원 저

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The Effects of Agent Orange in Patient with Pneumonia

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Purpose: Agent Orange (AO) is a herbicide and defoliant used by the United States and its military allies during the Vietnam War. Pneumonia is a common cause of death among Vietnam veterans in our hospital. There have been no previous studies researching any association between AO exposure and the prognosis for pneumonia. The primary objective of this study was to investigate associations between AO exposure and 30-day mortality due to pneumonia. The secondary objective was to examine the clinical factors associated with therapeutic outcomes in veterans with pneumonia, and to assess the prevalence of combined diseases in AO-exposed veterans.

Methods: This study retrospectively included veteran patients diagnosed with pneumonia in the emergency department and hospitalized between February 2014 and March 2018. The enrolled patients were grouped according to their defoliant exposure history, and the clinical information of defoliant-exposed and non-defoliant-exposed groups were compared. Patients were divided according to 30-day mortality, and significant factors influencing mortality were evaluated by using univariate analysis and multivariate analysis. The final multivariate model revealed the effect of AO exposure on therapeutic outcomes of pneumonia.

Results: A total of 1006 patients were analyzed. Of these, 276 patients had a history of AO exposure, whereas 730 patients had not been exposed. Factors positively associated with 30-day mortality were malignancy, respiratory rate, blood urea nitrogen, and albumin which was negatively associated with mortality.

Conclusion: Exposure to defoliant is not associated with 30-day mortality in patients with pneumonia. However, veterans with defoliant exposure are associated with a high prevalence of diabetes mellitus, hypertension, cerebrovascular accident, malignancy, and chronic kidney disease.

Key Words: Agent orange, Dioxin, Defoliant, Pneumonia, Veteran

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INTRODUCTION

Agent Orange (AO) was an herbicide and defoliant used by the United States and its military allies during the Vietnam War. From 1964 to 1973, about 320,000 Korean military participated in the Vietnam War and were exposed to AO. AO was a mixture of 2,4-

dichlorophenoxyacetic acid and 2,4,5-trichlorophe-noxyacetic acid, which also contained dioxin conta-minants, including 2,3,7,8-tetrachlorodibenzo-p-diox-in[1]. In Korea, about 142,448 Vietnam war veterans are alive and being treated for AO complications in veterans hospitals. Numerous research articles have been published regarding the health effects of AO[2-9]. Previous studies have reported deaths due to cancers of the stomach, small intestine, liver, larynx, lung, blad-der, and thyroid gland; in addition, chronic myeloid leukemia and angina pectoris, chronic obstructive pul-monary disease, chronic kidney disease and chronic liver disease were all increased with AO exposure[10]. Among defoliant related disease, following diseases (stroke, diabetes and chronic liver disease) were asso-ciated with mortality in patients with pneumonia[11]. Pneumonia is a leading cause of morbidity and mor-tality in old age[12,13]. There have been no previous studies investigating associations between AO expo-sure and the prognosis for pneumonia. The primary objective of this study was to investigate associations between AO exposure and 30-day mortality due to pneumonia. The secondary objective was to investi-gate the clinical factors associated with therapeutic outcomes in veterans with pneumonia and to assess the prevalence of combined disease in AO-exposed veterans.

METHODS

1. Hospital setting and study design

The study hospital was a 1,400-bed secondary acad-emic hospital with an annual Emergency Department (ED) census of 30,000. All patients presenting with pneumonia who were admitted to our ED have been registered in a pneumonia registry, since our ED was established in February 2014. We used the pneumonia registry and collected additional information by retro-spective electronic medical record (EMR) chart review. Veteran patients who were diagnosed with pneumonia in the ED and hospitalized between February 2014 and March 2018 were included. We collected patient data Patients who were discharged from the ED or trans-ferred to another hospital were excluded. Pneumonia severity index (PSI) or CURB-65 scoring system were used to evaluate disease severity and evaluate the need for hospital admission[14,15].

We divided enrolled patients according to defoliant exposure history and compared the clinical informa-tion for the defoliant-exposed and non-defoliant-exposed groups. We divided the patients according to 30-day mortality and investigated significant fac-tors influencing mortality by using univariate analy-ses and subsequent multivariate analyses. The final multivariate model showed the effect of AO exposure on therapeutic outcomes of pneumonia. This study was approved by our Institutional Review Board, and informed consent was waived due to the retrospec-tive nature of the study. (IRB number : 2019-04-008)

2. Data collection and classification

Based on the pneumonia registry, we established a standardized form that contained 80 variables, includ-ing demographic factors, clinical factors, laboratory data, and therapeutic results. Vital signs were record-ed at the triage stage in the ED. Initial laboratory data after ED admission were recorded. The demographic data included age, sex, diabetes mellitus (DM), hyper-tension (HTN), chronic lung disease, chronic liver dis-ease, congestive heart failure (CHF), chronic kidney disease (CKD), cerebrovascular accident (CVA), malig-nancy, tuberculosis (TB) history, nursing home resi-dency, and AO exposure history. The clinical parame-ters included systolic blood pressure (SBP), heart rate (HR), body temperature (BT), respiratory rate (RR), white blood cell (WBC) count, hemoglobin (Hb), platelet count, blood urea nitrogen (BUN), serum cre-atinine (Cr), blood glucose, serum albumin, serum C-reactive protein (CRP), serum sodium (Na), serum potas-sium (K), blood pH, arterial oxygen partial pressure (pO$_2$), and pleural effusion. The therapeutic results included 30-day mortality and in-hospital mortality. We classified patients with respect to community-acquired pneumonia (CAP), health care-associated pneumonia (HACP) or hospital-acquired pneumonia (HAP). HAP was defined as pneumonia that occurred

more than 48 hours after hospitalization. Patients who were hospitalized in an acute care hospital for more than two days within 90 days of the infection, resided in a nursing home or long-term care facility, attended a hemodialysis clinic, recently received intravenous antibiotics or chemotherapy, or sought wound care within 30 days of the infection were classified as having HACP[12,16-18]. In terms of cancer history, patients with active disease were classified as patients with cancer, while those with no evidence of disease were classified as patients without cancer. Patients who were unable to move by themselves were defined as bedridden.

Defoliant exposure history was identified by EMR review, which was provided by the Ministry of National Defense. The defoliant exposure history is registered according to Vietnam war record and the period of defoliant use. Exposure levels were recorded in three steps, but we did not use the data. We also classified patients with respect to sepsis and septic shock[19]. In cases of missing data, our research team re-examined the EMR and obtained additional information from patients by phone. We excluded cases without therapeutic results.

3. Statistical analyses

The means and standard deviations (SD) of continuous variables were calculated and the means compared using the Student's T-test. The frequencies (percentages) of binominal variables were analyzed using the x^2 or Fisher's exact test. Enrolled patients were divided into two groups according to their 30-day mortality, and the frequencies compared by univariate analyses. We selected the clinically significant variables with reference to the results in the univariate analyses. Multivariate logistics regression analyses were performed to find independent risk factors using the candidate variables. Variables were removed from the multivariate model in a stepwise manner, and the final model with the best fit was determined using Bayesian information criterion: this criterion introduces a penalty term to the number of parameters in a model, such that one model is considered better than another if it has a smaller Bayesian information criterion value[20]. The final model showed the effect of AO exposure and other significant factors associated with 30-day mortality due to pneumonia. A two-sided test was used with a 5% significance level. All calculations were conducted using Stata version 12.0 (StataCorp, College Station, TX).

RESULTS

A total of 1,893 patients were diagnosed with pneumonia in the ED and 1,023 patients were hospitalized
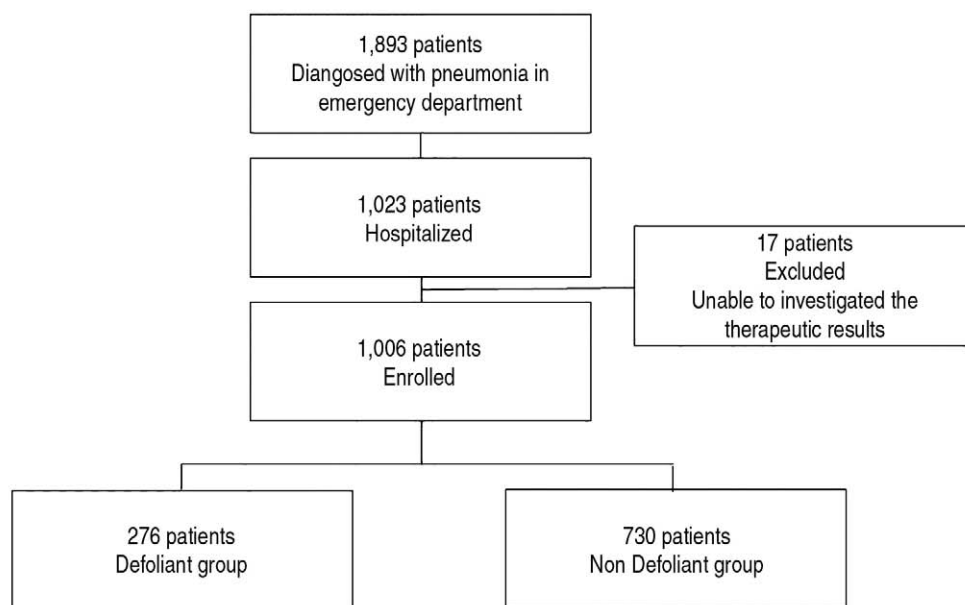

Fig. 1. Flow chart of study.

Table 1. Baseline characteristics of defoliant group and non-defoliant group

	Total (N=1,006)	Defoliant group (N=276)	Non-defoliant group (N=730)	*p*-value*
Epidemiological data				
Age (mean±SD+, years)	79.2±0.2	72.3±0.3	81.9±0.2	<0.001
Male, N (%)	1000 (99.4)	276 (100)	724 (99.1)	0.131
Diabetes mellitus, N (%)	370 (36.7%)	137 (49.6)	233 (31.9)	<0.001
Hypertension, N (%)	614 (61)	183 (66.3)	431 (59)	0.035
Chronic lung disease, N (%)	231 (22.9)	48 (17.3)	183 (25)	0.01
Chronic liver disease, N (%)	13 (1.2)	5 (1.8)	8 (1.1)	0.37
Congestive heart failure, N (%)	33 (3.2)	8 (2.9)	25 (3.4)	0.676
Chronic kidney disease, N (%)	117 (11.6)	47 (17)	70 (9.5)	0.001
Cerebrovascular accident, N (%)	271 (26.9)	93 (33.7)	178 (24.3)	0.003
Malignancy, N (%)	222 (22)	82 (29.7)	140 (19.1)	<0.001
History of tuberculosis, N (%)	148 (14.7)	30 (10.8)	118 (16.1)	0.034
Nursing home resident, N (%)	86 (8.5)	14 (5)	72 (9.8)	0.015
Bed ridden status, N (%)	212 (21)	62 (22.4)	150 (20.5)	0.056
Vital signs (mean±SD)				
Systolic blood pressure, mmHg	124±28.7	124.3±28.2	124±28.9	0.872
Heart rate, beats/min	71±17.3	72.5±17.8	70.5±17.1	0.107
Respiratory rate, cycles/min	22.5±5.3	22±4.4	22.6±5.6	0.109
Body temperature, °C	37.1±0.76	37.1±0.76	37.1±0.76	0.946
Laboratory data, mean±SD				
White blood cell count, ×10³/mm³	12.4±7	12±6.2	12.5±7.3	0.263
Hemoglobin, g/dL	11.1±2	11±2.1	11.1±1.9	0.368
Platelet, ×10³/mm³	224.7±109.2	231.8±106.9	222.1±110	0.207
Blood urea nitrogen, mg/dL	27.1±18.3	25.5±17	27.6±18.7	0.106
Creatinine, mg/dL	1.4±1.5	1.6±1.7	1.3±1.3	0.021
Glucose, mg/dL	158±77.1	166±85.9	155±73.3	0.039
Albumin, g/dL	3.2±0.7	3.3±0.7	3.2±0.6	0.1
C-reactive protein, mg/dL	145.5±96.7	145.9±101.1	145.4±95.1	0.939
Sodium, mEq/L	135.5±6.5	135.6±5.6	135.4±6.8	0.697
Potassium, mEq/L	4.1±0.6	4.1±0.7	4.1±0.6	0.574
pH	7.4±0.1	7.4±0.1	7.4±0.1	0.158
pO₂, mmHg	82.1±30.5	80±28.5	82.9±31.3	0.192
Pleural effusion on chest X-ray, N (%)	505±50.2	123±44.5	382±52.3	0.028
Pneumonia classifications				
Community-acquired pneumonia, N (%)	487 (48.9)	135 (48.9)	352 (48.2%)	0.438
Health care-associated pneumonia, N (%)	293 (29.1)	86 (31.1)	207 (28.3)	
Hospital-acquired pneumonia, N (%)	226 (22.4)	55 (19.9)	171 (23.4)	
Sepsis classifications, N (%)				
No-sepsis	780 (77.5)	216 (78.2)	564 (77.2)	0.907
Sepsis	72 (7.1)	20 (7.2)	52 (7.1)	
Septic shock	154 (15.3)	40 (14.4)	114 (15.6)	
Pneumonia severity index (PSI), N (%)				
Risk class I or II	18 (1.8)	4 (1.5)	13 (1.9)	<0.001
Risk class III	121 (12.9)	46 (18.2)	75 (10.9)	
Risk class IV	451 (48)	128 (50.7)	323 (47)	
Risk class V	349 (37.2)	74 (29.3)	275 (40)	
Mean PSI score (mean±SD)	123.6±31.8	117.3±30.1	125.9±31.2	<0.001
CURB-65 criteria score, N (%)				
0	11 (1.1)	1 (0.3)	10 (1.3)	<0.001

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Table 1. Baseline characteristics of defoliant group and non-defoliant group

	Total (N=1,006)	Defoliant group (N=276)	Non-defoliant group (N=730)	*p*-value*
1	285 (28.4)	101 (36.7)	184 (25.3)	
2	433 (43.2)	117 (42.5)	316 (43.3)	
3	203 (20.2)	44 (16)	159 (21.9)	
4	60 (5.9)	10 (3.6)	50 (6.8)	
5	9 (0.9)	2 (0.7)	7 (0.9)	
Mean CURB-65 (mean±SD)	2±0.9	1.8±0.8	2.1±0.9	0.0006
In hospital mortality N (%)	339 (33.8%)	83 (30.4)	256 (35)	0.164
30 day mortality, N (%)	260 (25.8)	65 (23.5)	195 (26.7)	0.307

* Univariate analysis of defoliant group and non-defoliant group.

† Standard deviation.

Continuous variables are presented as the mean with standard deviations and compared with the student T test.

Categorical data are presented as number (%) of patients and analyzed using the x^2 or Fisher exact test.

during the study period. We were unable to investigate the therapeutic results in 17 patients, therefore 1,006 patients were included in the final study population (Fig. 1). Table 1 presents the baseline characteristics of the enrolled patients and compares the clinical information of the defoliant-exposed and non-defoliant-exposed groups using univariate analyses. The mean age ± SD of the enrolled patients was 79.2 ±0.2 years, and 99.4% were men. The crude 30-day mortality was 25.8% and mortality was not significantly different in the two groups. There were 276 patients who had been exposed to AO, while 730 had not been exposed. The prevalence of DM, HTN, CKD, CVA, and malignancy were higher in the defoliant-exposed group, although the defoliant-exposed group was significantly younger. The two groups were not significantly different on initial vital signs. With respect to the laboratory data, creatinine and glucose concentrations were greater in the defoliant-exposed group and pleural effusion was more frequently diagnosed in the non-defoliant group. The number of patients who were classified as having sepsis or septic shock were not significantly different between the groups. In terms of pneumonia classification, the proportion of patients with CAP, HACP, or HAP were not different between the two groups. According to PSI and CURB65, disease severity was higher in the non-defoliant group (*p*<0.001).

In univariate analyses comparing the survival and non-survival groups, the following variables were significantly associated with 30-day mortality: age, DM, HTN, malignancy, bedridden status, vital signs (SBP, HR, RR, and BT), laboratory data (WBC, Hb, BUN, glucose, albumin, and pH). These factors were candidate variables for the multivariate analyses (Table 2). We performed multivariate logistic regression analyses with candidate variables and defoliant exposure history. Factors positively associated with 30-day mortality were malignancy, RR, BUN, and albumin which was negatively associated with mortality (Table 3). As a primary outcome, defoliant exposure history was not associated with 30-day mortality in patients with pneumonia. Defoliant exposure was associated with greater prevalence of DM, HTN, CVA, malignancy, and CKD.

DISCUSSION

The AO used in Vietnam caused sequelae in numerous Vietnam veterans. In 2007, the government of the Republic of Korea enacted a law requiring compensation and treatment for defoliant complications. Based on the provisions of this law, the Korean government has supported veterans who participated in the military campaign in Vietnam and citizens who worked in areas contaminated by AO. In Korea, the following 20 diseases are recognized as sequelae of defoliant intoxication: non-Hodgkin lymphoma, soft tissue sarcoma, chloracne, peripheral neuropathy, porphyria cutanea tarda, Hodgkin's disease, lung cancer,

laryngeal cancer, bronchial cancer, multiple myeloma, prostate cancer, Buerger's disease, diabetes mellitus, B cell chronic lymphocytic leukemia, chronic myelogenous leukemia, Parkinson's disease, ischemic heart disease, amyloid light-chain amyloidosis, salivary gland cancer, and gall bladder cancer. The following diseases are recognized as suspected complications of defoliant exposure: photodermatitis, psoriasis, seborrheic dermatitis, chronic urticaria, xerotic eczema, central nervous system diseases, cerebral infarction, multiple sclerosis, amyotrophic lateral sclerosis, myopathy, malignant neoplasms, liver disease, hypothyroidism, hypertension, cerebral hemorrhage, arteriosclerosis, and hyperlipidemia.

In our study, the defoliant-exposed group of veterans was younger than the non-exposed veterans. This result reflects the Vietnam War having been the last war in which the Korean army participated (1961-1971).

Table 2. Univariate analysis of 30-day survival and non-survival group

	30-day survival (N=746)	Non-survival (N=260)	p-value*
Epidemiological data			
Age (mean±SD[†])	78.6±8.4	81.1±7.7	<0.001
Male, N (%)	742 (99.4)	258 (99.2)	0.674
Diabetes mellitus, N (%)	290 (38.8)	80 (30.7)	0.02
Hypertension, N (%)	474 (63.5)	140 (53.8)	0.006
Chronic lung disease, N (%)	179 (23.9)	52 (20)	0.187
Chronic liver disease, N (%)	8 (1)	5 (1.9)	0.296
Congestive heart failure, N (%)	23 (3)	10 (3.8)	0.552
Chronic kidney disease, N (%)	89 (11.9)	28 (10.7)	0.615
Cerebrovascular accident, N (%)	209 (28)	62 (23.8)	0.192
Malignancy, N (%)	133 (17.8)	89 (34.2)	<0.001
History of tuberculosis, N (%)	113 (15.1)	35 (13.4)	0.509
Nursing home resident, N (%)	57 (7.6)	29 (11.1)	0.081
bed ridden status, N (%)	146 (19.5)	66 (25.3)	0.048
Vital signs (mean±SD)			
Systolic blood pressure, mmHg	126.9±28	115.8±29.1	<0.001
Heart rate, beats/min	72.4±16.7	67.1±18.2	<0.001
Respiratory rate, cycles/min	22±4.3	24±7.2	<0.001
Body temperature, °C	37.2±0.7	37±0.6	<0.001
Laboratory data, mean±SD			
White blood cell count, ×10³ mm³	12.3±6.8	12.5±11.6	0.734
Hemoglobin, g/dL	11.2±2	10.6±1.9	<0.001
Platelet, ×10³/mm³	225.6±105.4	222.3±119.6	0.683
Blood urea nitrogen, mg/dL	24.9±16.9	33.2±20.8	<0.001
Creatinine, mg/dL	1.4±1.5	1.4±1.3	0.871
Glucose, mg/dL	162±79.4	146±69	0.006
Albumin, g/dL	3.3±0.7	2.9±0.6	<0.001
C-reactive protein, mg/dL	142.4±98.3	154.4±91.7	0.085
Sodium, mEq/L	135.3±6.1	136.1±7.3	0.069
Potassium, mEq/L	4.1±0.6	4.1±0.8	0.148
pH	7.43±0.06	7.41±0.16	0.003
pO₂, mmHg	82±29.3	82.4±33.8	0.889
Pleural effusion on chest X-ray, N (%)	340 (45.5)	165 (63.4)	<0.001
Defoliant, N (%)	211 (28.2)	65 (25)	0.841

* Univariate analysis of 30 day survival and non-survival group.
[†] Standard deviation.
Continuous variables are presented as the mean with standard deviations and compared with the student T test.
Categorical data are presented as number (%) of patients and analyzed using the x^2 or Fisher exact test.

Table 3. Multivariate logistic regression analysis

	Adjusted OR*	95% CI[+]
Epidemiological data		
Age (years)	1.02	0.98-1.06
Diabetes mellitus	0.65	0.33-1.29
Hypertension	0.59	0.33-1.07
Malignancy	2.26	1.18-4.32
bed ridden status	0.57	0.57-1.19
Vital signs		
Systolic blood pressure, mmHg	0.98	0.96-1.01
Heart rate, beats/min	1.01	0.98-1.03
Respiratory rate, cycles/min	1.05	1.01-1.10
Body temperature, °C	0.63	0.4-1.01
Laboratory data, mean±SD		
White blood cell count, $\times 10^3$ mm³	1.01	0.95-1.04
Hemoglobin, g/dL	0.97	0.83-1.14
Blood urea nitrogen, mg/dL	1.01	1.01-1.03
Glucose, mg/dL	0.99	0.99-1.01
Albumin, g/dL	0.63	0.40-0.98
pH	0.07	0.01-2.2
Pleural effusion, N (%)	1.62	0.89-2.96
Defoliant	1.41	0.62-3.18

* Odds ratio

[+] Confidence interval

Although Vietnam veterans were younger, the prevalence of DM, HTN, CKD, CVA, and malignancy were greater in Vietnam veterans. In Korea, all of these diseases, except CKD, are recognized as complications of defoliant exposure. Further study of the associations between defoliant exposure and CKD is needed. In the defoliant-exposed group, serum creatinine, and blood glucose concentrations were greater than in the non-defoliant-exposed group. These results may have been related to the greater prevalence of CKD and DM in the defoliant-exposed group (Table 1)[10].

Most previous studies of the adverse effects of AO exposure have addressed chronic diseases, and studies of associations with acute diseases requiring critical care are lacking. Given pneumonia has been the leading cause of death in Vietnam veterans in our ED, we aimed to investigate whether defoliant exposure affected the course of pneumonia. This study was the first to investigate associations between historical defoliant exposure and therapeutic outcomes of pneumonia. Although we were unable to demonstrate clear associations between pneumonia and AO exposure, we will continue to investigate the influence of historical AO exposure on current acute disease.

In our study, clinical factors associated with 30-day mortality were malignancy, high RR, high BUN, and low albumin. In previous studies, these factors were found to be significant predictors of a poor prognosis in pneumonia[21,22]. Our study population consisted of elderly patients with an average age of 79 years and a 30-day mortality rate of 25.8%. The analyses indicated that malignancy, high RR, high BUN, and low albumin could be good predictors for mortality in elderly patients.

This study has several limitations. First, because the degree of defoliant exposure was not investigated, we couldn't investigate dose-response relationships for defoliant exposure. Second, the percentage of men among the enrolled patients was high, because almost all Korean veterans were male. Therefore, we could not determine if sex influenced the therapeutic results. Third, potential biases may have been introduced because of the retrospective nature of the study.

CONCLUSION

In conclusion, historical defoliant exposure was not associated with 30-day mortality due to pneumonia. Defoliant exposure was associated with high prevalence of DM, HTN, CVA, malignancy, and CKD.

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REFERENCES

1. Kang HK, Dalager NA, Needham LL, et al. Health status of Army Chemical Corps Vietnam veterans who sprayed defoliant in Vietnam. Am J Ind Med 2006;49:875-84.

2. Boehmer TK, Flanders WD, McGeehin MA, et al. Postservice mortality in Vietnam veterans: 30-year follow-up. Arch Intern Med 2004;164:1908-16.

3. Cypel Y, Kang H. Mortality patterns of Army Chemical Corps veterans who were occupationally exposed to herbicides in Vietnam. Ann Epidemiol 2010;20:339-46.

4. Dalager NA, Kang HK. Mortality among Army Chemical Corps Vietnam veterans. Am J Ind Med 1997;31:719-26.

5. Ketchum NS, Michalek JE. Postservice mortality of Air Force veterans occupationally exposed to herbicides during the Vietnam War: 20-year follow-up results. Mil Med 2005; 170:406-13.

6. McBride D, Cox B, Broughton J, et al. The mortality and cancer experience of New Zealand Vietnam war veterans: a cohort study. BMJ Open 2013;3:e003379.

7. Michalek JE, Ketchum NS, Akhtar FZ. Postservice mortality of US Air Force veterans occupationally exposed to herbicides in Vietnam: 15-year follow-up. Am J Epidemiol 1998;148:786-92.

8. Visintainer PF, Barone M, McGee H, et al. Proportionate mortality study of Vietnam-era veterans of Michigan. J Occup Environ Med 1995;37:423-8.

9. Watanabe KK, Kang HK. Military service in Vietnam and the risk of death from trauma and selected cancers. Ann Epidemiol 1995;5:407-12.

10. Yi SW, Ryu SY, Ohrr H, et al. Agent Orange exposure and risk of death in Korean Vietnam veterans: Korean Veterans Health Study. Int J Epidemiol 2014;43:1825-34.

11. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997;336:243-50.

12. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44:27-72.

13. Jackson ML, Neuzil KM, Thompson WW, et al. The burden of community-acquired pneumonia in seniors: results of a population-based study. Clin Infect Dis 2004;39:1642-50.

14. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997;336:243-50.

15. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003;58:377-82.

16. Tablan OC, Anderson LJ, Besser R, et al. Guidelines for preventing health-care--associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. MMWR Recomm Rep 2004; 53:1-36.

17. Niederman MS. Guidelines for the management of respiratory infection: why do we need them, how should they be developed, and can they be useful? Curr Opin Pulm Med 1996; 2:161-5.

18. American Thoracic S, Infectious Diseases Society of A. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388-416.

19. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med 2017; 43:304-77.

20. Moses T, Holland PW. A comparison of statistical selection strategies for univariate and bivariate log-linear models. Br J Math Stat Psychol 2010;63:557-74.

21. Bello S, Fandos S, Lasierra AB, et al. Red blood cell distribution width [RDW] and long-term mortality after community-acquired pneumonia. A comparison with proadrenomedullin. Respir Med 2015;109:1193-206.

22. Lee J, Kim K, Jo YH, et al. Severe thinness is associated with mortality in patients with community-acquired pneumonia: a prospective observational study. Am J Emerg Med 2015;33:209-13.