# Factors predicting mortality among patients with COVID-19 associated hospital acquired pneumonia: insights from a tertiary care center

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## Abstract

Hospital acquired pneumonia (HAP) is a severe and dangerous complication in patients admitted with COVID-19, causing significant morbidity and mortality globally. However, the early detection and subsequent management of high-risk cases may prevent disease progression and improve clinical outcomes. This study was undertaken in order to identify predictors of mortality in COVID-19 associated HAP. A retrospective study was performed on all patients who were admitted to a tertiary care center with COVID-19 associated HAP from July 2020 till November 2020. Data was collected on relevant demographic, clinical and laboratory parameters to determine their association with in-hospital mortality; 1574 files were reviewed, out of which 162 were included in the final study. The mean age of subjects was 59.4±13.8 and a majority were male (78.4%). There were 71 (48.3%) mortalities in the study sample. *Klebsiella pneumoniae* (31.5%) and *Pseudomonas aeruginosa* (30.2%) were the most common organisms overall. Clinically significant growth of *Aspergillus sp.* was observed in 41 (29.0%) of patients. On univariate analysis, several factors were found to be associated with mortality, including male gender (p=0.04), D-dimers >1.3 mg/L (p<0.001), ferritin >1000 µg/mL (p<0.001), LDH >500I.U/mL (p<0.001) and procalcitonin >2.0 µg/mL (p<0.001). On multivariate analysis, ferritin >1000ng/mL, initial site of care in Special Care Units or Intensive Care Units, developing respiratory failure and developing acute kidney injury were factors independently associated with mortality in our patient sample. These results indicate that serum ferritin levels may be a potentially useful biomarker in the management of COVID-19 associated HAP.

## Introduction

In the time since the first few cases of SARS-CoV-2 swept across the globe, the medical community's understanding of the infection has evolved dramatically. However, hospital acquired pneumonia (HAP) remains a serious and pervasive complication in the clinical course of patients with COVID-19 [1]. The pathogenesis of the condition is likely due to a host of potentially causative factors including prolonged requirements for mechanical ventilation; direct pulmonary lesions and ARDS precipitated by the SARS-CoV-2 virus allowing for bacterial colonization; and the use of immunomodulatory agents such as corticosteroids [2,3]. However, regardless of the underlying etiology, several studies have concluded that patients with COVID-19 associated HAP

have a poorer prognosis and higher rates of mortality [4], as is the case with other similar viral infections such as influenza [5].

Careful epidemiological research is therefore crucial in such cases as it allows for the identification, early detection and treatment of high-risk patients [6]. This is particularly important in low- and middle-income countries (LMICs) where assessment of patient prognosis is critical when deciding how to allocate an increasingly limited and constrained pool of resources [7]. Detailed analysis of potential risk factors would serve as an important tool in clinical decision making, thus allowing for direct, targeted and early interventions. Therefore, in order for such empirical tools to be applied to an LMIC setting, they would have to be derived from data generated from those settings themselves.

The current literature focuses on the predictors of adverse outcomes in patients with COVID-19 alone versus COVID-19 associated HAP [8,9]. This report, on the other hand, takes a different approach to the subject. The primary goal of this study was to look into the predictors of mortality in COVID-19 associated HAP patients. We hoped to identify clinical or laboratory markers associated with survival *versus* non-survival in such patients.

## Materials and Methods

### Study design and setting

This study was a retrospective single center cross sectional study conducted at the Aga Khan University Hospital (AKUH) in Karachi, Pakistan. AKUH is a Joint Commission International (JCI) accredited large, 650 bed tertiary care hospital catering to a racially and ethnically diverse population of patients from across the country. AKUH has also been at the forefront of Pakistan's response to the COVID-19 pandemic and has been heavily involved in the creation and implementation of nationwide protocols for the treatment and management of COVID-19 patients.

### Clinical definitions and criteria for inclusion

All patients aged 18 and above with both confirmed SARS-CoV-2 infection and culture proven HAP were included in this study. Confirmed SARS-CoV-2 infection was defined as a single positive rt-PCR assay tested upon hospital admission *via* a nasopharyngeal swab with no history of COVID-19 infection for at least 3 months prior. Since the beginning of the pandemic, our hospital has had a policy of mandatory COVID-19 PCR testing as a screening measure for all patients upon hospital admission, regardless of whether or not they display any symptoms of COVID-19 infection. In case of a positive test, all patients are triaged and, per institutional policy, managed in a separate COVID-19 ward or Special Care or Intensive Care Unit, depending on the severity of the patient's condition. Universal airborne and contact precautions were implemented during the care of all admitted patients.

Once admitted, patients are managed by a dedicated inpatient hospitalist or intensivist, and all further clinical testing or treatment, including sending any samples for culture, is at their discretion in accordance with recommended hospital guidelines and policy. For the purpose of this study, culture proven HAP was defined as bacterial growth of known nosocomial microbes on either respiratory tract specimens taken at least 48 h after the patients' admission to the hospital with new signs and symptoms of clinical infection (as determined by the treating physician) [10]. For fungal growth, COVID-19 associated pulmonary aspergillosis (CAPA) was diagnosed according to the criteria proposed by *Koehler et al.* [11]. It was recognized that certain microbial species may have grown on culture as a contaminant or as part of normal flora. Such cases were only included in this study if there was documented evidence that the treating physician deduced that the microbial growth was pathological and subsequently managed the patient accordingly. All laboratory analysis was conducted in-hospital at the clinical microbiology laboratory at the Aga Khan University, which is accredited by the College of American Pathologists (CAP). Data was collected retrospectively from 1st July 2020 till 30th November 2020 (Figure 1).

### Data collection and management

All data was collected retrospectively via codified electronic medical records through the AKUH Health Information Management System (HIMS). Data was anonymized using randomized three-digit codes prior to analysis and review. Data variables on patient demographics, relevant history, preexisting comorbidities, laboratory investigations, inpatient medication, clinical course, complications and outcomes were collected and compiled.

### Statistical analysis

The patient sample was divided into two categories: survivors and non-survivors, with the objective of investigating predictors of mortality in patients with COVID-19 associated HAP. Categorical data is reported as frequencies and percentages whereas continuous variables are reported as mean with standard deviation or median with interquartile range. All analysis was run on IBM SPSS Version 28. Univariate linear regression analysis was run on independent variables (exposures) which were likely to be associated with mortality with the results presented as p-values. All variables with a p-value <0.1 on univariate analysis were considered significant and taken forward to multivariate analysis. The results were calculated and presented as adjusted odd's ratios with 95% confidence intervals. For all statistical tests, a p-value of less than 0.05 was considered statistically significant.

## Results

A total of 1574 patient records were reviewed for inclusion, out of which 162 (10.3%) patients fulfilled the selection criteria and were included in the study. Of these, there were 91 (56.2%) survivors and 71 (43.8%) non-survivors. The overall demographic and clinical characteristics of the patients are compiled and pre-

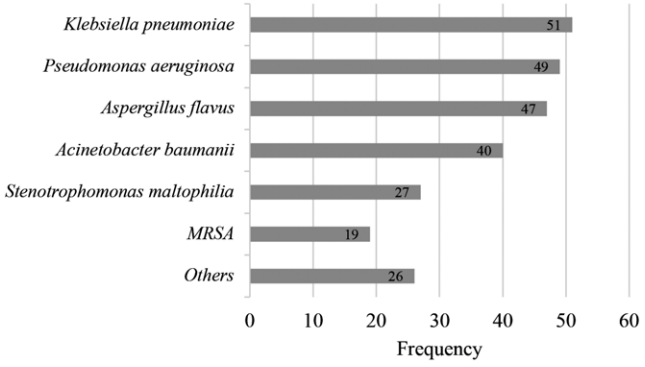


**Figure 1.** Frequency of organisms grown in culture.

sented in Table 1. The mean age of the subjects was 59.4±13.8 years, and the majority were of male gender (n=127, 78.4%). *Klebsiella pneumoniae* was the most common bacterial organism grown in culture (31.5%), followed by *Pseudomonas aeruginosa* (30.2%). Forty-seven (29.0%) patients were diagnosed with CAPA, with growth of *Aspergillus sp. on culture*. 50% of all cultures grew more than 1 organism. 68 (42.0%) patients were initially admitted to the general ward, 54 (33.3%) were admitted to special care units and 40 (24.7%) were admitted to the intensive care units. The median length of stay was 12 days (IQR=6-19 days).

**Table 1.** Baseline demographics and clinical characteristics of survivors and non-survivors with COVID-19 associated hospital acquired pneumonia.

| Variable | Overall (n=162) | Survivors (n=91) | Non-survivors (n=71) | p-value |
|---|---|---|---|---|
| Demographics | | | | |
| Age (in years) | 59.4±13.8 | 57.59±13.4 | 61.83±14.1 | |
| Age >60 years | 79 (48.8) | 42 (46.2) | 37 (52.1) | 0.45 |
| Male gender | 127 (78.4) | 66 (72.5) | 61 (85.9) | 0.04 |
| Initial site of care | | | | |
| Ward | 68 (42.0) | 55 (60.4) | 13 (18.3) | <0.001 |
| Special care | 54 (33.3) | 27 (29.7) | 27 (38) | <0.001 |
| Intensive care | 40 (24.7) | 9 (9.9) | 31 (43.7) | <0.001 |
| Comorbidities | | | | |
| Diabetes | 94 (58) | 50 (55.6) | 44 (62.9) | 0.35 |
| Hypertension | 84 (51.9) | 49 (53.8) | 35 (49.3) | 0.57 |
| Coronary artery disease | 24 (14.8) | 10 (11) | 14 (19.7) | 0.12 |
| Chronic kidney disease | 15 (9.3) | 9 (9.9) | 6 (8.5) | 0.75 |
| Obstructive airway disease | 15 (9.3) | 9 (9.9) | 6 (8.5) | 0.75 |
| Laboratory findings | | | | |
| Anemic (Hb<11 mg/dL) | 31 (19.1) | 13 (14.3) | 18 (25.4) | 0.08 |
| Leukocytosis (>11.3x10$^9$/L) | 72 (44.4) | 39 (42.9) | 33 (46.5) | 0.44 |
| Lymphopenia (<17.5%) | 134 (82.7) | 78 (85.7) | 56 (78.9) | 0.20 |
| High D-dimer (>1.3 mg/L) | 125 (77.2) | 61 (71.8) | 64 (94.1) | <0.001 |
| High ferritin (>1000 µg/ml) | 103 (63.6) | 43 (49.4) | 60 (87.0) | <0.001 |
| High LDH (>500 IU/L) | 118 (76.1) | 52 (60.5) | 66 (95.7) | <0.001 |
| High procalcitonin (>2.0 ng/mL) | 45 (27.8) | 15 (17.2) | 30 (43.5) | <0.001 |
| High CRP (>14 md/dL) | 150 (93.2) | 83 (91.2) | 67 (95.7) | 0.26 |
| Creatinine (>1.3 mg/dL) | 85 (52.8) | 41 (45.1) | 44 (62.9) | 0.03 |
| Hyponatremia (<136 mmol/L) | 68 (42) | 41 (45.1) | 27 (38.0) | 0.37 |
| Acidosis (pH <7.35) | 32 (20.3) | 12 (13.8) | 20 (28.2) | 0.03 |
| Alkalosis (pH> 7.45) | 46 (29.1) | 30 (34.5) | 16 (22.5) | 0.10 |
| Hypoxemic ($pO_2$ <70 mmHg) | 92 (56.8) | 47 (54.0) | 45 (63.4) | 0.24 |
| Hypercapnic ($pCO_2$ >48 mmHg) | 19 (11.7) | 8 (9.2) | 11 (15.5) | 0.23 |
| Number of organisms in culture | | | | |
| One | 81 (50.0) | 44 (48.4) | 37 (52.1) | 0.97 |
| Two | 48 (29.6) | 27 (29.7) | 21 (29.6) | 0.83 |
| Three or more | 33 (20.4) | 20 (22.0) | 13 (18.3) | 0.63 |
| Culture data | | | | |
| *Klebsiella pneumoniae* | 51 (31.5) | 34 (37.4) | 17 (23.9) | 0.07 |
| *Pseudomonas aeruginosa* | 49 (30.2) | 29 (31.9) | 20 (28.2) | 0.61 |
| *Aspergillus* sp. | 47 (29.0) | 23 (25.3) | 24 (33.8) | 0.24 |
| *Acinetobacter baumanii* | 40 (24.7) | 18 (19.8) | 22 (31.0) | 0.10 |
| *Stenotrophomonas maltophilia* | 27 (16.7) | 14 (15.4) | 13 (18.3) | 0.62 |
| *MRSA* | 19 (11.7) | 13 (14.3) | 6 (8.5) | 0.26 |
| Others | 26 (16.0) | 15 (16.5) | 11 (15.5) | 0.87 |
| In-hospital medications | | | | |
| Systemic steroids | 154 (95.1) | 87 (95.6) | 67 (94.4) | 0.71 |
| Anticoagulation | 136 (84) | 72 (79.1) | 64 (90.1) | 0.06 |
| Tocilizumab | 68 (42) | 32 (35.2) | 36 (50.7) | 0.04 |
| Remdesivir | 42 (25.9) | 30 (33) | 12 (16.9) | 0.02 |
| Complications | | | | |
| Intubation and mechanical ventilation | 85 (52.5) | 28 (30.8) | 57 (80.3) | <0.001 |
| Respiratory failure | 74 (45.7) | 19 (20.9) | 55 (77.5) | <0.001 |
| Acute kidney injury | 60 (37) | 20 (22.0) | 40 (56.3) | <0.001 |
| ACS/NSTEMI | 21 (13.0) | 4 (4.4) | 17 (23.9) | - |
| Septic shock | 18 (11.1) | 5 (5.5) | 13 (18.3) | 0.01 |
| Pneumothorax | 13 (8.0) | 4 (4.4) | 9 (12.7) | - |
| Length of stay | 12 (6-9) | 10 (6-16) | 13 (7-22) | 0.21 |

Hb, hemoglobin; LDH, lactate dehydrogenase; CRP, C-reactive protein; MRSA, methicillin resistant staphylococcus aureus; ACS, acute coronary syndrome; NSTEMI, non-ST elevation myocardial infarction.

Table 2 presents the analysis of all variables associated with mortality in patients with HAP and COVID-19. On univariate analysis male gender (p=0.04) was the only demographic variable found to be associated with mortality. Furthermore, non-survivors were also more likely to have elevated D-dimers >1.3 mg/L (p<0.001), ferritin >1000 µg/mL (p<0.001), LDH >500 IU/mL (p<0.001) and procalcitonin >2.0 µg/mL (p<0.001). On multivariate analysis, our results indicate that high ferritin >1000 µg/mL (aOR=11.65, 95% CI=2.47-54.95), initial site of care in Special Care Units (aOR=5.73, 95% CI=1.46-22.40) or Intensive Care Units (aOR=12.28, 95% CI=2.41-62.45) and developing respiratory failure (aOR=14.19, 95% CI=3.66-55.01) or acute kidney injury (aOR=4.56, 95% CI=1.03-20.12) were factors significantly associated with mortality in our patient sample.

## Discussion

This study compares the clinical and demographic characteristics of survivors and non-survivors in cases of bacterial or fungal COVID-19 associated hospital acquired pneumonia. In doing so we explore several important and potentially clinically useful predictors of mortality in such a patient cohort. This study revealed three important findings: ferritin, LDH, procalcitonin and D-dimers are all statistically associated with an increased risk of mortality; there was a relatively high (43.8%) mortality rate in our patient sample; there was a high reported prevalence (29.0%) of COVID-19 associated pulmonary aspergillosis.

Inflammatory biomarkers such as ferritin, LDH and D-dimers are well established indicators of the severity of COVID-19 infections [12-14]. However, in our study, only high serum Ferritin levels (>1000ng/mL) at the time of admission were found to be independently associated with non-survival on multivariate analysis. This indicates that ferritin is likely a valuable prognostic marker in patients with COVID-19 associated HAP. This contrasts with current literature on prognostic markers of COVID-19 alone, in which data suggests that LDH is likely more clinically useful in this regard. We propose that the clinical utility of ferritin as a prognostic marker in COVID-19 associated HAP is likely because of high circulating levels of IL-6 in such infections, which may be responsible for both driving up ferritin production, and worsening disease prognosis [15]. We identified several other independent predictors of mortality in our patient sample. Initial site of care (in Special Care or Intensive Care Units) and developing certain complications (acute kidney injury and respiratory failure) were significantly associated with mortality. Both findings are widely reported and are likely due to increased requirements for mechanical ventilation and systemic septic inflammation leading to hemodynamic and immunological dysfunction [16,17].

The mortality rate reported in this study is comparable to those reported in studies with similar sample sizes investigating hospital acquired infections (HAI) or HAP, Sharfan *et al*. and Bardi *et al*. report mortality rates of 66% and 54%, respectively [18,19]. Of particular interest, a large study by Budhiraja *et al*. found that mortality rates amongst patients COVID-19 with secondary bacterial or fungal infections was nearly 8 times higher than in those with COVID-19 alone [20]. Furthermore, our results indicate that baseline age and demographic characteristics were not significant risk factors for mortality in such patients, similar to the study by De Santis *et al*. [21]. A wider comparison of this finding with current literature is difficult, as existing studies which investigate COVID-19 associated secondary bacterial/fungal infections often group together HAP and community acquired pneumonia (CAP) when reporting their findings. As CAP tends to have better outcomes, this may skew the results of such studies [22].

Understanding the organisms involved in COVID-19 associated HAP is crucial to guide antimicrobial stewardship and prevent their misuse or overuse. The most common organisms isolated in culture in this study were *Aspergillus sp., Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter* and *MRSA*, which concurs with existing literature [23-25]. COVID-19 CAPA is a well-recognized disease taking root during the COVID-19 pandemic. Its etiology is likely due to a combination of factors including immune dysfunction directly due to COVID-19 viral infection and

**Table 2.** Crude and adjusted estimates of factors associated with mortality in COVID-19 associated hospital acquired pneumonia.

| Variable | Odd's ratio crude | 95% CI | Odd's ratio adj | 95% CI |
|---|---|---|---|---|
| Male gender | 2.35 | 1.04-5.29 | 0.66 | 0.15-2.83 |
| Initial site of care | | | | |
| Special care | 4.23 | 1.88-9.47 | 5.73 | 1.46-22.40 |
| Intensive care | 14.57 | 5.59-37.95 | 12.28 | 2.41-62.45 |
| High D-dimer (>1.3 mg/L) | 6.30 | 2.06-19.20 | 0.73 | 0.57-7.49 |
| High ferritin (>1000 µg/mL) | 6.82 | 3.01-13.12 | 11.65 | 2.47-54.95 |
| High LDH (>500 IU/L) | 14.39 | 4.18-49.47 | 3.49 | 0.54-22.56 |
| High procalcitonin (>2.0 ng/mL) | 3.69 | 1.78-7.68 | 2.83 | 0.64-12.40 |
| Creatinine (>1.3 mg/dL) | 2.06 | 1.09-3.90 | 0.62 | 0.14-2.74 |
| Acidosis (pH <7.35) | 2.45 | 1.10-5.45 | 1.08 | 0.24-4.88 |
| Tocilizumab | 1.89 | 1.01-3.57 | 3.68 | 0.85-15.94 |
| Remdesivir | 0.41 | 0.19-0.88 | 0.64 | 0.15-2.74 |
| Intubation and mechanical ventilation | 9.16 | 4.39-19.10 | 1.69 | 0.37-7.71 |
| Respiratory failure | 13.02 | 6.14-27.63 | 14.19 | 3.66-55.01 |
| Acute kidney injury | 4.58 | 2.31-9.07 | 4.56 | 1.03-20.12 |
| Septic shock | 3.86 | 1.30-11.40 | 0.89 | 0.14-5.90 |
| Growth of *Acinetobacter* sp. | 1.82 | 0.89-3.74 | 1.15* | 0.18-7.12 |

*Variables on culture results were adjusted for "number of organisms" grown in culture as well as covariates.

a significant increase in the use of corticosteroids for its management [26]. This is in line with our own findings, wherein the vast majority of patients (95.1%) received systemic corticosteroids during their hospital admission. These findings therefore suggest that, in line with the recommendations by Koehler *et al*. [11], clinicians must strongly consider CAPA in patients admitted with COVID-19 with clinical deterioration and appropriately screen for fungal disease etiologies in such patients.

This study contributes to a limited pool of literature from LMICs which specifically investigates factors associated with mortality from HAP and COVID-19. There are, however, several important limitations to this study. Firstly, this is a single center study, due to which our results may not be generalizable to the broader regional population. Furthermore, the relatively small sample size for this study also limits the statistical power of the results. Pooled data from further studies at multiple centers would be needed to improve this Lastly, as this was a retrospective study, clinical data collection protocols could not be standardized per the exact requirements of the study objectives. Nevertheless, we believe this study contributes to a limited pool of literature from LMICs which specifically investigates factors associated with mortality from HAP and COVID-19 and serves as an important foundation for future work in this field.

## Conclusions

Hospital acquired pneumonia is a prevalent complication in patients admitted with COVID-19 and is associated with high rates of in-hospital mortality. COVID-19 associated pulmonary aspergillosis are reported, and therefore should be suspected in cases with a high degree of clinical evidence for the disease or in patients not responding to empirical or therapeutic antibiotic regimes. Serum ferritin concentrations at the time of admission appear to be directly associated with increased risk of mortality and may be utilized for risk stratification of admitted patients. We recommend further research including randomized trials to verify the accuracy of these findings and identify potential predictors of mortality and adverse outcomes in patients admitted with COVID-19 associated HAP.

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