

# Serial C1 Inhibitor Levels in Patients with Ventilator-Associated Pneumonia: A Prospective Observational Study

Gurhan TASKIN<sup>1</sup>, Ali SELCUK<sup>2</sup>, Serhat UYSAL<sup>3</sup>

<sup>1</sup>University of Health Sciences, Trabzon Kanuni Training and Research Hospital, Department of Intensive Care, Trabzon, Turkey

<sup>2</sup>University of Health Sciences, Regional Training and Research Hospital, Department of Immunology and Allergic Diseases, Erzurum, Turkey

<sup>3</sup>University of Health Sciences, Trabzon Kanuni Training and Research Hospital, Department of Infectious Disease and Clinical Microbiology, Trabzon, Turkey

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**Corresponding Author:** Gurhan Taskin  
**E mail:** drgurhantaskin@gmail.com

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## ABSTRACT

**Objective:** C1-inhibitor (C1-INH), an acute-phase protein, regulates the activation of the complement cascade and acts as a down-regulator of the inflammatory process. In experimental models, it was shown that pneumonia with mechanical ventilation is associated with an increase of complement activation in the lungs. The primary aim of this study was to evaluate the serial changes of C1-INH levels in patients with ventilator-associated pneumonia (VAP).

**Methods:** Twelve patients were included in this prospective and observational study conducted between June 2018 and February 2019. Blood samples for C1-INH levels were obtained at the time of VAP diagnosis and on the 2<sup>nd</sup>, 4<sup>th</sup>, and 6<sup>th</sup> days following diagnosis (total of 48 samplings). At the time of C1-INH sampling, patients were screened for clinical pulmonary infection score, arterial blood gas analysis, mechanical ventilation parameters, complete blood count, C-reactive protein, procalcitonin levels, and other routine laboratory tests.

**Results:** No differences were found between surviving (n=7) and non-surviving (n=5) patients in terms of C1-INH levels at any measurement time (days 0, 2, 4 and 6) (p=0.982, p=0.677, p=0.790, p=0.930, respectively). VAP patients with septic shock had higher C1-INH levels than patients without shock, on the days following the diagnosis. C1-INH levels significantly correlated with concurrently measured white blood cell (R<sup>2</sup>=0.095, p=0.030), lactate (R<sup>2</sup>=0.109, p=0.012), procalcitonin (R<sup>2</sup>=0.120, p=0.009), alanine aminotransferase (R<sup>2</sup>=0.179, p=0.002) levels, and PaO<sub>2</sub> / FiO<sub>2</sub> ratio (R<sup>2</sup>=0.091, p=0.022).

**Conclusion:** Serial monitoring of C1-INH levels may aid in prediction of prognosis in the early phase of VAP patients, especially those accompanied by septic shock.

**Keywords:** C1 inhibitor, ventilator-associated pneumonia, sepsis, septic shock, prognosis

## Introduction

To date, some laboratory and clinical parameters have been studied as predictors of prognosis and indicators of treatment response in patients with ventilator-associated pneumonia (VAP) (1-4). But, the prognostic value of these parameters is still controversial. In order to predict the prognosis of VAP, biological markers that can be used, especially in the early stage of the disease, are still needed.

C1-inhibitor (C1-INH), an acute-phase protein, regulates the activation of the complement cascade by inhibiting the classical and lectin pathway, and acts as a down-regulator of the inflammatory process (5, 6). As the synthesis of C1-INH fails to meet the demand relatively during inflammation, complement activation may progress to an excessive response (7, 8).

Therefore, increased complement activation in the lung may also cause additional lung damage in patients with VAP. To date, C1-INH has not been evaluated as a prognostic biomarker during a culture-proven VAP episode.

The main purpose of this prospective study was to evaluate the serial change of C1-INH levels in VAP prognosis.

## Materials and Methods

### Ethics approval and informed volunteer consent

This single-center, prospective and observational study was conducted in a 10-bed adult intensive care unit (ICU) of Trabzon Kanuni Training and Research Hospital, from June 2018 to February 2019. The study was conducted in accordance

with the Declaration of Helsinki, and ethical approval was obtained from the local Ethics Committee of Clinical Trials (09 May 2018, Approval No.: 2018-20). The legal representatives of patients deemed eligible to be included in the study, or first-degree relatives in the case of the absence of a legal representative, were fully informed about the study. Those who agreed to the patient's participation completed the informed consent form before the patient was enrolled in the study.

### Diagnosis of VAP

VAP refers to pneumonia that develops at least 2 days after endotracheal intubation (9, 10). In these patients, the following criteria were used for diagnosis: VAP was regarded as possible if new or progressive radiographic lung infiltrates with at least two of the three following features: fever  $\geq 38^{\circ}\text{C}$  or hypothermia  $<36^{\circ}\text{C}$ , leukocytes  $\geq 12,000/\text{mm}^3$  or  $\leq 4,000/\text{mm}^3$ , or new/increased purulent endotracheal secretions ( $>25$  neutrophils and  $<10$  squamous epithelial cells [x100]) (9, 10). Quantitative culture of deep endotracheal aspirate results with  $\geq 10^5$  colony forming units (CFU)/mL was used to confirm VAP diagnosis (10). Patients diagnosed with VAP in the first 4 days of mechanical ventilation (MV) were defined as early-onset VAP, and those diagnosed with VAP on the 5<sup>th</sup> day or later were defined as late-onset VAP (9, 10).

### Study design and data collection

Patients under 18 years of age, patients with known hepatic disease or transaminase levels  $\geq 3$ -fold higher than normal, patients with hereditary angioedema, patients with hypocomplementemia, and pregnant patients were excluded from the study. Two milliliters of venous blood samples were obtained from the included patients at the time of VAP diagnosis (day 0) and on the 2<sup>nd</sup>, 4<sup>th</sup>, and 6<sup>th</sup> days after diagnosis. After centrifugation at 1500 rpm for 15 minutes, serum was separated and stored at  $-20^{\circ}\text{C}$  until the C1-INH level was studied. Quantitative levels of serum C1-INH were studied by a nephelometric method in Siemens BN Prospec (Siemens Healthcare Diagnostics, Erlangen, Germany). At the same time as blood sampling for C1-INH measurement (days 0, 2, 4, and 6), complete blood count (CBC), C reactive protein (CRP), procalcitonin, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), serum creatinine levels, erythrocyte sedimentation rate (ESR), arterial blood gas analysis (pH, lactate, partial arterial oxygen pressure [ $\text{PaO}_2$ ]), MV parameters (fraction of inspired oxygen [ $\text{FiO}_2$ ], positive end-expiratory pressure [PEEP]), and clinical pulmonary infection score (CPIS) were recorded prospectively. Each patient's age, sex, primary diagnosis at ICU admission, comorbid diseases, deep endotracheal aspirate culture results, length of ICU stay before VAP, duration of MV before VAP, mortality at 28<sup>th</sup> day following VAP diagnosis, and the date of death were recorded prospectively. Acute Physiology and Chronic Health Assessment II (APACHE II) scores calculated within the first 24 hours after ICU admission were recorded. The presence of sepsis and septic shock was investigated using the Sepsis-3 definitions during the study period (11). Bacteria found to be resistant to at least 1 antibiotic from 3 different antibiotic groups in a susceptibility test of deep endotracheal aspirate culture were identified as multidrug-resistant (MDR) bacteria (12).

### Statistical analysis

The mean (standard deviation) was used to represent parametric continuous variables, and the median (minimum–maximum) was used to represent nonparametric variables. Kolmogorov–Smirnov test, skewness and kurtosis coefficients, and histogram graphs were used to differentiate parametric and nonparametric variables from continuous data of the patients. Ante-study analysis to reach 70% power calculated that at least 10 samples were needed; post-study power analysis was not applied. The Student's t-test (independent t-test) was used for parametric variables and Mann–Whitney U-test was used for nonparametric variables. We performed simple linear regression analysis to assess correlations.  $p < .05$  was considered statistically significant. The data analysis was done using Statistical Package for Social Sciences (SPSS) version 15.

### Results

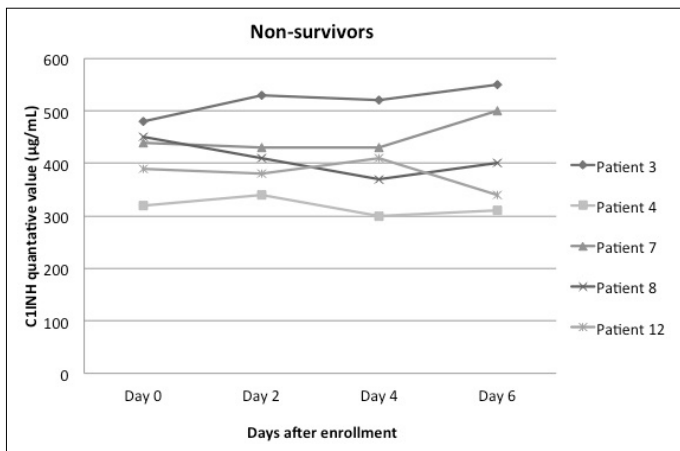
Between June 2018 and February 2019, a total of 12 VAP patients, 7 of whom were women, were included in the study. The mean age of the included patients was  $73.6 \pm 14.6$  years. The median APACHE II score of the patients was 26 (min. 17–max. 35). Comorbidities observed were cerebrovascular disease (CVD) in 6 patients (50%), non-hematologic malignancy in 4 (33.3%), chronic obstructive pulmonary disease (COPD) in 4 (33.3%), diabetes mellitus (DM) in 3 (25%), congestive heart failure (CHF) in 3 (25%), and chronic renal failure (CRF) in 2 (16.7%). The median length of ICU stay before VAP was 15.5 days (min. 6–max. 65) and the median duration of MV before VAP was 10 days (min. 6–max. 51).

All included patients (100%) had late-onset VAP. Gram-negative bacilli (GNB) were dominant among the microorganisms found to be the causative pathogen. In seven patients (58.3%), the causative microorganism of VAP was MDR bacterium. The demographic, microbiologic, and clinical characteristics of VAP patients are shown in Table 1.

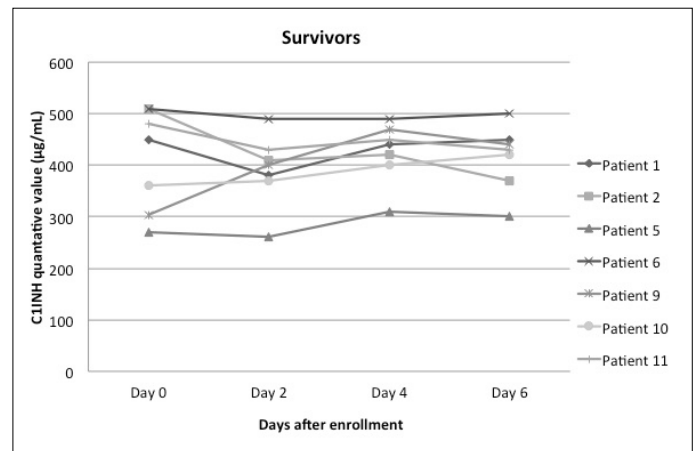
The 28-day mortality was seen in 5 patients (41.6%). No difference was found between surviving and non-surviving patients, in terms of C1-INH levels at any measurement time (days 0, 2, 4, and 6) ( $p = 0.982$ ,  $p = 0.677$ ,  $p = 0.790$ ,  $p = 0.930$ , respectively) (Table 2). The curves of the serial values of C1-INH for all patients (survivors and non-survivors) showed at Figure 1. In the study period, all patients (100 %) had sepsis, and 4 (33.3 %) of them had septic shock concurrent with VAP. Patients with septic shock had higher C1-INH levels than those with not, especially on days after diagnosis (Figure 2). However, the difference was not statistically significant (days 0, 2, 4, and 6) ( $p = 0.864$ ,  $p = 0.798$ ,  $p = 0.396$ ,  $p = 0.734$ , respectively). Three (75 %) of VAP patients with concurrent septic shock died.

No statistically significant difference was found between the surviving and non-surviving patients with respect to their age, sex, hospital stay before ICU admission, ICU stay and MV days before diagnosis, and comorbidities.

The correlation analysis between clinical parameters, laboratory findings and concurrently measured C1-INH levels in VAP



**Figure 1A.** Serial change of C1-inhibitor levels of survived ventilator-associated pneumonia patients. C1-INH; C1-inhibitor.



**Figure 1B.** Serial change of C1-inhibitor levels of non-survived ventilator-associated pneumonia patients. C1-INH; C1-inhibitor.

**Table 1.** Demographic, microbiologic and clinical characteristics of patients.

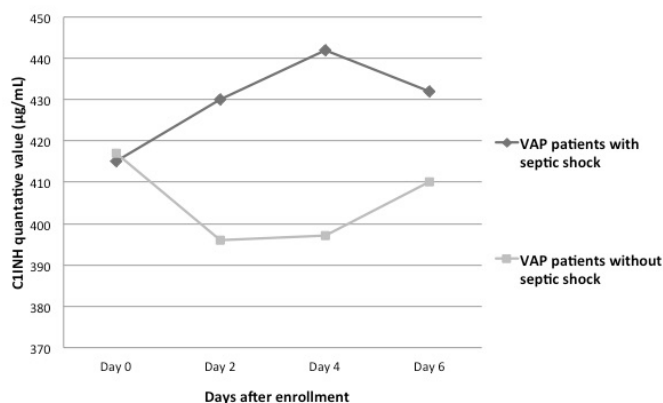
Patient No.	Age (years)	Sex	APACHE II score	Diagnosis at ICU admission	Comorbidities	Length of ICU stay before VAP (days)	Length of MV before VAP (days)	Microorganisms identified as VAP causative pathogens	28-day mortality
1	89	F	33	Sepsis, AKI	None	29	9	<i>Acinetobacter iwoffii</i>	Survive
2	76	F	29	Sepsis	DM, CVD	15	6	<i>Escherichia coli</i> <i>Pseudomonas aeruginosa</i>	Survive
3	35	M	29	Sepsis, pneumonia	Malignancy (Sarcoma)	34	34	<i>Escherichia coli</i>	Dead
4	82	M	24	Pneumonia	CVD, COPD, Malignancy (Lung Cancer)	7	7	<i>Klebsiella pneumoniae</i> <i>Acinetobacter baumannii</i>	Dead
5	70	M	35	Cardiac arrest	CHF, CVD, COPD, Malignancy (Lung Cancer)	9	9	<i>Pseudomonas aeruginosa</i>	Survive
6	64	F	31	Stroke	DM, COPD	65	15	<i>Acinetobacter baumannii</i> <i>Pseudomonas aeruginosa</i>	Survive
7	84	F	22	Intracerebral hemorrhage	HT, CVD	16	16	<i>Pseudomonas aeruginosa</i>	Dead
8	76	M	20	Sepsis, pneumonia, AKI	CHF, malignancy (prostate carcinoma)	51	51	<i>Acinetobacter baumannii</i> <i>Pseudomonas aeruginosa</i>	Dead
9	81	F	23	Acute pulmonary edema	CHF, DM, CVD	6	6	<i>Staphylococcus aureus</i>	Survive
10	65	M	17	Pneumonia	COPD	11	11	<i>Stenotrophomonas maltophilia</i>	Survive
11	73	F	28	Sepsis, Pneumonia	CRF, CVD	14	14	<i>Pseudomonas aeruginosa</i>	Survive
12	88	F	19	Pneumonia, AKI	CRF, HT	16	9	<i>Delftia acidovorans</i>	Dead

VAP, ventilator-associated pneumonia; APACHE II, Acute Physiology and Chronic Health Evaluation II; F, female; M, male; ICU, intensive care unit; MV, mechanical ventilation; AKI, acute kidney injury; DM, diabetes mellitus; CVD, cerebrovascular disease; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; HT, hypertension; CRF, chronic renal failure.

**Table 2.** Comparison of serial changes of C1-inhibitor levels between survivors and non-survivors in ventilator-associated pneumonia patients.

C1-INH levels	Survivors n=7 (58.3 %)	Non-survivors n=5 (41.7 %)	p value
Day 0, µg/mL	417.1 ± 94.1	416.0 ± 62.6	0.982
Day 2, µg/mL	400.0 ± 72.1	418.0 ± 71.2	0.677
Day 4, µg/mL	417.1 ± 61.0	406.0 ± 80.8	0.790
Day 6, µg/mL	415.7 ± 63.9	420.0 ± 102.7	0.930

C1-INH, C1 inhibitor.

**Figure 2.** Comparison of the serial change of C1-inhibitor levels in ventilator-associated pneumonia patients according to the presence of septic shock. C1-INH; C1-inhibitor, VAP; ventilator-associated pneumonia.**Table 3.** Correlation analysis between clinical and laboratory parameters and C1-inhibitor levels in ventilator-associated pneumonia patients.

Variables	Adjusted R <sup>2</sup> (square)	Standardized Coefficient	95% Confidence interval for Beta		p value
			Beta	Lower	
WBC, /mm <sup>3</sup>	0.095	0.344	5.83x10 <sup>-7</sup>	106x10 <sup>-7</sup>	.030*
Lactate, mmol/L	0.109	0.358	5x10 <sup>-3</sup>	38x10 <sup>-3</sup>	.012*
Procalcitonin, ng/mL	0.120	0.372	4.9x10 <sup>-4</sup>	32.76x10 <sup>-4</sup>	.009*
ALT, U/L	0.179	-0.443	-16x10 <sup>-4</sup>	-4x10 <sup>-4</sup>	.002*
PaO <sub>2</sub> /FiO <sub>2</sub> ratio	0.091	-0.333	-63x10 <sup>-5</sup>	-5x10 <sup>-5</sup>	.022*
CRP, mg/L	-	-	-	-	.223
ESR, mm/hr <sup>‡</sup>	-	-	-	-	.392
Albumin, g/dL	-	-	-	-	.459
pH	-	-	-	-	.693
PEEP, cmH <sub>2</sub> O	-	-	-	-	.936
AST, U/L	-	-	-	-	.852
Creatinine, mg/dL	-	-	-	-	.688
BUN, mg/dL	-	-	-	-	.628
APACHE II score	-	-	-	-	.603
CPIS	-	-	-	-	.275

C1-INH, C1 inhibitor; WBC, white blood cell; ALT, alanine aminotransferase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PEEP, positive end-expiratory pressure; AST, aspartate aminotransferase; PaO<sub>2</sub>, partial pressure of arterial oxygen; FiO<sub>2</sub>, fraction of inspired oxygen; BUN, blood urea nitrogen; APACHE II, acute physiology and chronic health evaluation II; VAP, ventilator-associated pneumonia; CPIS, clinic pulmonary infection score.

<sup>‡</sup>A total of sixteen results of ESR measurements were excluded from the analysis due to the fact that they were obviously incorrect due to calibration problems occurring on different machines.

\*= p<0.05

patients is shown in Table 3. Despite R<sup>2</sup> values of correlations were not high, significant correlations were found between the concurrently measured C1-INH level and the levels of white blood cell (WBC) (R<sup>2</sup> = 0.095, p = 0.030), lactate (R<sup>2</sup> = 0.109, p = 0.012), procalcitonin (R<sup>2</sup> = 0.120, p = 0.009), ALT (R<sup>2</sup> = 0.179, p = 0.002), and PaO<sub>2</sub> / FiO<sub>2</sub> ratio (R<sup>2</sup> = 0.091, p = 0.022). A total of sixteen results of ESR measurements were excluded from the analysis due to the fact that they were obviously incorrect due to calibration problems occurring on different machines. There was no correlation between C1-INH levels and levels of CRP (p = 0.223), ESR (p = 0.392), albumin (p = 0.459), pH (p = 0.693), PEEP (p = 0.936), AST (p = 0.852), creatinine (p = 0.688), BUN (p = 0.628), APACHE II score (p = 0.603), and CPIS (p = 0.275).

## Discussion

In this study, it was shown that the serial change of C1-INH levels did not differ between survivor and non-survivor groups in VAP patients. In our study, patients with septic shock had higher C1-INH trends in days following the diagnosis than with not. Furthermore, C1-INH levels had correlations with still in use and noteworthy prognostic parameters such as levels of procalcitonin, lactate and PaO<sub>2</sub> / FiO<sub>2</sub> ratio. To our knowledge, this is the first study reporting prognostic evaluation of C1-INH levels in patients with VAP. In addition, serial monitoring of C1-INH levels was performed for the first time in these patients. In animal models, it was shown that MV with pneumonia is associated with an

increase of the classical and/or lectin complement activation in the lungs (13). Furthermore, in human studies, excessive activation of complement has been shown to be related with progress in lung injury (14-16). So that, we hypothesized that serial monitoring of C1-INH levels may have a prognostic significance in VAP patients. Although, no statistically significant difference was found between surviving and non-surviving VAP patients, our study indicates some considerable findings about possible prognostic role of C1-INH levels in VAP patients. In our study, it was shown that increased complement activation via enhanced inflammation could cause remarkable changes in the C1-INH levels, especially in cases accompanied by septic shock. Activation of the complement system as part of the inflammatory response in patients with sepsis is a known mechanism (17). The complement system regulator C1-INH also increases in order to prevent excessive activation (18). In many experimental and animal studies, the treatment of C1-INH concentrates on sepsis has been reported to decrease vascular permeability, improve microcirculation, and even increase survival (19-21). On the other hand, Tapisiz et al. reported that functional C1-INH levels did not differ between septic newborns and controls. Additionally, they found no difference between newborns with sepsis and severe sepsis and septic shock in terms of C1-INH levels (22). In our study, although not shown statistical significance, shock patients' C1-INH levels were higher than sepsis patients ( $430.0 \pm 67.8$  vs.  $396.3 \pm 71.3$ ,  $442.5 \pm 66.0$  vs.  $397.5 \pm 65.8$ ,  $432.5 \pm 88.4$  vs.  $410.0 \pm 77.4$ , on the 2<sup>nd</sup>, 4<sup>th</sup> and 6<sup>th</sup> days after diagnosis, respectively). That might be due to small sample size of our study, larger sample calculations would give more convincing results. About half of patients with VAP are accompanied by septic shock and septic shock is the one of the significant independent risk factors for mortality in VAP patients (23). Additionally, as confirming this relationship, in our study, a significant correlation was found between C1-INH and lactate levels, whose prognostic value for septic shock is well-known. Lactate is an important metabolic marker that shows tissue hypoperfusion and deterioration in microcirculation, and indicates morbidity and mortality in most of critically ill patients (24). Since high lactate levels are thought to reflect the presence and severity of organ dysfunction, it is considered as a sign of circulatory impairment and shock (24-26). The positive correlation between simultaneously measured C1-INH and lactate levels revealed in our study, suggests that C1-INH levels may be useful in predicting septic shock severity and consequently mortality in VAP patients.

To date, many studies have evaluated the potential of infection biomarker procalcitonin to improve the diagnostic efficacy of patients with sepsis or pneumonia and its impact on decisions regarding antibiotic therapy (27-30). Also, it has been showed to be associated with severity of pneumonia (31). Additionally, procalcitonin is thought to have substantial prognostic value in VAP patients. Previously, Luyt et al., evaluating procalcitonin kinetics in patients with VAP, reported that a procalcitonin value greater than 0.5 ng/mL on day 7 of diagnosis was the strongest independent prognostic marker that could predict death and VAP recurrence (4). In another study, Seligman et al. reported that procalcitonin levels on the 4<sup>th</sup> day of diagnosis had the highest positive and negative predictive value of VAP mortality (32). In addition, Hillas et al. reported that changes in procalcitonin levels were significantly correlated in predicting survival in VAP

patients (33). In the current study, C1-INH levels shown to be correlated with two important infectious inflammatory markers—procalcitonin and WBC.

Crude mortality in critically ill patients with VAP has been reported as ranging from 25% to 70% (34-36). Due to an increase in the frequency of MDR pathogens related nosocomial infections, late-onset VAP has higher mortality rates than early-onset VAP (37). In this study, the 28-day mortality rate was 41.6% in critically ill patients with late-onset VAP, and more than half of them (58%) had MDR pathogen caused VAP. Therefore, it can be stated that the mortality rate observed in our study is consistent with the literature data.

Another noteworthy finding of this study is the significant negative correlation between C1-INH level and PaO<sub>2</sub>/FiO<sub>2</sub> ratio, which are thought to be an objective indicator of oxygenation. The PaO<sub>2</sub>/FiO<sub>2</sub> ratio in patients with VAP has been shown to be an important clinical parameter, in terms of clinical outcomes, in some studies (3, 4). A retrospective study by Esperatti et al. including 335 patients, reported that lack of improvement in PaO<sub>2</sub>/FiO<sub>2</sub> ratios within 5 days following the diagnosis of VAP is a strong indicator of mortality (38). An increase in C1-INH levels may indicate an augmentation in the activation of the complement system and thus an exacerbation of inflammation and deterioration in oxygenation. We think these findings suggest that C1-INH levels have a prognostic role in VAP patients.

Although *in vivo* and *in vitro* studies have shown synthesis in many different cell types, hepatocytes are the major source for C1-INH synthesis (39). ALT is a proven biomarker of hepatocellular injury and is also used for follow-up (40). In our study, a negative correlation was found between C1-INH and ALT levels. This result may suggest that C1-INH levels have a linear relationship with hepatocyte functions.

We acknowledge that certain limitations of this study should be underlined. Firstly, our study population is relatively small; these results need to be confirmed in a larger study group. Secondly, in our study, included patients had relatively high APACHE II scores, prolonged ICU stay, and long-term MV requirement than previous studies in this field, and all patients had sepsis during VAP. Therefore, there may have been other factors we could not evaluate and that may have influenced the results.

## Conclusions

In this study; it was shown that the serial change of C1-INH did not differ between survivor and non-survivor groups. But our study provides useful information about VAP prognosis. In subgroup analysis, patients with septic shock had higher C1-INH trends in days following the diagnosis than with not. Furthermore, C1-INH levels had significant correlations with still in use and noteworthy prognostic parameters such as levels of procalcitonin, lactate and PaO<sub>2</sub>/FiO<sub>2</sub> ratio. We think that, further studies of the serial change of C1-INH levels in VAP patients with larger populations may lead to new topics in the prediction of prognosis and assessment of treatment response.

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**AUTHOR CONTRIBUTIONS:**

**Concept:** GT, AS; **Design:** GT, AS, SU; **Supervision:** GT, SU, AS; **Materials:** GT, SU; **Data Collection and/or Processing:** GT, SU, AS; **Analysis and/or Interpretation:** GT, AS, SU; **Literature Search:** GT, AS; **Writing Manuscript:** GT, AS; **Critical Review:** GT, AS, SU.

**Ethics Committee Approval:** Ethical approval was obtained from the Trabzon Kanuni Ethics Committee of Clinical Trials (09 May 2018, Approval No.: 2018-20).

**Informed Consent:** The legal representatives of patients deemed eligible to be included in the study, or first-degree relatives in the case of the absence of a legal representative, were fully informed about the study. Those who agreed to the patient's participation completed the informed consent form before the patient was enrolled in the study.

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**Conflict of Interest:** Authors have no conflicts of interest to declare.

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