Before 2007, we have ten avian A(H5N1) influenza cases in NHP-Hanoi, which we reported before (*J Infect Dis* 2009)[5]. We had been able to collect the same data and samples (TLF/NPA) of the prospective study of those ten cases and confirmed nine cases among ten matched in the criteria of above prospective study as severe ARDS. Thus we had 9 cases of avian influenza A(H5N1) infection induced severe ARDS.

Viral genome detection

Influenza type A and B were detected by rapid influenza detection Kit (Mizuho Medie, Tokyo, Japan) from TLF/NPA samples of each patient. Then influenza viral genomes of the type A including A(H5N1), A(H1N1)pdm09, A(H3N2) and type B were examined by RT-PCR method with viral detection primers in each patients. Additionally, in case that a clinician decided to detect other viral genomes, it was able to examine following viral genomes by PCR or RT-PCR method with viral detection primers; HRV, ADV, RSV, Measles, and CMV. All examinations above had been performed by NHP biological laboratory.

Treatment design

In this study, the antibiotics were used for bacterial infection according to the sensitivity analysis after the pathogen of pneumonia was decided by PCR. When CMV, or influenza viral genome was identified, gancicrovir, or ocertamivir was administrated, respectively. The prophylactic use of antibiotics was also performed according to the standard formula.

The AECC-1998 and the ARDS Network study had not recommended the steroid administration for ARDS/ALI patients both in the acute phase nor the chronic phase of ARDS in adults[9,10]. Also World Health Organization (WHO) treatment strategy in the Avian Influenza A(H5N1)infection[11] had neither recommended steroid use. Based on these recommendations, steroid was not selected in this study. Instead, a intravenous immunoglobulin therapy for sever ARDS, two grams/kg IVIG therapy against the ARDS was performed. The following infusion protocol of immunoglobulin is employed as 1 gram/kg/day for 1 hour in two days, one or two days after admission to PICU-NHP. Because ethically randomized control study is difficult, this study was planned as observational study. Thus the IVIG therapy in this study was planned to do for all patients within criteria. Finally the patient's parents had decided either perform the IVIG therapy or not, mainly according to their financial support, not depends on the clinician's decision.

Statistics

Statistical methods

Fisher's exact test was employed for bivariate analysis of categorical data. The nonparametric Mann-Whitney test was used for two-group comparisons of continuous data. Survival curves and rates were calculated by the Kaplan-Meier method. The log rank (Mantel-Cox) test was used for the comparison of two survival curves. All statistical analyses were done with SPSS software (version 14.0).

Role of the funding source

S.K. reviewed the clinical data, which were provided by L.T.N., director of NHP, who had full access to the data, in an anonymous format suitable for the purposes of the study. T.T.B.P., L.T.N., K.S., H.N., and S.K. made the final decision for this publication.

Results

One hundred-two of 106 patients enrolled in the prospective study were diagnosed as severe ARDS matched in the criteria and 4 cases were dropped out from the study because the P/F ratio of these 4 cases did not become ≤ 100 during the stay in PICU-NHP. And 9 cases were enrolled from retrospective study, as mentioned before. The mortality rate of 102 severe ARDS cases (P/F ≤ 100) at PICU of NHP-Hanoi is 47%.

Viral genome detection

In 30 patients among 102 cases in the prospective study, the following viruses were detected from TLF/NPA samples; 8 cases were Influenza viruses: avian influenza A(H5N1) [3 cases], A(H1N1)pdm09 [4 cases], A(H3N2) [1 case] and 22 cases were other viruses: CMV [5 cases], HRV [12 cases], ADV [6 cases], RSV [4 cases], and Measles [1 case]. In some patients double or triple kinds of viral genomes were detected, among them Rhinovirus was most frequently existed. Thus totally 17 cases were enrolled as Influenza-ARDS group (I-group) and 22 cases as not Influenza-ARDS (NI-group) group.

Patient's background and laboratorial examinations

In the patients' background data, differences were observed in gender, age and body weight between I-group and NI-group (I-group: M:F=12:5, age 5.80 ± 3.71 years, weight 16.38 ± 7.41 kg; NI-group: M:F=4:18, age 1.30 ± 3.00 years, weight 4.51 ± 2.03 kg) (table 1). In the Respiratory parameters, significant differences were observed in pH and $PaCO_2$ values of arterial blood gas analysis (ABGA) between the groups. Also blood examination test showed significantly higher AST/ALT values in the serum, and lower white blood cells and platelets counts in the I-group (table 2).

Comparison between I- and NI-group

Survival probability analysis showed the significant differences between the groups (p=0.0023 by log-lank test, p=0.0013 by Wilcoxon test) (figure 1) resulting longer survival days in NI-group (I-group: 13, NI-group: 31 days). Test of equality of survival distributions (Kaplan-Meier method) for the different levels of cause category showed significant difference between groups; Log-lank test: Peto-Peto p = 0.0005, Cochran-Mantel-Haenszel p = 0.0001; Wilcoxon test: Gehan-Breslow p = 0.0003, Peto-Prentice p = 0.0003. Mortality rate was also much higher in I-group than NI-group (I-group: 88%, NI-group 64%).

IVIG therapy in Influenza group

IVIG therapy was performed in 4 patients among 17 patients in I-group, and rest of 13 cases immunoglobulin were not administered during the stay in PICU-NHP with patient's parental decision. No differences were observed in gender, age or body weight between IVIG therapy and no IVIG groups (IVIG (+): M:F=3:1, age 5.35 ± 3.70 years, weight 15.88 ± 7.53 kg; IVIG (−): M:F=9:4, age 5.35 ± 3.70 years, weight 18.00 ± 7.83 kg). Respiratory parameters and blood examination showed also no differences between groups. Significant difference was observed only in survival probability between groups with

Table 1. Difference in background data between I-group and NI-group

	I-group n=17		NI-group n=22		P value
	M or + or D	F or - or A	M or + or D	F or - or A	
Gender	12	5	4	18	0.0012
Age (year)	5.80±3.71		0.39±0.49		0
Weight (kg)	16.38±7.41		4.51±2.30		0
P/F ≤ 100 on admission	13	4	19	3	0.4247
Prognosis	15 (88%)	2	14 (64%)	8	0.0811
MODS	8	9	14	8	0.3005
BT onset	38.85±0.77		37.28±0.86		0
Days onset	12.71±5.29		26.00±12.48		0.0006

Table 2. Difference in arterial gas analysis and blood examination data between I-group and NI-group

	I-group n=17	NI-group n=22	P value
pH	7.43±0.11	7.29±0.10	0.0004
PaO_2	61.96±49.39	52.12±16.35	0.8762
$PaCO_2$	34.87±12.94	58.02±17.03	0.0001
FiO_2	0.86±0.25	0.89±0.21	0.9853
P/F	96.45±137.36	64.58±32.36	0.9543
P/F lowest	39.18±18.80	44.27±21.89	0.5515
AST	1943.75±3510.36	188.24±248.58	0.0015
ALT	741.29±1406.39	139.84±400.27	0.0174
LDH	1615.09±854.76	1170.92±1003.37	0.1427
WBC	4526±3746	14575±7382	0
RBC	3730±1103	3822±1018	0.5946
PLT	141.69±61.30	350.05±109.23	0
CRP	6.39±10.26	4.13±6.52	0.4992
PT	76.50±33.81	79.54±21.78	0.8262

Kaplan-Meier method (Log-lank test: Peto-Peto p=0.0360, Cochran-Mantel-Haenszel p=0.0104; Wilcoxon test: Gehan-Breslow p=0.0409, Peto-Prentice p=0.0467) between IVIG (+) and IVIG (-) groups (figure 2) resulting in the longer survival time (days) (IVIG (+): 20.5 vs. IVIG (-): 11.0 days).

Discussion

In our study, totally 102 cases were diagnosed as severe ARDS matched in the criteria and 9 cases were enrolled from retrospective study, as mentioned before[5]. In 30 patients among 102 cases in the prospective study, 8 cases were influenza viruses and 22 cases were other viruses. We analyzed totally 39 cases of viral infection related severe ARDS cases. Among them, 17 cases were enrolled as Influenza-ARDS group (I-group) and 22 cases as not Influenza-ARDS (NI-group) group. The survival probability analysis showed more than twice longer survival days in NI-group, which indicated that influenza virus infection might be one of the factors of severity in pediatric ARDS (Figure 1).

In the patients' background data, differences were observed in gender, age and body weight between I-group and NI-group. The A/H5N1 cases that induced severe ARDS in NHP-Hanoi were elder compared to the other severe ARDS patients[5]. This might be the reason that both age and weight were higher in I-group. Blood examination test showed significantly higher AST/ALT values in the serum, and lower white blood cells and platelets counts in I-group (table 2). These results also reflect the influence of the number of A/H5N1 cases in I-group, because the elevation of serum aminotransferases, leukopenia and thrombocytopenia are relatively common features in H5N1 patients[5,12].

In the Respiratory parameters, $PaCO_2$ values of arterial blood gas analysis (ABGA) was higher in NI-group on admission, consequently pH values showed acidosis in NI-group. The lower $PaCO_2$ values indicated that the ventilation capacity was higher in I-group than in NI-group, however oxygenation capacity failed similarly in both groups (PaO_2 had no significant difference). This fact might come from the differences of mechanism developing ARDS. In influenza induced ARDS, it is pointed out that the influenza viruses infected into epithelial cells and destroy the alveolar directly[13]. Because the diffusion capacity of carbon dioxide through the alveolar epithelium is twenty times higher than that of oxygenation capacity[14], once alveolar membrane destroyed by influenza viral infection to alveolar epithelial cells, oxygenation failure occurs first then carbon dioxide retention gradually develops depend on the areas of destroyed alveolar membrane. Thus influenza induced ARDS patients might be less severe in respiratory parameters on PICU admission, then respiratory failure rapidly progressed to die. Survival probability analysis showed the significant differences between the groups (p=0.0023 by log-lank test, p=0.0013 by Wilcoxon test) (figure 1) resulting longer survival days in not-influenza group (I-group: 13, NI-group: 31 days).

Among viral infected pneumonia, influenza virus might be more severe pathogen for ARDS (Table 1). Severity of the Avian influenza A(H5N1) was discussed as followings; 1) NS1 gene of H5N1 influenza virus is suspected to play an important role on the severity of the diseases[15]. The RNA binding domain of influenza A virus NS1 protein affects secretion of tumor necrosis factor α, interleukin-6, and interferon in primary murine tracheal epithelial cells[16]. 2) NS1 and H_2O_2-MPO stimulate chemokine production associated with inflammatory responses. In NS1-transfected cells concentrations of IL-8 and MCP-1 increased associated with MPO concentration[17].

In Vietnam, several viral infections occurred severe ARDS and the mortality rate of ARDS associated with viral infection was high. The mortality rate of 102 cases of severe ARDS cases in this study was 47%, however in the viruses detected cases (I- plus NI -group) it significantly increased to 70%. To our knowledge, the mortality rate by age has not been discussed precisely for pediatric patients with ARDS. The mortality rate among pediatric patients of acute lung injury with a P/F ratio below 100 was reported to be ~35%[18]. The mortality rate of virus not detected cases of NHP-Hanoi in this study is 36.7%, which showed that PICU of NHP-Hanoi made appropriate therapy against the severe ARDS. In the avian influenza A(H5N1) infected pediatric ARDS cases, high mortality rate and the difference of survival curve between not-H5N1 cases has been reported previously[5]. In adults, several studies suggested that the viral infection in patients with pneumonia were frequently requiring ICU admission and might cause severe forms of pneumonia[19,20]. From the Berlin definition, which is the latest definition and statistical study in ARDS, the mortality rate of mild, moderate and severe ARDS are significantly different as 27, 32 and 45%[7]. The definition of severe ARDS is P/F ratio ≤ 100, that is very similar to our study criteria. Thus the overall mortality of 47% in this study thought to be appropriate, although the Berlin definition is not for pediatric patients. And the mortality rate of 70% in viral infected ARDS cases in our study is obviously too high compared to severe ARDS in the Berlin Definition.

The treatment protocol against the inflammation of the lung was controversial. One study for the ARDS with sepsis showed the effectiveness for low-dose methylprednisolone (MP) infusion[21], the available evidence does not support the use of MP in treating early or late ALI/ARDS[8]. The AECC-1998 and the ARDS Network study and the WHO treatment strategy had not recommended the steroid administration for ARDS/ALI patients[9,10] and also in the Avian Influenza A(H5N1) infection[11], respectively. Thus we decided not to use steroid infusion for the patients in this study, instead to choose the administration of immunoglobulin. In our study, significant differences was observed in survival probability between IVIG (+) and IVIG (–) groups (figure 2) resulting in the longer survival time (days) (IVIG (+): 20.5 vs. IVIG (–): 11.0 days). Although our study was not randomized control study of IVIG therapy, still the biases of clinicians were minimum. Our result showed a possibility that the IVIG therapy will be effective against severe ARDS with pneumonia.

Concerning about intravenous immunoglobulin therapy, the 2g/kg IVIG therapy has been established to be a standard anti-inflammatory therapy against the Kawasaki disease[22]. And this IVIG therapy might be one of the strongest therapies against inflammatory diseases and reduces vascular oxidative stress in patients with Kawasaki disease[22]. Thus theoretically, the IVIG therapy could be effective to the severe ARDS.

The limitation of this study is that this study is not etiological study. We had done PCR study of TLF/NPA samples in every

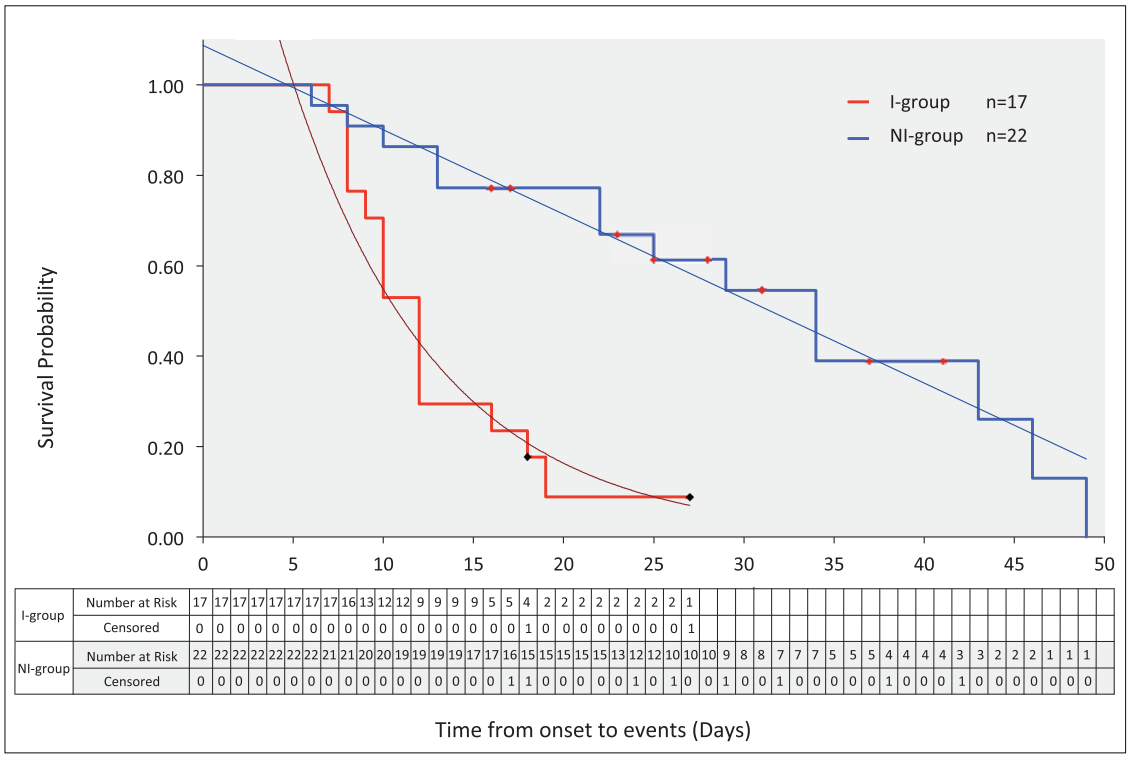

Figure 1. Survival probability curve-of patients infected with influenza virus and non-influenza virus.
Survival time (days) of each group; I-group: n=17/13.00 days, NI-group: n=22/31.143 days. Survival profile was performed with Kaplan-Meier method.

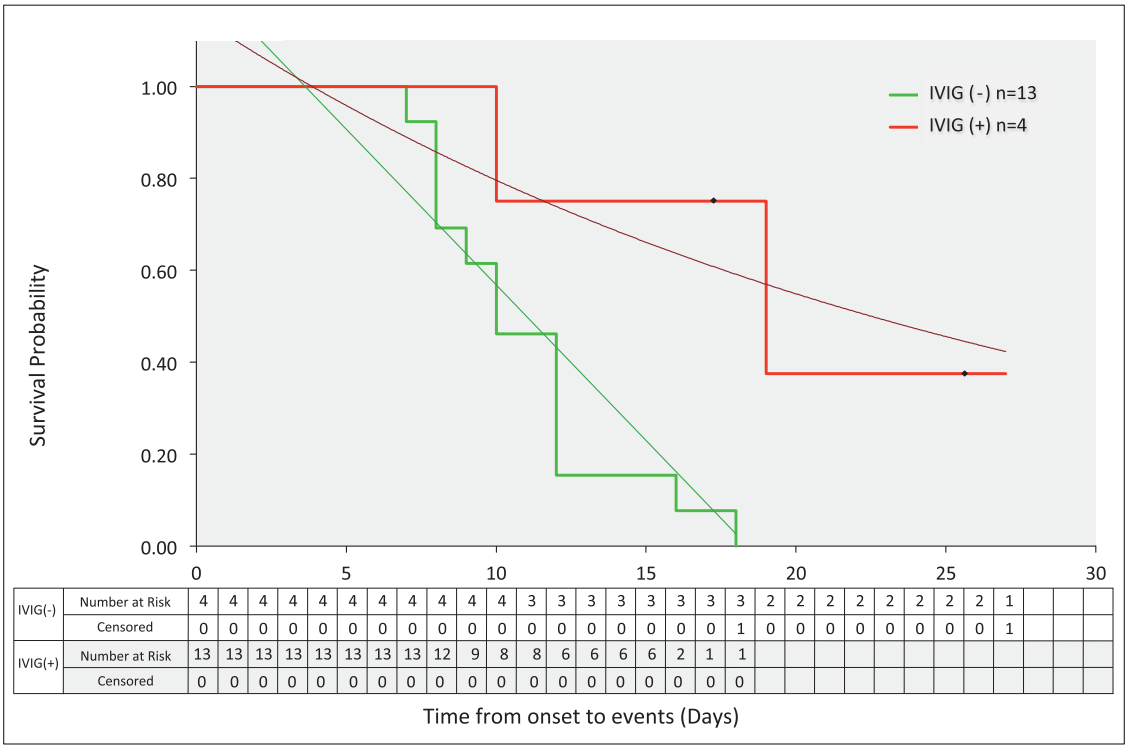

Figure 2. Survival probability curve of patients treatment with IVIG or without IVIG.
Survival time of each group; IVIG(+), n=4, 20.5 days, IVIG(-), n=13 11.0 days.

samples on A(H5N1) influenza virus, but other viral genomes were checked only clinician's decision, thus there might be a possibility that more patients would have the viral infection.

In Vietnam, several viral infections occurred severe ARDS and the mortality rate of ARDS associated with viral infection was very high. Among them in the influenza-associated ARDS, mortality rate was much higher than the others (Influenza: 88%, not Influenza 64%). These results reinforce the importance of further research on the etiology of viral infection induced severe ARDS, especially H5N1 influenza. Our study will pro-

vide the crucial clinical information for development of the strategies of future therapeutic options. There might be a possibility that the IVIG therapy will be effective against sever ARDS with pneumonia.

Acknowledgement

This study was supported by the Health and Labour Sciences Research Grants on Emerging and Re-emerging Infectious Diseases (H22 Shinko-Ippan-014) from the Ministry of Health, Labour and Welfare, Japan.

Disclosure

The authors have no financial conflict of interest.

References

1) Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, Stern EJ, Hudson LD. Incidence and outcomes of acute lung injury. N Engl J Med 2005; 353: 1685-1693.
2) Timmons OD, Havens PL, Fackler JC. Predicting death in pediatric patients with acute respiratory failure. Chest 1995; 108: 789-797.
3) Dahlem P, van Aalderen WM, Bos AP. Pediatric acute lung injury. Paediatr Respir Rev 2007; 8: 348-362.
4) Randolph AG. Management of acute lung injury and acute respiratory distress syndrome in children. Crit Care Med 2009; 37: 2448-2454.
5) Kawachi S, Luong ST, Shigematsu M, Furuya H, Phung TTB, Phan PH, Nunoi H, Nguyen LT, Suzuki K. Risk parameters of fulminant acute respiratory distress syndrome followed by avian influenza A(H5N1) infection in Vietnamese children. J Infect Dis 2009; 200: 510-515.
6) Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R. The American-European consensus conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994; 149: 818-824.
7) Rubenfeld GD. The ARDS Definition Task Force: Acute respiratory distress syndrome. The Berlin definition. JAMA 2012; 307: 2526-2533.
8) Artigas A, Bernard GR, Carlet J, Dreyfuss D, Gattinoni L, Hudson L, Lamy M, Marini JJ, Matthay MA, Pinsky MR, Spragg R, Suter PM. The American-European consensus conference on ARDS, Part 2. Ventilatory, pharmacologic, supportive therapy, study design strategies, and issues related to recovery and remodeling. Am J Respir Crit Care Med 1998; 157: 1332-1347.
9) Meduri GU, Golden E, Freire AX, Taylor E. Methylprednisolone infusion in early severe ARDS. Results of a randomized controlled trial. CHEST 2007; 131: 954-963.
10) Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, Thompson BT, Ancukiewicz M. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 2006; 354: 1671-1684.
11) World Health Organization. Clinical management of human infection with avian influenza A (H5N1) virus: Updated advice 15 August 2007.
12) Writing Committee of the Second World Health Organization. Consultation on clinical aspects of human infection with avian influenza A (H5N1) virus. Update on avian influenza A (H5N1) virus infection in humans. N Engl J Med 2008; 358: 261-273.
13) Nakajima N, Tin NV, Sato Y, Thach HN, Katano H, Diep PH, Kumasaka T, Thuy NT, Hasegawa H, San LT, Kawachi S, Liem NT, Suzuki K, Sata T. Pathological study of archival lung tissues from 5 fatal cases of avian H5N1 influenza in Vietnam. Modern Pathology 2013; 26: 357-369.
14) Lumb AB, Pearl RG. Chapter 9 Diffusion of respiratory gases, in Nun's Applied respiratory physiology sixth edition, Elsevier Butterworth-Heinemann, London, GB, 2009, p139.
15) Seo SH, Hoffmann E, Webster RG. Lethal H5N1 influenza viruses escape host anti-viral cytokine responses. Nat Med 2002; 8: 950-954.
16) Melén K, Kinnunen L, Fagerlund R, Ikonen N, Twu KY, Krug RM, Julkunen I. Nuclear and nucleolar targeting of influenza A virus NS1 protein: striking differences between different virus subtypes. J Virology 2007; 81: 5995-6006.
17) Phung TTB, Sugamata R, Uno K, Aratani Y, Ozato K, Kawachi S, Nguyen LT, Nakayama T, Suzuki K. Key role of regulated upon activation normal T-cell expressed and secreted, nonstructural protein1 and myeloperoxidase in cytokine storm induced by influenza virus PR-8 (A/H1N1) infection in A549 bronchial epithelial cells. Microbiol Immunol 2011; 55: 874-884.
18) Flori HR, Glidden DV, Rutherford GW, Matthay MA. Pediatric acute lung injury: prospective evaluation of risk factors associated with mortality. Am J Respir Crit Care Med 2005; 171: 995-1001.
19) Angeles Marcos M, Camps M, Pumarola T, Antonio Martinez J, Martinez E, Mensa J, Garcia E, Peñarroja G, Dambrava P, Casas I, Jiménez de Anta MT, Torres A. The role of viruses in the aetiology of community-acquired pneumonia in adults. Antivir Ther 2006; 11: 351-359.
20) Choi SH, Hong SB, Ko GB, Lee Y, Park HJ, Park SY, Moon SM, Cho OH, Park KH, Chong YP, Kim SH, Huh JW, Sung H, Do KH, Lee SO, Kim MN, Jeong JY, Lim CM, Kim YS, Woo JH, Koh Y. Viral infection in patients with severe pneumonia requiring intensive care unit admission. Am J Respir Crit Care Med 2012; 186: 325-332.
21) Meduri GU, Golden E, Freire AX, Taylor E. Methylprednisolone infusion in early severe ARDS. Results of a randomized controlled trial. CHEST 2007; 131: 954-963.
22) Takatsuki S, Ito Y, Takeuchi D, Hoshida H, Nakayama T, Matsuura H, Saji T. IVIG reduced vascular oxidative stress in patients with Kawasaki disease. Circ J 2009; 73: 1315-1318.