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An Analysis of Patients Followed Up in the Intensive Care Unit with the Diagnosis of Acute Respiratory Distress Syndrome

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Abstract

Objective: To examine the factors thought to have an effect on the mortality of patients with acute respiratory distress syndrome (ARDS) in the intensive care unit (ICU).

Methods: A retrospective evaluation of 100 patients diagnosed with ARDS in the ICU between January 2009 and January 2013 was made. Surviving and deceased patients were compared with respect to the effect of the general characteristics, aetiological and prognostic factors, mechanical ventilation (MV) applications (especially permissive hypercapnia resulting from the restriction of the tidal volume predicted to avoid excessive distention of the alveoli), laboratory test values, multiorgan dysfunction rates, Acute Physiologic Assessment and Chronic Health Evaluation II score, Lung Injury Score, Glasgow Coma Score, Sequential Organ Failure Assessment scores, arterial blood gas parameters and partial pressure of arterial oxygen/fraction of inspired oxygen ratio values on mortality.

Results: There were 100 patients with ARDS comprising 61 males and 39 females with a mean age of 57.0±13.0 (range: 20-82) years and length of stay in the ICU of 38.7±13 days. The aetiological causes of ARDS were determined as pneumonia in 37 patients, trauma (traffic accidents inside or outside the vehicle and other accidents) in 14, sepsis in 19, pulmonary contusion in 9, non-pulmonary infection in 6, intoxication in 5, multiple blood transfusions in 4, firearms injury in 4 and acute pancreatitis in 2. Forty-four patients died.

Conclusion: Survival rates were increased in patients with ARDS with early diagnosis and ICU support, lung protective MV strategy and permissive hypercapnia.

Keywords: Acute lung injury, acute respiratory distress syndrome, intensive care unit, permissive hypercapnia

Introduction

Acute respiratory distress syndrome (ARDS) is a severe clinical process that occurs as a result of acute lung damage. ARDS was first described in 1967 by Asbaugh et al. (1) as a syndrome of severe respiratory failure with widespread infiltrations seen on the pulmonary radiograph, reduced compliance and hypoxaemia unresponsive to oxygen treatment. The most commonly used definition of ARDS, the work of the European Society of Intensive Care Medicine (ESICM) in conjunction with the American Thoracic Society on the new definition of ARDS at the ESICM 24th Congress in Berlin, Germany, has been presented by Marco Ranieri (2). The criteria of this definition are shown in Table 1.

Acute respiratory distress syndrome may develop through direct causes, such as aspiration pneumonia, pulmonary thromboembolism, smoke and toxic gas inhalation, or through indirect routes, such as sepsis, non-pulmonary infections, trauma, pancreatitis, blood transfusions or drug toxicity. Cases where lung injury develops through a direct route are defined as primary ARDS, and cases that develop associated with causes outside the lungs are defined as secondary (extrapulmonary). There are significant differences between primary and secondary ARDS with respect

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Table 1. ARDS Berlin definition

The Berlin definition of acute respiratory distress syndrome	
Timing	Within I week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities-not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload.
	Need objective assessment (e.g. echocardiography) to exclude hydrostatic oedema if no risk factor present
Oxygenation[b]	
Mild	200 mmHg $<PaO_2/FiO_2 \leq$300 mmHg with PEEP or CPAP ≥5 cmH_2O[c]
Moderate	100 mmHg $<PaO_2/FiO_2 \leq$200 mmHg with PEEP ≥5 cmH_2O
Severe	$PaO_2/FiO_2 \leq$100 mmHg with PEEP ≥5 cmH_2O

CPAP: continuous positive airway pressure; FiO_2: fraction of inspired oxygen; PaO_2: partial pressure of arterial oxygen; PEEP: positive end expiratory pressure; [a]Chest radiograph or computed tomography scan; [b]If altitude is higher than 1,000 m, the correction factor should be calculated as follows: [PaO_2/FiO_2 (barometric pressure/760)]; [c]This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

to clinical findings, prognosis and survival. There is alveolar epithelial cell damage in pulmonary ARDS, whereas there is vascular endothelial damage in cases with extrapulmonary damage. The underlying reasons in adult patients are known to be primarily sepsis, followed by pneumonia, trauma and aspiration of gastric contents (3-6).

Despite treatments, such as mechanical ventilation (MV), permissive hypercapnia, high-frequency oscillatory ventilation, nitric oxide and extracorporeal membrane oxygenation in the treatment of patients with ARDS, the mortality rates are still very high. With the addition of organ failure other than the lungs to the clinical table, related to severe sepsis or septic shock together with acute lung injury (ALI), the mortality rates are increased (7-11). In parallel with the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, Glasgow Coma Score (GCS) and Lung Injury Score (LIS), the mortality rate is known to increase, and the duration on MV and the length of stay in the intensive care unit (ICU) are prolonged.

The aim of the present study was to evaluate patients diagnosed with ARDS in the ICU of our hospital between January 2009 and January 2013 with respect to the effect on the mortality rates of the general characteristics; aetiological and prognostic factors; MV applications; laboratory test values; mortality and multiorgan dysfunction rates; APACHE II, LIS, GCS and SOFA scores; arterial blood gas parameters and partial pressure of arterial oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio values.

Methods

A retrospective examination was made of the records of patients admitted to the ICU of our hospital between January 2009 and January 2013. The ICU of our hospital is an eight-bed unit with six open beds and two isolation rooms. Patients were also evaluated by retrospective examination of patient records and records of the ICU electronic database. Approved by the Ethics Committee of Dicle University Faculty of Medicine Hospital (decision no. 2013/468).

The study included 100 (61 male and 39 female) patients who developed ARDS on admission to the ICU or during the observation period in the ICU. Patients were divided into two groups: surviving and deceased patients. The criteria of ESICM in Berlin, Germany were considered as the basis for the diagnosis of ARDS (Table 1).

Patients who died in the first 24 h, with cancer in the terminal stage, who were pregnant and aged <18 years or >90 years were excluded from the study. Patients were accepted as ARDS with an oxygen rate of ≤200 according to the worst PaO_2/FiO_2 value in the previous 24 h. In patients with frequent ARDS episodes, only the period of the first episode was evaluated in the study. Pulmonary ARDS was defined as diseases caused by direct lung injury, such as pneumonia or pulmonary contusion, and extrapulmonary ARDS was defined as diseases including sepsis, trauma (traffic accidents inside or outside the vehicle and other accidents), non-pulmonary infections, intoxication, multiple blood transfusions, firearms injuries or acute pancreatitis. Data on demographic characteristics including age and gender, diagnoses causing ARDS, the worst PaO_2/FiO_2 value in the first 24 h, pH value, C-reactive protein levels during diagnosis, immunosuppression status and chronic organ failure were recorded.

For patients diagnosed with ARDS and those who developed acute major organ failure within 72 h, the SOFA, LIS, GCS and APACHE II scores were calculated and recorded.

APACHE II score: This is a scoring system that measures the previous comorbidity status with patient age and the worst measurements (laboratory and vital signs) of ICU patients in the first 24 h of admittance to the ICU.

SOFA score: This is a scoring system that evaluates six organ systems (respiratory, cardiovascular, kidneys, central nervous system, liver and coagulation) for the evaluation of organ failure that develops in patients with severe sepsis. It provides an evaluation of the course of severe sepsis in patients. A worsening score is related to increasing mortality. Every patient with severe sepsis in the ICU is followed up using the SOFA score.

Treatment

Despite all work done, treatment of the pathophysiology causing ARDS is not possible. For this reason, treatment cannot be advanced beyond symptomatic and supportive. Treatment can be divided into two categories: non-pharmacological (eg, ventilation therapy, pronation, high-frequency ventilation, extracorporeal life therapy, liquid ventilation and fluid regime) and pharmacological (eg, surfactant, nitric oxide and corticosteroid).

Mechanical ventilation is life-saving in the treatment of ARDS. Although mild forms of ARDS can be injured by non-invasive positive pressure ventilation, invasive MV is necessary in severe forms. If the 'baby lung' model in ARDS is considered, a low tidal volume (VT) ventilation strategy should be applied to protect it from volume and barotrauma. The recommended VT is <6 mL kg^{-1}. Certainly, the most important aspect is ventilator treatment, and positive end-expiratory pressure (PEEP) has positive effects, such as increasing functional residual capacity, inhibition of atelectasis, migration of oedema fluid from the alveoli to the interstitial site and increased surfactant activity; it is titrated at varying levels according to the patient to the ideal level for each patient. We aimed to titrate the PEEP level, which will not impair haemodynamics and target arterial oxygen saturation >0.90 when the target is FiO_2 <0.6. In our study, we applied low VT, pressure limited ventilation and permissive hypercapnia. Permissive hypercapnia is permitted up to PCO_2 <100 mmHg, pH >7.2.

Statistical analysis

Statistical analyses of data were performed using the Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) 16.0 software (LEAD Technologies Inc., USA). Numerical data were expressed by frequency analysis. Mean±standard deviation and minimum and maximum values were calculated. For group comparisons, the Mann-Whitney U test was used for non-parametric, continuous, numerical values. For categorical and nominal values, the chi-square test was applied. A p value of <0.05 was accepted as statistically significant.

Results

A total of 1320 patients were admitted to the Reanimation Clinic ICU between January 2009 and January 2013. MV support was applied to 943 patients because of respiratory failure. The study included 100 patients diagnosed with ARDS comprising 61 males and 39 females with a mean age of 57±13 (range: 20-82) years (Table 2).

Patients were separated into two groups as those who survived (Group I) and those who did not survive (Group II). The mean ages of the patients were 52.7±13 years in Group I and 64.2±9 years in Group II. The mean age of the patients in Group II was statistically significantly higher (p=0.0001) (Table 2).

The mean APACHE II score was calculated as 30±7 (range: 14-46), mean GCS as 7 (range: 4-9), mean SOFA score as 13±4.2 (range: 3-20) and mean LIS as 2.7±0.1 (range: 2.3-3).

The mean LIS scores were 2.6±0.1 in Group I and 2.7±0.1 in Group II, and the difference between the groups was statisti-

Table 2. Characteristics of patients

Characteristics	Group I (n=56) Mean±SD	Group II (n=44) Mean±SD	p
Age	52.7±13	64.2±9	0.0001
Gender (female/male)	24 F/32 M	15 F/29 M	0.2
LIS (AHS)	2.6±0.1	2.7±0.1	0.001
APACHE II	25±5	37±5	0.0001
GCS	7.3±0.9	6.4±1.3	0.001
SOFA	12.5±4.4	14.9±3.5	0.003
Length of stay in the ICU (day)	26±11	49±16	0.0001
Duration of mechanical ventilation (day)	13±8	23±7	0.0001
Mechanical ventilation application			
PEEP	11.6±1.6	12.4±1.4	0.01
Frequency	19±4	20±4	0.01
pH	7.27±0.8	7.25±0.7	0.1
PaO_2 (mmHg)	74±15	64±11	0.002
CO_2 (mmHg)	47±10	58±15	0.0001
HCO_3 (mmol L^{-1})	18±4	19±5	0.2
PaO_2/FiO_2 (mmHg)	141±19	122±22	0.0001

LIS: Lung Injury Score; AHS: Acute Lung Injury; APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II score; GCS: Glasgow Coma Score; SOFA: Sequential Organ Failure Assessment score; ICU: intensive care unit; PEEP: positive end-expiratory pressure; PaO_2: partial pressure of arterial oxygen; FiO_2: fraction of inspired oxygen; CO_2: carbon dioxide; HCO_3: bicarbonate

cally significant (p=0.001). The APACHE II scores were 25±5 in Group I and 37±5 in Group II. The APACHE II score of Group II was statistically significantly higher (p=0.0001). The GCS scores were 7.3±0.9 in Group I and 6.4±1.3 in Group II. The GCS score of Group II was statistically significantly lower (p=0.001). The SOFA scores were 12.5±4.4 in Group I and 14.9±3.5 in Group II. The SOFA score of Group II was statistically significantly higher (p=0.003) (Table 2).

The mean lengths of stay in the ICU were 26±11 days in Group I and 49±16 days in Group II (p=0.0001). The durations of MV were 13±8 days in Group I and 23±7 days in Group II (p=0.0001) (Table 2).

The PaO_2 values were 74±15 in Group I and 64±11 in Group II. The PaO_2 value in Group II was found to be statistically significantly lower (p=0.002). The PCO_2 values were 47±10 in Group I and 58±15 in Group II, and the value in Group II was statistically significantly higher (p=0.0001). The PaO_2/FiO_2 ratios were 141±19 in Group I and 122±22 in Group II, and the difference between the groups was statistically significant (p=0.0001) (Table 2).

The frequency value was 19±4 (range: 12-34). Of 100 patients, there were 46 (46%) with pulmonary ARDS and 54 (54%) with extrapulmonary ARDS. The causes of pulmonary ARDS were determined as pneumonia (37%) and pulmonary contusion (9%), and the causes of extrapulmonary ARDS were sepsis (19%), trauma (14%), non-pulmonary infection (6%), intoxication (5%), firearms injury (4%), multiple blood transfusions (4%) and acute pancreatitis (2%) (Table 3).

Table 4 shows the chronic organ failure during diagnosis and comorbidities. In patients with respiratory failure together with cardiac disease and those with renal failure together with diabetes, the mortality rate was observed to be statistically significantly higher than other comorbidities (p=0.0001).

A high rate of organ failure was determined in patients with ARDS. Respiratory failure was most frequently seen in 94% of patients with ARDS, followed by acute renal failure in 90% and cardiovascular system failure in 76%. Table 5 shows the rates of organ failure.

Of the patients applied with MV, airway pressure release ventilation (APRV) was applied to 57%, Adaptive support ventilation (ASV) to 3%, Two-level pressure control ventilation (DuoPAP) to 6% and synchronised intermittent mandatory ventilation (SIMV) mode to 4%. The mean duration of the application of MV was 17±9 (range: 3-42) days, and the mean PEEP was 11.9±1.5 (range: 8-14). When the survival rates of those with organ failure were examined, there was a statistically significant increase in the mortality rate in the presence of multiple organ failure and septic shock (p=0.001). In patients applied with sedation, midazolam was administered to 83, propofol to 13, and thiopental to 4. A total of 22 patients received inotropic support. Mortality was seen in 18 of the 22 patients who received inotropic support and in 26 of the 78 patients who did not require inotropes. The mortality rate of those who required inotropic support was statistically significantly higher (p=0.0001).

Table 3. Diagnosis at admission to the intensive care unit

Aetiological reasons	No.		Total (n=100)
	Survivors (n=56)	Exitus (n=44)	
Pneumonia	20	17	37
Sepsis	10	9	19
Trauma	8	6	14
Pulmonary contusion	6	3	9
Non-pulmonary infection	4	2	6
Intoxication	2	3	5
Acute pancreatitis	0	2	2
Multiple blood transfusions	4	0	4
Firearms injury	2	2	4

Table 4. Comorbidities of patients

Chronic organ failures	ARDS (n=100)
Respiratory	34 (34%)
Cardiovascular*	17 (17%)
Renal	14 (14%)
Diabetes mellitus	15 (15%)
Neurological#	2 (2%)
Haematological	6 (6%)
Immunosuppressive&	4 (4%)
Liver	2 (2%)

*Coronary artery disease or heart failure. #Alzheimer, Parkinson or cerebrovascular disease. &Steroid or other immunosuppressive drug use, chemotherapy or radiotherapy. ARDS: acute respiratory distress syndrome

Table 5. Acute organ failure in the first 24 h in patients with ARDS

Acute organ failures	ARDS (n=100)
Respiratory	94 (94%)
Cardiovascular	76 (76%)
Renal	90 (90%)
Neurological	24 (24%)
Haematological	6 (6%)
Liver	6 (6%)
Severe sepsis/shock	28 (28%)

ARDS: acute respiratory distress syndrome

Discussion

In the present study, we aimed to compare the surviving and non-surviving patients with ARDS who were treated and monitored in the Reanimation ICU, with respect to age; aetiology; mechanical ventilation applications; laboratory test values; mortality and multiorgan dysfunction rates; APACHE II, LIS, GCS and SOFA scores; arterial blood gas parameters and PaO_2/FiO_2 ratios.

Mechanical ventilation is the most important, life-saving step in the treatment of ARDS. In the mild form of ARDS, non-invasive MV can be attempted. However, in the majority of ARDS cases, especially in severe ARDS cases, invasive MV is necessary (12). With new ventilation modes, such as APRV and BiPAP, MV can be applied without restricting spontaneous respiration. When modes are compared with a control, the advantage is provided of increasing oxygenation by correcting the V/Q balance while continuing MV at the same time as spontaneous respiration. Contraction of the diaphragm is increased, providing easier access to the underlying atelectatic lung regions (13). Nevertheless, there is no single best ventilation mode that can be applied to all ARDS cases (14). In the current study, the MV modes used were APRV, DuoPAP, ASV and SIMV modes. No statistically significant difference was determined between the modes with respect to mortality.

In a 2011 ALIEN study performed by Villar et al. (15), the APACHE II score was found to be 21.6±5.9, and LIS 2.9±0.6. Agarwal et al. (16) reported the APACHE II score as 17.2±8.7 and the SOFA score as 6.9±3.6. In a study conducted in Dokuz Eylul University Medical Faculty Internal Medicine ICU, the APACHE II score was found to be 29.4±7.6 (range: 12-44), and the SOFA score 11.1±4.6 (range: 2-21) (17). In the current study, the APACHE II score was determined as 30±7, the SOFA score as 13.6±4.2 and the LIS score as 2.7±0.1. As the clinical picture of Group II patients was more severe than that of Group I patients, this was reflected in the APACHE II ($p=0.0001$), SOFA ($p=0.003$) and LIS ($p=0.001$). The APACHE II and SOFA scores of the current study were found to be similar to those of previous studies in Turkey, but higher than those of some other studies worldwide. It can be considered that these high rates could be due to the fact that as our hospital is a regional hospital, the most critical patients in the region are admitted, and the ICU is the final place of admittance for the most critical patients within the hospital.

The length of stay in the ICU is an important factor affecting mortality. Prolongation of this time entails risks, such as infection and pulmonary embolism, increasing the mortality rates (18, 19). In a previous study in Turkey, it was reported that the mortality rates are increased in patients staying >14 days in the ICU (17). In the European Prevalence of Infection in Intensive Care study that was conducted in the ICUs of various European countries, it was reported that in patients with a length of stay of >21 days in the ICU, the relative mortality risk increases 2.5-fold (20). In the current study, when the surviving patients (Group I) were compared with the non-surviving patients (Group II), a statistically significant difference was determined with respect to length of stay in the ICU and MV. The lengths of stay in the ICU were 26±11 days in Group I and 49±16 days in Group II ($p=0.0001$). The durations of MV were 13±8 days in Group I and 23±7 days in Group II ($p=0.0001$). As the length of stay in the ICU and the duration of MV increased, there was a significant increase in the mortality rates, as has been reported in previous studies (21).

In the current study, the PaO_2/FiO_2 ratio was found to be 132±22 (range: 58-188), with 141±19 in Group I and 122±22 in Group II. In the ALIVE study, it was observed that as the PaO_2/FiO_2 ratio decreased, there is a significant increase in the mortality rate, supporting the prognostic importance of the severity of ALI (7). In the ALIEN study (15), the PaO_2/FiO_2 ratio was found to be 114±40. Hernu et al. (22) reported the PaO_2/FiO_2 ratio as 239 (220-260) in the mild form of ARDS, 140 (119-165) in the moderate form and 77 (64-89) in the severe form. In the study by Agarwal et al. (16), the mean PaO_2/FiO_2 ratio was reported as 150.9 in ALI/ARDS. Similar to these previously reported results, the PaO_2/FiO_2 ratio of patients admitted to the ICU who died was found to be statistically significantly low ($p<0.0001$).

In the ALIVE study, it was shown that as the pH level of the patient decreased, the mortality rate increases, and in cases with pH <7.25, in particular, the mortality rate increases significantly (7). Generally, in patients with ARDS ventilated with high PEEP and low VT, respiratory acidosis develops associated with elevated $PaCO_2$. Owing to reduced peripheral vascular resistance in patients with ARDS, increased brain perfusion, increased cardiac flow, easier separation of oxygen from haemoglobin in an acidic environment and increased oxygen diffusion, it is recommended that permissive hypercapnia, which will be pH 7.25-7.30, is allowed to develop (23, 24). For the first time, Hickling et al. (25) published a 'lung protective ventilation' model using low VT, pressure limited ventilation and permissive hypercapnia in 1990. Permissive hypercapnia is permitted up to PCO_2 <100 mmHg, pH >7.2. Contraindications for permissive hypercapnia are high intracranial pressure, severe pulmonary hypertension and convulsions. In 1995, Amato et al. (26) developed an alternative 'lung protective' model and called it the 'open lung' model. In the open lung model, high pressure is applied for a very short period to provide lung opening. Low VT is used for protection from voltaic trauma immediately, whereas high PEEP is

applied to maintain an open lung. The inspiratory/expiration rate is set to 1/2 in the ventilator treatment. However, in severe ARDS cases that do not respond to conventional treatment, an inverse ratio application that reverses the inspiratory and expiratory rate can be performed in the pressure-controlled ventilation mode together with the open lung model (27). Deep sedation or even neuromuscular blockade is often necessary. The general view accepted as the mechanism of action is that it opens the alveoli with low peak pressure and provides optimal ventilation distribution. There are studies that show that mortality is decreased (28). In our ICU, we are applying permissive hypercapnia, which is a result of restriction of prescribed VT to avoid excessive distention of the alveoli in patients with ARDS.

If acidosis is of respiratory origin in patients with ARDS, optimal pressure, inspiration/expiration ratio, PEEP level and respiration frequency are adjusted according to the results of the patient's blood gas analyses. If the cause of the acidosis is metabolic, the most frequent cause is lactic acidosis associated with impaired oxygen transport. Optimal inotropic and fluid support is provided, and if no response is obtained, haemodialysis is applied to the patient. In the current study, the pH level was determined as 7.26±0.07 (range: 7.07-7.44). As no significant difference was observed between the pH levels of Group I and Group II patients, it was concluded that permissive hypercapnia in patients with ARDS did not increase the mortality rates. When the groups were compared, the mean initial PCO_2 value was seen to be statistically significantly high in Group II at 52 (p=0.0001), and the mean PaO_2 value was statistically significantly low at 70 (p=0.002).

Hernu et al. (22) reported that according to the Berlin definition of ARDS, the mean PaO_2 values are 117 in patients with mild ARDS, 86 in moderate ARDS and 64 in severe ARDS. The mean $PaCO_2$ values are found to be 41 in patients with mild ARDS, 42 in moderate and 43 in severe ARDS. The values of patients with moderate and severe ARDS in the current study were found to be close to the values reported by Hernu et al. (22) using the Berlin definition of ARDS.

Conclusion

Although the mortality rate of ARDS has decreased in recent years, it is still high (41%-46%). The mortality rates can be reduced by the application of permissive hypercapnia and a lung-preserving MV strategy, such as low VT and optimal PEEP support, which will keep the alveoli open. As the PaO_2/FiO_2 ratio at diagnosis decreases, the mortality rates increase, supporting the prognostic importance of ARDS severity and seriousness. Furthermore, as a result of our literature scanning, we concluded that the studies performed in our country are limited. We believe that there is a need for further multicentre studies related to ARDS.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dicle University School of Medicine (Decision No: 2013/468).

Informed Consent: Written informed consent was obtained from relatives of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Ö.K.; Design - Ö.K.; Supervision - Ö.K., E.G.; Resources - Ö.K., E.G.; Materials - Ö.K.; Data Collection and/or Processing - Ö.K.; Analysis and/or Interpretation - A.K., Ö.K.; Literature Search - Ö.K., E.G., A.K.; Writing Manuscript - Ö.K.; Critical Review - E.G., A.K.; Other - A.K., E.G.

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