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Prognostic Factors for Hospital Mortality and ICU Admission in Patients With ANCA-Related Pulmonary Vasculitis

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Abstract

Background—The objective of this study was to evaluate the factors predictive of 28-day mortality and admission to Intensive Care Unit (ICU) in patients with ANCA-related pulmonary vasculitis.

Methods—We reviewed the medical records and imaging studies of 65 patients diagnosed with ANCA-related vasculitis hospitalized with pulmonary complications between February 1985 and November 2002. All patients underwent open or video-assisted thoracoscopic lung biopsy, had a positive ANCA serology, and were negative for glomerular basement membrane antibodies.

Results—At presentation, 72% had dyspnea, 68% fever, 47% cough, 45% elevated blood pressure, 32.3% hemoptysis, 26.1% sinus involvement, 15% renal failure, and 4.6% scleritis. Pathological findings included alveolar hemorrhage (60%), granulomatous inflammation (46%), and capillaritis (38%). A significant number required mechanical ventilation (27.7%), hemodialysis (24.6%), continuous renal replacement therapy (3.1%), and plasmapheresis (3.1%). The 28-day mortality was 16.9% (11/65). Mechanical ventilation (OR 68, $P < 0.005$), admission to ICU (OR 18.5, $P < 0.01$), and blood transfusion (OR 22.4, $P < 0.004$) were strong predictors of increased mortality within 28 days after admission. Respiratory failure (OR 31, $P < 0.0007$), hemoptysis (OR 2.9, $P < 0.06$), smoking (OR 5.9, $P < 0.02$), and acute renal failure (OR 7.8, $P < 0.01$) were also predictors for admission to the ICU.

Conclusion—In patients with ANCA-related pulmonary vasculitis several clinical factors, but not pathologic findings or ANCA titers, are associated with ICU admission and/or 28-day mortality.

KEY INDEXING TERMS

ANCA; Pulmonary vasculitis; Mortality; Hospitalization; Predictive factors; Prognosis

Antineutrophil cytoplasmic antibodies (ANCA) are antibodies directed against neutrophil cytoplasmic antigens, and were first described in 1982 by Davies et al[1] in patients with

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pauci-immune glomerulonephritis. These autoantibodies are detected by immunofluorescence and 2 distinct patterns are described: cytoplasmic (C-ANCA) which are directed against proteinase-3, and perinuclear (P-ANCA) which are directed against myeloperoxidase and other antigenic determinants. Subsequent research showed an association between the presence of these antibodies and Wegener's granulomatosis, Churg-Strauss, and microscopic polyangiitis.[2–6] Clinical manifestations of ANCA-associated vasculitis include a progressive type of glomerulonephritis and/or pulmonary complications such as capillaritis and diffuse alveolar hemorrhage. Pulmonary capillaritis has been reported in 12% to 29% of patients with microscopic polyangiitis and in 17% to 35% of patients with Wegener's granulomatosis.[5,7–9] Repeated episodes of alveolar hemorrhage due to pulmonary capillaritis can result in irreversible interstitial fibrosis, particularly in patients with Wegener's granulomatosis who are mostly middle aged. In addition, the mortality rates from ANCA-related pulmonary vasculitis range between 25% and 50%.[10–14]

Several studies have shown that ANCA-related vasculitis is associated with higher incidence of respiratory involvement. Furthermore, there is evidence both in vitro and in vivo to suggest a potential role for ANCA in the pathogenesis of ANCA-related pulmonary vasculitis.[15,16] Cohen and Clark showed that the majority of patients with vasculitis and positive serology for ANCA had respiratory tract involvement compared with ANCA-negative patients.[17]

There is a paucity of data in the literature regarding predictors of mortality and Intensive Care Unit (ICU) admission in ANCA-related lung disease mainly because the disease is relatively rare and diagnostic criteria are not firmly established. Most studies available examined the prognostic factors associated with ANCA-related renal vasculitities, and fewer addressed the outcome predictors of ANCA-related pulmonary vasculitities.[18–20] To bridge this gap in knowledge, we reviewed a case series of 65 patients admitted to Emory University Hospital with ANCA-related vasculities with lung involvement that had open or video-assisted thoracoscopic lung biopsy and a positive serology for ANCA between February 1985 and November 2002. From this case series, we estimated the predictors for ICU admission and the 28-day mortality using the initial symptoms and clinical findings during the hospitalization, as well as pathological findings and radiographic features.

Study Population

We conducted a chart review for patients who were diagnosed with ANCA-related vasculitis during hospitalization from February 1985 through November 2002 at Emory University Hospital in Atlanta, Georgia. ANCA-related pulmonary vasculitis cases were further defined by the following inclusion criteria: positive ANCA serology, open or thoracoscopic lung biopsy, evidence of vasculitis in the histology, and negative serum glomerular basement membrane antibodies. Cases were ascertained during the hospitalization in which the patient met the inclusion criteria, independently of whether it was the initial or a subsequent hospitalization. The study was approved by the Emory Institutional Human Investigations Committee.

Data Collection

The medical records were extracted for the presenting symptoms and clinical signs compatible with vasculitis (hemoptysis, dyspnea, sinuses, cough, fever, arthralgia, and hypertension), as well as the duration of symptoms, previous medical history, smoking history, alcohol abuse, admission laboratory tests (basic metabolic profile, blood cell count, urine analysis, and arterial blood gas), evidence for extra-pulmonary involvement, radiological findings, causes of death, ANCA pattern, ANCA level, requirements of blood transfusions, continuous renal replacement therapy (CRRT), hemodialysis, requirement for mechanical ventilatory support, histopathologic pattern on lung biopsies, ICU admission, ICU and hospital length of stay and in-hospital mortality. Radiographic reports and histopathologic reports of lung biopsy or other organs were also reviewed. Renal involvement was defined as active sediment on urine analysis and serum creatinine over 1.4.

Statistical Analysis

We initially compared the distribution of outcome variables across patients who were hospitalized but not admitted to an ICU, patients hospitalized to the ICU, patients who died within 28 days after admission, and those who survived beyond 28 days. The 28-day in-hospital mortality has been used in other similar studies, and was therefore used as the mortality outcome in our study.[20] We initially performed univariate analysis to determine predictors of outcomes (28-day in-hospital mortality, mechanical ventilation, and admission to the intensive care unit), subsequently; we performed a multivariate logistic regression analysis and retained the significant predictors of ICU admission or mortality from the univariate analysis. Factors that were statistically significant were retained for the multivariate analysis. Covariates were selected as confounders in stepwise fashion using as criteria more than 10% change in the odds ratio, a *P* value less than 0.05 was considered statistically significant. All analyses were done with SAS software version 9.1 (SAS Institute, Cary, NC).

Demographics and Entry Characteristics

Sixty-five patients comprised the study population that met the serological and pathological entry criteria. The patients had a median age at diagnosis of 60 years. The cohort included 35 (54%) males and 30 (46%) females. The sex ratio for the survival group was 1/1 (male/female) and for the 28-day mortality group was 8/3. All patients were Caucasian except for 1 patient who was African American. By definition, all patients had lung involvement, 26 (40%) patients had additional renal involvement, and 12 out of the 26 patients with renal involvement (18.5%) had a kidney biopsy. We compared the baseline characteristics of the patients who died with those who survived and we observed that the patients who died were older, anemic, had higher blood urea nitrogen, higher oxygen requirements, higher white blood cells count, longer ICU and hospital length of stay, higher requirement for mechanical ventilation, blood transfusion, and an increased rate of secondary infections (Table 1). As shown in Figure 1, the majority of deaths occurred during the first 10 days of hospitalization. However, the mortality was skewed to the right with some deaths occurring after 20 days of hospitalization.

Clinical Features

The most frequent clinical manifestations of patients who died within 28 days of hospitalization were dyspnea, sinusitis, cough, fever, respiratory failure, hypertension, and anemia (Table 2). It should also be noted that anemia, hypertension, and acute respiratory failure requiring mechanical ventilation on admission were significantly associated with 28 days mortality ($P < 0.05$).

Pathological Features

An open or video-assisted thoracoscopic lung biopsy was performed in all 65 patients. The most common pathologic finding was alveolar hemorrhage, which was seen in 39 (60%) patients; 7 patients in the 28-day mortality group and 32 patients in the survival group ($P = 0.78$). Capillaritis was seen in 38 (58.5%) patients; 6 patients in the 28-day mortality group and 32 patients in the survival group ($P = 0.77$). Necrotizing granulomatous inflammation was seen in 30 (46%) patients; 6 patients in the 28-day mortality group and 32 patients in the survival group ($P = 0.54$). Ninety percent of the patients with necrotizing granulomas were CANCA positive and 10% were P-ANCA positive consistent with the observations of Bosch et al.[9] One patient (1.5%) had diffuse alveolar damage and 6 patients (7.8%) had a usual interstitial pneumonitis-pattern of pulmonary fibrosis.

Roentgenographic Features

All patients had initial abnormal chest radiographs and chest computed tomography. The chest x-rays findings included opacities with an alveolar filling pattern suggestive of alveolar hemorrhage in 21 patients (32%), cavitary lesions in 14 (21.5%), single nodule or multiple nodules in 16 (24.6%), pulmonary infiltrates in 37 (58%), and pleural effusion in 15 (23%). Bilateral pulmonary infiltrates represented the most common x-ray finding in both groups; 7/11 (64%) patients in the 28-day mortality group and 28/54 (52%) patients in the survival group ($P = 0.41$). However, ground glass opacities were the most common chest computed tomography finding in both groups; 7/11 (64%) patients in the 28-day mortality group and 19/54 (35%) patients in the survival group ($P = 0.27$).

Treatment

All patients received corticosteroids except for 1 patient. Cyclophosphamide was used in 51 (78.5%) patients. However, the combination of steroids and cyclophosphamide or either one was not associated with 28-day mortality or ICU admission. A total of 44.6% of patients taking immunosuppressive regimens were reported to develop either myeolsupression or infectious complications. Other treatments modalities used were hemodialysis in 16 patients (24.6%), CRRT in 2 patients (3.02%), and plasmapheresis in 2 patients (3.02%).

Predictors of 28-day Mortality

The preliminary analysis of the variables for 28-day mortality by univariate logistic regression demonstrated a significant association with anemia, hypertension, acute renal failure, respiratory failure, blood transfusion, pleural effusion on imaging study, hemodialysis, and secondary infection as a complication of treatments or hospitalization. However, univariate and multivariate analyses (Table 3) after adjusting for age, sex,

hypertension, anemia, acute renal failure, pleural effusion on imaging study, and respiratory failure, showed that mechanical ventilation, admission to ICU, and blood transfusion were the predictors associated with increased odds of death at 28-day.

Predictors of Admission to ICU

To test for predictors of admission to the ICU that were present on initial hospitalization, we analyzed the presenting clinical features by using univariate logistic regression and multivariate analysis (Table 4) after adjusting for age, sex, hypertension, anemia, acute renal failure, coronary artery disease, chronic obstructive lung disease, diabetes mellitus, and infiltrates on chest computed tomography. We found that respiratory failure, hemoptysis, smoking, and acute renal failure were strong predictors for ICU admission.

Discussion

In this retrospective single hospital study of 65 patients with ANCA-related pulmonary vasculitis, we found that respiratory failure requiring mechanical ventilation, admission to ICU, and blood transfusions were strong predictors of 28-day mortality. Moreover, respiratory failure, hemoptysis, smoking, and acute renal failure were strong predictors of admission to the ICU.

ANCAs are circulating autoantibodies that play an important role in the pathogenesis of pulmonary vasculitis through neutrophil activation. Under the stimulation of pro-inflammatory cytokines like interleukin-1, transforming growth factor-β, tumor necrosis factor-α, or microbial products, ANCA antigens translocate to the surface of neutrophils becoming accessible to ANCA.[18] Importantly, ANCA facilitates neutrophil adherence to vascular endothelial cells and indirectly mediates endothelial cell injury and the transmigration of neutrophils into the perivascular space.[15,21,22] ANCA-associated pulmonary vasculitis can present with isolated pulmonary involvement, but is more commonly seen as part of a generalized disorder. Pulmonary involvement includes solitary or multiple nodules, which can cavitate and be surrounded by thick walls of inflammatory tissue. Diffuse alveolar hemorrhage and localized or diffuse infiltrates are also common pulmonary manifestations of systemic vasculitis.

We selected a well-defined cohort of patients with documented lung disease associated with other features of ANCA-related vasculitis in an attempt to characterize the clinical presentation and 28-day outcome of patients with pulmonary manifestations of ANCA-related vasculitis. All of our patients had open lung biopsy or video-assisted thorascopic biopsy. However, lung biopsy may not be indicated in the setting of immune pulmonary vasculitis when a diagnosis can be made through the evaluation of other tissues or by serum assay of ANCA and anti GBM-antibody.[7,9] Moreover, pulmonary capillaritis is a relatively nonspecific pathological finding, which can be found in other diseases presenting with pulmonary disease such as Wagener’s granulomatosis, systemic lupus erythematosus, rheumatoid arthritis, microscopic polyangiitis, and polymyosistis.[12,23,24]

In our study population, we found that mechanical ventilation, admission to the ICU, and blood transfusion were associated with increased odds of death within 28 days from

hospitalization. Respiratory involvement requiring mechanical ventilation was a strong predictor for the 28-day mortality ($P = 0.0003$), which was similar to observations reported in other studies.[7] Advanced age and male sex have been identified as predictors of worse outcome in patients with ANCA-related renal vasculitis.[7,8,17] However, there are no data confirming that these observations are applicable to ANCA-related lung vasculitis. Here, we found that age and sex were not predictors of mortality even though the majority of patients who died were males (8/11, 73%); however, due to the small number of subjects on the study, the possibility of a type II error cannot be excluded. Several studies have shown that renal failure is a strong predictor of poor renal outcome in patients with systemic vasculitis. Nevertheless, other studies have not found renal failure to be a predictor of in-hospital mortality.[8,19,20,25–27] We found that having a creatinine level greater than 1.4 at presentation was a strong predictor for admission to the ICU ($P = 0.012$).

C-ANCA pattern was not a prognostic aid in determining the risk of death within 28 days from hospitalization in our study, and other studies have also failed to show the degree of vasculitis activity as predictor of outcome[28]; however, ANCA levels have been shown to be an independent predictor of mortality in other studies.[19] This difference could be due to the fact that all ANCA positive patients were enrolled including patients with Wegner's granulomatosis. Note that in a few of our study patients, ANCA was detected before 1990 at a time when ELISA was not used for specific ANCA assays (antiproteinease 3 or antimyeloperoxidase). The majority of our patients had pulmonary infiltrates on chest radiograph (58%) and ground glass opacities on chest-computed tomography (40%). These radiographic findings were consistent with those reported by Lauque et al[29] who showed that the majority of their 29 study patients with microscopic polyangiitis had diffuse or patchy ground glass densities on chest-computed tomography imaging at the time of presentation.

The role of immunosuppressants in ANCA related pulmonary vasculitis has not been fully evaluated. The combination of steroids and cyclophosphamide represents the standard therapy and can lead to control of the disease in 80% to 90% of patients. However, this regimen is associated with treatment-related morbidity in more than 50% of the patients.[30] In our study, we found that corticosteroids and cyclophosphamide did not affect the 28-day mortality, ICU admission, the need for mechanical ventilation and ICU and hospital length of stay. However, we were not able to ascertain how much time were individual patients taking cytotoxic agents; this lack of information could potentially bias the association with the 28-day mortality towards the null.

Most studies have evaluated corticosteroids and cyclophosphamide for treatment and prevention of relapses targeting the kidneys as a prognostic factor and, to our knowledge, no studies have analyzed this parameter against lung disease.[19,31] Further studies taking into account lung involvement as a prognostic factor are needed to determine the indication, duration and benefits of immunosuppressive therapy.

Infections and myelosuppression were the most frequent side effects of treatment in 29 patients (44.6%), and was associated with mortality in 5 out of 11 (45.4%) patients in the 28-day mortality group. The infections occurred when patients were on the combination of

corticosteroids and cyclophosphamide. Typically, this practice is common due to the severity of the pulmonary and renal involvement that often requires intensive immunosuppressive therapy despite the infection risk.[32]

Several limitations must be considered when interpreting the results of this study, which include its retrospective nature, small study size, no patients followed beyond 28-day, and the fact that it represents a single center study. Further, we did not adjust our results using the acute physiological score and chronic health evaluation, which have been associated with mortality in this group of patients.[20] Also, patients were selected during a wide time range from 1985 till 2002, in which advances in medical technology and critical care strategy have been made to improve patient outcomes such as tight blood glucose control and low tidal volume ventilation for patients in acute respiratory distress syndrome. Further, we do not have information regarding whether cases were ascertained during an initial or subsequent hospitalizations, which could potentially have biased our results. Lastly, given that the majority of patients who died also had the strong predictors (ie, nearly all patients who died also received mechanical ventilation) this led to very high OR with large 95% CI; these imprecise estimates are a reflection of the small sample size of patients in our study.

However, our study is the first to highlight the clinical predictors of 28-day mortality and ICU admission in patients with ANCA-related pulmonary vasculitis. Also, the study includes 65 patients with histological confirmation of pulmonary vasculitis and positive serology for ANCA, which makes it one of the largest cohorts described in the ANCA-related pulmonary vasculitis literature.

In conclusion, we found that in the setting of ANCA-related pulmonary vasculitis, respiratory failure requiring mechanical ventilation, blood transfusion, admission to ICU, acute renal failure, hemoptysis, and history of smoking are predictors of increased odds of death within 28 days from hospitalization and of ICU admission. The early institution of treatment and aggressive medical care of patients predicted to have high mortality might prove beneficial and should be investigated prospectively.

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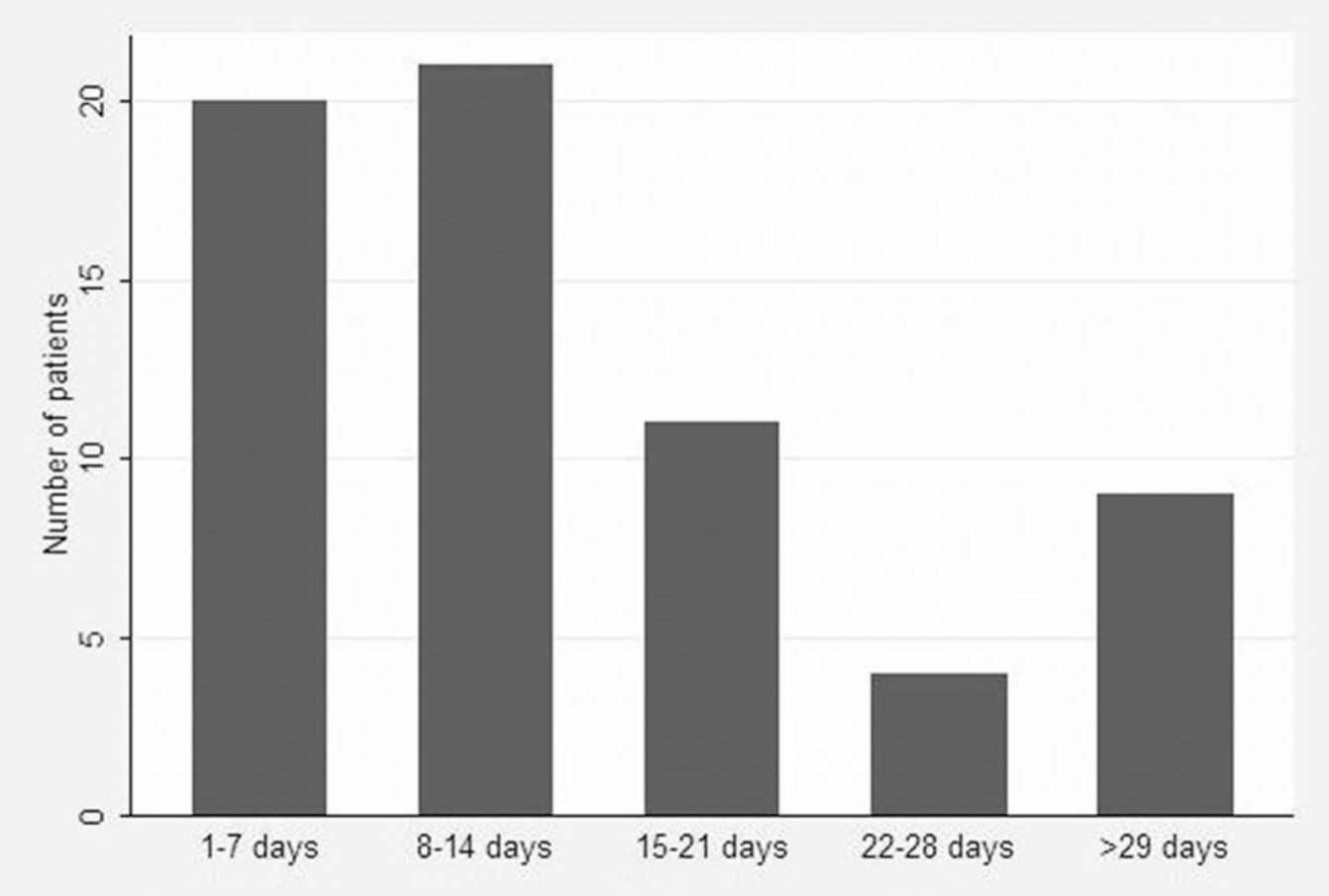

Figure 1.
Length of hospital stay.

Table 1

Baseline Patient Characteristics in 28-day Mortality Group and the Survivor Group

Variable	28-day Death (11 Pts) 17%	Survivors (54 Pts) 83%	Total Population
Mean age (range)[a]	60 (39–81)	47 (10–83)	49 (10–83)
Gender (Female %)	27%	50%	46%
BUN (95% CI)[a]	53 (23–85)	29 (22–37)	33 (24–41)
F_{IO_2} (%) (95% CI)[a]	54 (35–74)	31 (25–39)	35 (28–42)
HCT (95% CI)	28 (25–32)	32 (30–34)	31 (30–33)
Hemoglobin (95% CI)[b]	9.6 (9–11)	10.75 (10–12)	10 (10–11)
ICU length of stay (95% CI)[a]	16 (10–22)	4 (1–8)	6 (2–9.5)
PH (95% CI)	7.40 (7.3–7.45)	7.39 (3.8–7.41)	7.4 (7.3–7.41)
WBC (95% CI)[b]	15.4 (10–21)	11.8 (10–13)	12 (10–14)
MV length of use (95% CI)[a]	11.5 (6–17)	3.6 (1–7)	5 (2–8)
Hospital length of stay (95% CI)	21 (12–33)	14 (9–20)	16 (11–21)
Hemodialysis	5 (45%)	11 (20%)	0.07
Cytoxan	7 (63%)	44 (81%)	0.1
Alveolar hemorrhage	7 (64%)	32 (59%)	0.7
Capillarities on pathology	6 (54%)	32 (59%)	0.7
Necrotizing granuloma on path	6 (54%)	24 (44%)	0.5
P-ANCA	2 (18%)	10 (18%)	0.9
Systemic steroids	11 (100%)	53 (98%)	0.6
C-ANCA	8 (73%)	42 (78%)	0.7
Blood transfusion[a]	7 (63%)	7 (13%)	0.0002
Mechanical ventilation[a]	9 (82%)	9 (17%)	0.0001
Secondary infection[a]	5 (45%)	6 (11%)	0.005
Tobacco use	5 (45%)	16 (30%)	0.3

Continuous variables are shown as mean and 95% confidence intervals. Percentages represent the proportion of patients.

[a] $P < 0.05$.

[b] $P = 0.05$.

Baseline or initial hospitalization values for: BUN, Blood urea nitrogen; F_{IO_2}, Fraction of inspired oxygen; %, HCT, Hematocrit; Hgb, hemoglobin; ICU, Intensive care unit; ANCA, Antinuclear cytoplasmic antibodies.

Table 2

Initial Clinical Findings of Patients with ANCA-Related Lung Disease

	28-day Death (11 Pts) 17%	Survivors (54 Pts) 83%	Total Population
Hemoptysis	4(36%)	17(31%)	21(32%)
Dyspnea	8(73%)	26(48%)	34(52%)
Sinusitis	8(73%)	28(52%)	36(50%)
Cough	8(73%)	23(42%)	31(47%)
Fever	9(82%)	35(65%)	44(67%)
Arthralgias	5(45%)	28(52%)	33(41%)
Respiratory failure[a]	6(55%)	8(15%)	14(21%)
Hypertension[a]	8(73%)	21(39%)	29(44%)
ARF	3(27%)	11(20%)	14(21%)
Anemia[a]	4(36%)	6(11%)	11(15%)

[a] $P < 0.05$.

[b] $P = 0.05$.

ARF, acute renal failure.

Table 3

Univariate and Multivariate Analysis of the Predictors of 28-day Mortality

Variable	Univariate OR (95% CI)	Multivariate OR (95% CI)
Mechanical ventilation	23 (4–122)	51 (3–947)
Admission to ICU	28 (3–243)	10 (1–118)
Blood transfusion	12 (2–50)	37 (3–510)

Multivariate analysis adjusted for: Age, gender, hypertension, anemia, acute renal failure, pleural effusion on chest CT, and respiratory failure.

Table 4

Univariate and Multivariate Analysis of the Predictors of Intensive Care Unit Admission

Variable	Odd Ratio (95% CI)	Multivariate OR (95% CI)
Respiratory failure	19 (4–99)	28 (3–200)
Hemoptysis	3.5 (1–10)	3.1 (0.8–11)
Smoking	3.6 (2–12)	5 (0.9–27)
Hemodyalisis	4 (1.2–13)	
BUN >19		6 (1.4–24)
Creatinine >1.4		8 (1.7–43)

The categorical variables for BUN and creatinine were based on the median distribution values for the study population.

Multivariate analysis adjusted for: age, sex, HTN, anemia, acute renal failure, coronary artery diseases, chronic obstructive lung disease, diabetes, and pleural effusion on chest CT.

BUN, Blood urea nitrogen; CR, serum creatinine.