Risk Parameters of Fulminant Acute Respiratory Distress Syndrome and Avian Influenza (H5N1) Infection in Vietnamese Children

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A clinical picture of patients with acute respiratory distress syndrome (ARDS) induced by highly pathogenic avian influenza A (H5N1) has been reported. We reviewed 37 sets of clinical data for pediatric patients with ARDS at the National Hospital of Pediatrics (Hanoi, Vietnam); 12 patients with H5N1-positive and 25 with H5N1-negative ARDS were enrolled. The H5N1-negative patients had a clinical picture and mortality rate similar to that for the pediatric ARDS patients. However, the H5N1-positive patients had ARDS with normal ventilation capacity at the time of hospital admission, then rapidly proceeded to severe respiratory failure. The survival probability and days until final outcome in groups of H5N1-positive (n = 12) vs. H5N1-negative (n = 25) patients were 17% versus 52% and 12.3 ± 5.7 days (median, 11 days) versus 21.5 ± 13.8 days (median, 22 days), respectively. Our observations clarified the clinical picture of H5N1-induced fulminant ARDS and also confirmed that relatively older age (∼6 years of age), high fever at onset, and leukopenia and/or thrombocytopenia at the time of hospital admission are risk parameters for H5N1-induced fulminant ARDS.

Highly pathogenic avian influenza A (H5N1) came to the attention of the international scientific community for the first time in 1997 [1, 2]. The current global spread of human infection by this subtype started in 2003 in Hong Kong [2, 3], during the global outbreak of severe acute respiratory syndrome [4, 5]. Vietnam reported the first human case of H5N1 infection in January 2004 [6] and a suspected human-to-human transmission family cluster in the following months [7]. Since then, many clinical case reports have been reported from several countries, such as Thailand, Indonesia, and Vietnam [8–14]. However, it is still difficult to detect most infection at first examination without a clear history of patient contact with sick poultry.

The fatality rate associated with pediatric acute respiratory distress syndrome (ARDS) has decreased during recent decades because of advances in medical treatment, especially respiratory management as a lung-protective therapy [15]. However, the majority of patients with H5N1 subtype influenza virus infection experienced or presented ARDS during their clinical courses, often followed by a serious outcome. The histopathology of these cases demonstrated diffuse alveolar damage in the lung, which also suggests ARDS as a clinical condition of the respiratory system [16–18]. Because of the significant possibility that H5N1 subtype influenza will be the source of the next pandemic influenza strain [19, 20], the pathophysiology of the clinical course of H5N1
Table 1. Clinical Features of H5N1-Positive and H5N1-Negative Patients

| Feature                  | H5N1-positive patients (n = 12) | H5N1-negative patients (n = 25) | P     |
|--------------------------|---------------------------------|---------------------------------|-------|
| Age, year                | Mean value ± SD 6.7 ± 3.9       | Mean value ± SD 1.2 ± 2.9       | <.001 |
| pH                       | Median value 6                 | Median value 0.3                |       |
| PaO₂, mmHg               | 7.46 ± 0.07                    | 7.29 ± 0.17                    | <.001 |
| PaCO₂, mmHg              | 61.4 ± 59.3                    | 58.9 ± 23.8                    | .253  |
| FiO₂                     | 32.5 ± 12.4                    | 47.5 ± 18.1                    | .009  |
| Body temperature at onset, °C | 0.81 ± 0.28                   | 0.82 ± 0.27                    | .987  |
| WBC count, cells/mm³a    | 39.1 ± 0.4                     | 37.7 ± 1                       | <.001 |
| Platelet count × 10⁴, cells/mm³a | 123.5 ± 52.3                  | 366 ± 179.5                    | <.001 |
| AST level, IU/Lᵃ         | 1723 ± 2784                    | 259 ± 653                      | <.001 |
| ALT level, IU/Lᵃ         | 628 ± 1042                     | 221 ± 845                      | <.001 |
| Prognosis                | Alive                           | Dead                            |       |
|                          | 2 (16.7)                       | 13 (52.0)                      | .091  |
|                          | Dead                            | 10 (83.3)                      | 12 (48.0) |<.001 |
| Sex                      | Male                            | 8 (66.7)                       |       |
|                          | Female                          | 4 (33.3)                       |       |
|                          | Multiple organ failure          | Yes                             |       |
|                          | No                              | 11 (91.7)                      |       |

NOTE. P values <.05 indicate statistically significant differences between H5N1-positive and H5N1-negative groups. ALT, alanine aminotransferase; AST, aspartate aminotransferase; SD, standard deviation; WBC, white blood cell.

MATERIALS AND METHODS

Data source. Clinical and laboratory data for pediatric patients (aged >1 month) with severe illness examined at the NHP from December 2003 through June 2008 were analyzed. Patients examined prior to 2007 were enrolled in the study retrospectively by hospital record review and were followed prospectively after hospital admission. The diagnosis of ARDS was made according to international standards [21], which involve acute onset; PaO₂/FiO₂ ratio (P/F ratio) <200, independent of controlled mechanical ventilation; and bilateral infiltration observed on chest radiography without left heart failure or with pulmonary artery wedge pressure <18 mmHg. We enrolled patients with severe ARDS whose P/F ratios were <100 during their clinical courses. H5N1 infection was confirmed with throat and/or nasal swabs tested by reverse-transcriptase polymerase chain reaction at the hospital laboratory or at the National Institute of Hygiene Epidemiology (Hanoi). The study was reviewed by the ethical committee of the International Medical Center Japan in 2007, and the design was approved on 28 September 2007.

Statistical methods. Fisher’s exact test was employed for bivariate analysis of categorical data. The nonparametric Mann-Whitney test was used for 2-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 2 survival curves. All statistical analyses were performed with SPSS, version 14.0 (SPSS).

RESULTS

Thirty-nine patients with ARDS who met the inclusion criteria visited the hospital during the study period, but 2 were excluded...
| Patient | Sex  | Age, years | Duration, days | Prognosis | Blood pH | Respiratory parameters | Liver function levels, IU/L | Blood counts | Platelet count | Cause of ARDS |
|---------|------|------------|----------------|-----------|----------|------------------------|-----------------------------|---------------|---------------|----------------|
| 1       | M    | 0.25      | 22             | Y es      | 38.0     | 7.22                   | 58.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 2       | M    | 0.18      | 36             | Y es      | 37.2     | 7.32                   | 57.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 3       | F    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 4       | M    | 0.18      | 27             | Y es      | 37.8     | 7.55                   | 52.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 5       | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 6       | F    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 7       | M    | 0.18      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 8       | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 9       | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 10      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 11      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 12      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 13      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 14      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 15      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 16      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 17      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 18      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 19      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 20      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 21      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 22      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 23      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 24      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 25      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 26      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 27      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 28      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 29      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 30      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 31      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 32      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 33      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 34      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 35      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 36      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 37      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 38      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 39      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |
| 40      | M    | 0.12      | 27             | Y es      | 37.5     | 7.49                   | 55.0                        | 38            | 59            | Pneumonia (adenovirus) |

**Table 2. Summary of All Clinical Data**

- **H5N1 positive (n=12)**
- **H5N1 negative (n=25)**

**NOTE.**
- ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; BT, body temperature; MOF, multiple organ failure; NT, not tested; P/F, PaO2/FiO2 ratio.
- Blood gas, PaCO2, pH, pO2, rHb, and Troponin I are measured in mmol/L, mg/dL, and ng/mL, respectively.
- WBC and RBC counts are cells/mm^3.

- The duration represents the time from onset of illness to death or hospital discharge.
because of insufficient medical data. Twelve of 37 patients were shown to be positive for H5N1 influenza by polymerase chain reaction performed in the laboratory of the NHP (table 1).

Most patients in the H5N1-positive group experienced rapid deterioration of ARDS and died of respiratory failure even with proper medical care. Although 3 patients had thrombocytopenia (patients 1, 4, and 7) and 7 (patients 6–12) had increased serum aminotransferase levels (table 2), multiple organ failure was not followed by pathological investigation for H5N1-positive patients (data not shown).

The P/F ratio of all patients enrolled in this study was <100 during their clinical courses. However, PaCO₂ level at hospital admission was lower among H5N1-positive than among the H5N1-negative patients, illustrating that ventilation capacity was higher in the H5N1-positive group, compared with the H5N1-negative group. These clinical features of ARDS in the H5N1-negative group made us wonder why ARDS in the H5N1-positive group was not more severe than that in the H5N1-negative group on hospital admission. The survival probability and days until final outcome (± standard deviation) among H5N1-positive (n = 12) and H5N1-negative (n = 25) patients were 17% ± 52% and 12.3 ± 5.7 days (median, 11 days) and 21.5 ± 13.8 days (median, 22 days), respectively, demonstrating that the survival probability in the H5N1-positive group was significantly lower than that in the H5N1-negative group (P = .022, by log-rank test; P = .038, by Tarone-Ware test) (figure 1). These observations are the first step toward examining the clinical data for the H5N1-positive patients, which we designated as having fulminant ARDS.

As summarized in table 1, leukopenia and thrombocytopenia were observed in the H5N1-positive group, but leukophilia and normal-range thrombocyte levels were observed in the H5N1-negative group. Serum aspartate aminotransferase and alanine aminotransferase levels were also increased in the H5N1-positive but not the H5N1-negative group. Clinically, body temperature at illness onset in the H5N1-positive group was significantly higher than that in the negative group. We observed differences in clinical features between the H5N1-positive and H5N1-negative groups; we also analyzed differences with regard to sex, age distribution, and prognosis between these groups. The number of male patients in the H5N1-positive group was significantly higher than that in the H5N1-negative group, and H5N1-positive patients were significantly older than those in the H5N1-negative group. The mean time from illness onset until death (± standard deviation) was 10.4 ± 3.3 days (median, 10.5 days) in H5N1-positive group (n = 10) and 11.7 ± 3.3 days (median, 9 days) in H5N1-negative group (n = 12), and the mean time until hospital discharge (recovery) was 26 ± 18 days (median, 22 days) in the H5N1-positive group (n = 2) and 30.5 ± 11.8 days (median, 35 days) in the H5N1-negative group (n = 13). No significant differences were observed between groups with regard to time from illness onset to death.

DISCUSSION

H5N1-infected patients were significantly older than patients in the comparator group. To our knowledge, the mortality rate by age has not been discussed precisely for pediatric patients with ARDS; Flori et al [22] collectively discussed age and mortality in their analysis of 328 patients with ARDS who were aged between 36 weeks (corrected gestational age) and 18 years, and the mortality rate among patients with a P/F ratio <100 was ~35%. The observed significant difference in mortality rate by age could prove that relatively older age (6.7 ± 3.9 vs 1.2 ± 2.9 years) is one of the risk factors for H5N1 infection.

ARDS frequently results in a lethal outcome attributable not only to respiratory failure but also to multiple organ failure [15, 23, 24]. Our study confirmed that survival of patients with ARDS aged <16 years is drastically improved by medical care, but that these patients die of respiratory failure and multiple organ failure [14]. On the other hand, most patients in the H5N1-positive group still showed rapid progress and deterioration of ARDS and died of respiratory failure, even with proper medical care followed by pathological investigation. Although aspartate aminotransferase and alanine aminotransferase levels were higher in the H5N1-positive but not the H5N1-negative group, the elevation of serum aminotransferase levels is a relatively common feature in H5N1 patients [6, 9, 25]. A
review of 2 groups of patients in large case studies has shown that elevated aminotransferase levels are not thought to be specific in H5N1 patients [26, 27]. These observations strongly suggest that H5N1-infected patients die because of rapidly progressive respiratory failure before revealing typical multiple organ failure status accompanied by failure of multiple organs such as liver, heart, and kidney.

Physiologically, we further analyzed data regarding the P/F ratio, which is a good parameter of oxygenation capacity for respiratory function. P/F ratios were <100 in both H5N1-positive and -negative patients, which means that the oxygenation capacity in both groups was severely damaged. Surprisingly, PaCO₂ levels revealed that ventilation capacity was normal in H5N1-positive patients but was severely damaged in H5N1-negative patients with ARDS; that is, H5N1-negative patients experienced more severe respiratory failure than did H5N1-positive patients on hospital admission. The log-rank test and the more severely conditioned Tarone-Ware test also showed a significant difference in survival probability between the H5N1-positive and H5N1-negative groups. H5N1-positive patients started with normal ventilation capacity on hospital admission, then rapidly proceeded to severe respiratory failure and death. Patients in the H5N1-positive group demonstrated a shorter duration until final outcome than patients in the H5N1-negative group; therefore, we designated these as fulminant ARDS patients. The initial check of blood gas levels may be an early diagnostic indicator of H5N1 infection. There may also be some mechanisms that influence cell activity during H5N1 infection and accelerate alveolar damage, resulting in death [28, 29]. Pathology and immunomodulator activity in H5N1 infection have been discussed elsewhere [30], but precise mechanisms have not been clarified yet [31].

Body temperature was significantly higher in H5N1-positive patients at the onset of disease, compared with H5N1-negative patients. This seasonal influenza-like symptom appears early in the course of the disease, with a body temperature >38°C in almost all infected patients [26]. Significant leukopenia and thrombocytopenia were observed in the H5N1-positive group (P <.001). Leukopenia and thrombocytopenia are observed in the majority of patients with H5N1 [26, 27]. There has been some discussion of the possibility that lymphopenia and increased levels of lactate dehydrogenase at presentation are associated with a poor prognosis [27]. Further investigation into lymphopenia and liver function in H5N1 patients is necessary for clarification.

We have demonstrated here that H5N1 infection with ARDS starts with high fever but relatively mild respiratory symptoms, then proceeds to serious respiratory failure with lower survival probability and shorter periods of illness (fulminant ARDS), compared with ARDS without H5N1 infection. Leukopenia, thrombocytopenia, and liver function on hospital admission might be risk parameters and early indicators of patients with H5N1 influenza virus infection.

Acknowledgments

We thank a coordinator, Ms. Yen, and all members of the NHP and the Ministry of Health in Vietnam for their cooperation.

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