ECRONICON OPEN ACCESS

EC EMERGENCY MEDICINE AND CRITICAL CARE
Research Article

The Search for Prognostic Factors in Critical Care Patients with Covid-19

Lamay Rahman*, Iman Abdul-Khaliq, Jaseem Baliyambra, Tarek Hassan, Ahmed El-Desoky, Jitendra Siyani, Chaudry Ali, Shilpa Muthusamy, Mustafa Hamza, Muhammad Younis and Lalith Jayasekera

Anaesthetic and Critical Care Department, Basildon University Hospital, Essex, UK

***Corresponding Author:** Lamay Rahman, Anaesthetic and Critical Care Department, Basildon University Hospital, Essex, UK.

Received: November 07, 2020; **Published:** January 29, 2020

Abstract

Background: With the novel nature of Covid-19 a lot of work has been done in looking at treatment options but there has been limited studies, particularly in the critical care setting, in looking for prognostic predictors in patient demographics, laboratory results and treatments given once in critical care. This study aimed to find those prognostic factors.

Methods: A retrospective study was carried out at a single critical care unit at a district general hospital. 74 patients admitted to critical care between March and May 2020 had their medical notes and laboratory results analyzed and collated. Data collected included patient demographics, pre-critical care treatments and investigations and in-critical care treatments and investigations.

Results: Patients were divided into 2 groups based on their critical care outcome. Increasing age ($p < 0.0001$), a lower initial P02 on admission to ITU (9.92 vs 11.27, P = 0.04), a greater acidosis level at any point during the ITU stay (pH 7.08 vs pH 7.22, P = <0.0001), a higher pCO2 level at any point during the ITU stay (pCO2 9.92 vs 8.88, P = 0.04), a higher peak urea level during the ITU stay (26.5 vs 21.1, P = 0.04), admission lactate levels (2.6 vs 1.37, P = 0.009), peak lactate levels at any point during ITU stay (5.8 vs 2.61, P=0.0001), initial white cell count on admission to ITU (11.5 vs 9.3, P = 0.04), peak white cell count (22.9 vs 16.4, P = 0.0002), peak neutrophil count (19.8 vs 13.3, P = 0.0003), requirement of 2 or more inotropes (28.5% vs 5.71%, P = 0.03 for 2 inotropes), an arrythmia at any point during ITU stay requiring electrical or chemical intervention (51.2% vs 17.1%, P=0.03) were all significant prognostic factors in patients admitted to critical care.

Conclusion: The study found that there was a number of clinical factors spanning patient demographics, pre-critical care treatment failures and in critical care investigations and treatments were strong prognostic factors for critical care outcome in patients that were admitted with Covid-19.

Keywords: *Covid-19; Prognosis; Risk; Prognostic Factors*

Introduction

In December 2019 a cluster of cases of pneumonia with unknown etiology was made aware to the WHO China Country office and as of 3rd January 2020 the number of cases totaled 44 [1]. In January 2020 the cause was identified as a new coronavirus named SARS-CoV-2 or Coivd-19 [2]. After the initial outbreak in China, over the next few months there has been spread across the globe with 215 countries affected with at least 1 positive reported case as of 29th August 2020 [3]. The outbreak was officially termed a pandemic by the world health organization on 12th March 2020 [4].

As of 31st July 2020 in the UK there had been 13,379 patients admitted to an intensive care unit (ICU) in the UK with a confirmed Covid-19 positive test and diagnosis. Within those 13,379 patients, 10,341 patients had a documented outcome in which an ICU mortality rate was found to be 39.7% [5].

There has been increasing number of studies looking into risk factors for outcome with this novel virus but there have been very few studies looking into predictive clinical factors, investigation results and treatments required on overall outcome. Even fewer have been looking at these aspects in regards to critical care outcome. This study aimed to find any significant factors that would be predictive of poor outcome.

Methods

Study design and participants

This was a retrospective observational study of 74 patients with confirmed Covid-19 via positive RNA polymerase chain reaction result from either nasal and pharyngeal swabbing or sputum testing. This study was carried out in patients admitted to intensive care unit (ICU) at a district general hospital in Essex, UK at any point between March and May 2020. All patients with a positive RNA diagnosis were eligible to be included in the study. All patients included were adults (greater than 18 years of age) and all patients were admitted either directly from the emergency department or from the wards.

All patients that were admitted to ICU were admitted for invasive ventilation. Non-invasive forms of ventilation that were attempted, were tried on the medical wards prior to ICU admission. No patients were admitted for renal support and/or inotropic support only.

Data collection

A uniform 7 page proforma was created with specific data to be collected. The proforma was made to be self-explanatory. The data was collected retrospectively from the patient's written medical notes, written nursing observation charts, and electronic investigation reports.

Data collected included patient demographics, pre-ICU investigation and treatments, in-ICU investigations, treatments and any complications. Data was collected by nine data collectors using the proforma and the results collated and analysed by one person.

Statistical analysis

Data was collated and tabulated as raw figures and then was analysed into percentages as a substitute for frequency of categorical data. Continuous variable data was calculated into means and the means analysed for differences. Continuous data was compared using welch t-test and categorical data was compared using chi-square test. Values less then $p<0.05$ was considered statistically significant. Those found to be statistically significant were then included in a multivariate regression analysis.

Results

A total of 79 patients were eligible to be included in the study. 4 patients were excluded as their patient notes were incomplete. 1 patient was excluded as that patient was still admitted to ITU at the time of analysis. This left 74 patients eligible to be analysed.

These 74 patients were divided into 2 group – survival group and mortality group based on their final outcome.

Patient demographics and pre-ICU investigations and treatments are demonstrated in table 1. The results show a strong correlation between increasing age and mortality ($p < 0.0001$) which is more prevalent in patients above aged 70 and beyond (35.8% mortality vs 8.57% survival, $p = 0.02$). The results also demonstrated that those patients requiring invasive ventilation after 3 days of Continuous Positive Airway Pressure (CPAP) was linked to poor outcome (0% survival in those requiring invasive ventilation post 3days of CPAP).

	Survival Group	Mortality Group	p-Value
Overall Outcome	47%	53%	
Gender -			
Male	48.2%	51.8%	0.91
Female	44.4%	55.6%	0.82
Age -			<0.0001
20 -29 years	0%	2.56%	
30-39 years	8.57%	0%	
40-49 years	20%	0%	
50-59 years	37.1%	23%	0.33
60-69 years	25.7%	39%	0.40
70-79 years	8.57%	35.8%	0.02
BMI -			0.30
<25 kg/m^2	20%	20.5%	0.96
25-30 kg/m^2	34.2%	26.3%	0.42
30-35 kg/m^2	31.4%	30.7%	0.96
35-40 kg/m^2	11.4%	7.69%	0.61
>40 kg/m^2	2.85%	5.12%	0.63
Ethnicity -			
Asian	2.85%	5.12%	0.63
Black	22.8%	17.9%	0.66
white	68.5%	76.9%	0.74
other	5.71%	0%	
Co-morbidities -			
Asthma	14.20%	17.90%	0.73
COPD	8.57%	10.20%	0.82
IHD	2.85%	7.69%	0.38
HTN	51.40%	58.90%	0.72
DM	31.40%	25.60%	0.68
Prev Stroke	2.85%	10.20%	0.25
CKD	2.85%	12.80%	0.14
Duration of symptoms pre-admission -			
0 - 5 days	29.4%	19.4%	0.52
5 - 10 days	35.2%	38.8%	0.79
10 - 15 days	26.4%	25%	0.99
15 - 20 days	2.94%	9%	0.23
20 - 25 days	5.88%	5.55%	0.91
25 - 30 days	0%	2.77%	
Number of days on CPAP -			
0 days	75	61.5	0.60
1 days	15.6	10.2	0.63
2 days	3.1	5.12	0.63
3 days	6.25	7.69	0.75
4 days	0	5.12	
5 days	0	7.69	
6 days	0	2.56	
Pre-ICU investigations-			
D-Dimer (ng/ml)	2493	5081	0.146
Creatinine (µmol/L)	146	185	0.240

Table 1: *Showing Patient Demographics and Pre-Critical Care Investigations and Treatments.*

**COPD= Chronic Obstructive Pulmonary Disease, IHD= Ishacemic Heart Disease, HTN= Hypertension, DM= Diabetes Mellitus, CKD=Chrnoic Kidney Disease.*

***Values are Represented as Means.*

The data suggests that in ICU there was not a significant difference in mortality due to ethnicity, BMI, duration of symptoms pre-admission or co-morbidity prevalence once the patient is admitted to ICU for invasive ventilation.

Table 2 demonstrated in ICU investigations. A number of statistically significant differences was found between the groups. In regards to arterial blood gas investigations, a lower initial P02 on admission to ICU (9.92 vs 11.27, P = 0.04), a lower peak acidosis level at any point during the ICU stay (pH 7.08 vs pH 7.22, P = < 0.0001) and a higher pCO2 level at any point during the ICU stay (pCO2 9.92 vs 8.88, P = 0.04) and all shown to be linked to increased mortality. Initial pH and pCo2 on admission to ICU was found to not have a significant bearing on outcome.

	Survival Group	Mortality Group	p-Value
Blood gas -			
Initial pH	7.32	7.28	0.07
Initial pCO2 (kPa)	6.06	6.49	0.13
Initial pO2 (kPa)	11.27	9.92	0.04
Lowest pH	7.22	7.08	<0.0001
Highest pCO2 (kPa)	8.88	9.92	0.04
Renal results -			
Initial Urea (mmol/L)	9.72	12.3	0.12
Initial Creatinine (µmol/L)	143	188.5	0.21
Peak Urea (mmol/L)	21.1	26.5	0.04
Peak Creatinine (µmol/L)	235.1	308.1	0.12
Admission lactate (mmol/L)	1.37	2.6	0.009
Peak lactate (mmol/L)	2.61	5.8	0.0001
Infection markers -			
Initial White cell count (WCC) (10^9/L)	9.3	11.5	0.04
Initial Neutrophil count (10^9/L)	7.27	10	0.06
Initial lymphocyte count (10^9/L)	1.34	0.97	0.24
Initial C-reactive Protein(CRP) (mg/L)	201	204	0.37
Peak WCC (10^9/L)	16.4	22.9	0.0002
Peak Neutrophil count (10^9/L)	13.3	19.8	0.0003
Lowest lymphocyte count (10^9/L)	0.54	0.5	0.28
Peak CRP (mg/L)	336	321	0.29
Misc -			
Initial D-dimer (ng/ml)	2943	4806	0.19
Peak D-dimer (ng/ml)	3020	4976	0.13

Table 2: *Showing In-Critical Care investigations.*

***Values are Represented as Means.*

With renal function investigations a higher peak urea level during the ICU stay (26.5 vs 21.1, P = 0.04) was found to be linked to mortality. Admission lactate levels (2.6 vs 1.37, P = 0.009) as well as peak lactate levels at any point during ICU stay (5.8 vs 2.61, P = 0.0001) were

both linked to increased mortality. Creatinine was found to have no significant effect on mortality. Initial Urea count on admission to ICU was found to have no effect on mortality, suggesting that initial renal function was not a predictive factor for mortality.

Infection marker analysis showed that an initial white cell count on admission to ICU (11.5 vs 9.3, P = 0.04) was linked to increased mortality. A higher peak white cell count (22.9 vs 16.4, P = 0.0002) as well as a higher peak neutrophil count (19.8 vs 13.3, P = 0.0003) at any point during the ICU stay was found to be linked with increased mortality. Lymphocyte and CRP was found to be non-significant between the 2 groups.

Table 3 demonstrates treatments given in ICU, ventilatory settings as well as patient complications. With treatments given in ICU, those requiring two or more inotropes to maintain an adequate mean arterial blood pressure, there was a significant increase in risk of mortality (28.5% vs 5.71%, P=0.03 for 2 inotropes; 0% survival for those requiring 3 inotropes). A more positive fluid balance at the end of 10 days was also suggestive of poor outcome (P=0.04). With ventilatory support, a high initial peak pressure (27.9 vs 25.9, P=0.04) was suggestive of poor outcome. Conversely, days being ventilated (22.1 vs 12.1, P=<0.001) and being tracheostomised (54.2% vs 20.5%, P=0.04) were suggestive of good outcome. With patient complications, having an arrythmia at any point during ICU stay requiring electrical or chemical intervention (51.2% vs 17.1%, P=0.03) was found to be strongly suggestive of poor outcome.

	Survival Group	Mortality Group	p-Value
Treatment -			
Early noradrenaline frequency	2.8%	26.3%	0.16
Renal replacement therapy	40%	60%	0.29
Fluid balance after 10 days (or discharge if earlier)	+1954 mls	+3586 mls	0.04
Muscle relaxant use (days)	6.63	6.02	0.39
Transfusion prevalence	44%	23%	0.19
Inotropic support (number of inotropes used) -			
Nil	11.4%	0%	
Single	82.8%	45.7%	0.12
Double	5.71%	28.5%	0.03
Triple	0%	25.7%	
Ventilatory settings -			
Initial Fio2	0.79	0.83	0.23
Initial PEEP (cmH20)	10.4	10.8	0.27
Initial Pmax (cmH20)	25.9	27.9	0.04
Max PEEP (cmH20)	13.3	13.7	0.30
Days ventilated	22.1	12.1	<0.001
Tracheostomy prevalence	54.2%	20.5%	0.04
Number of times proned (frequency)-			
0	51.4%	51.2%	0.77
1	22.8%	17.9%	0.67
2	5.71%	5.12%	0.91
3	14.2%	10.2%	0.64
4	2.85%	2.56%	0.94
>5	2.85%	12.8%	0.15
Complications -			
Arrythmia	17.10%	51.20%	0.03
MI	2.85%	15.30%	0.09
Early Proning	8.33%	30.70%	0.05
PE	2.8%	12.8%	0.15
Seizure	2.7%	7.69%	0.38
Chest drain required	8.57%	20.5%	0.21

Table 3: *Demonstrating In-Critical care Treatments and Complications.*

**MI=Myocardial Infarction, PE=Pulmonary Embolus **Values Demonstrated are Means*

****Percentages Represent Frequency Within the Group.*

The use of renal replacement therapy was found to have no significant predictive value in mortality. This was also true for the use of muscle relaxant usage between the 2 groups as well as the prevalence of blood transfusions.

Initial oxygen requirements post intubation, initial positive end expiratory pressure (PEEP) requirements and maximum PEEP requirements whilst being ventilated as well as choice of ventilation mode and number of times being proned was shown to have no predictive value in mortality. Early proning was found to have a P-value of 0.05 suggesting that early proning may have some predictive value in outcome.

Patient complications including suffering a myocardial infarction (MI) during the admission, developing a pulmonary embolism (PE) or seizures, and suffering a complication requiring a chest drain was shown to have no effect on overall outcome. Due to low numbers of patients in this study having confirmed MI and PE, thus reducing the power, this was not reflective of the international findings [12].

Based on the factors to be found statistically significant (Age, Initial pO2, Lowest pH, Highest pCO2, admission lactate level, peak lactate level, initial white cell count, initial neutrophil count, peak white cell count, peak neutrophil count, peak urea level, fluid balance, initial Pmax, days ventilated, presence of arrythmia, and requirement of early proning) a multivariate regression analysis was performed with outcome being the dependent value. The results are demonstrated in table 4. The R-squared value for the regression was found to be 0.692. The multivariate regression analysis demonstrated that the most statistically significant factors in predicting mortality was increasing age, requirement of early proning, presence of arrythmia and number of days on ventilator.

Significant Characteristic	p-Value
Age (years)	0.005
Initial pO2 (kPa)	0.366
Lowest pH	0.505
Highest pCO2 (kPa)	0.761
Admission lactate level (mmol/L)	0.169
Peak lactate level (mmol/L)	0.430
Initial White Cell Count (10^9/L)	0.122
Initial Neutrophil Count (10^9/L)	0.154
Peak White Cell Count (10^9/L)	0.961
Peak Neutrophil Count (10^9/L)	0.489
Peak Urea Level (mmol/L)	0.976
Fluid balance (mls)	0.441
Initial Pmax (cmH20)	0.729
Days ventilated	<0.001
Arrythmia present	0.048
Early proning required	0.011

Table 4: *Demonstrating multivariate regression with selected significant values.*

Discussion

This study looked at a multitude of factors in attempt to find prognostic factors in relation to outcome of those suffering from Covid-19 in the critical care setting. Due to the nature of the patients admitted to intensive care in the study, it is important to remember all these patients were in receipt of advanced respiratory support and not a range of basic oxygen requirements or non-invasive forms of ventilation. The overall mortality rate during this period (March to May) for this unit was 52.7% which was comparable to the UK mortality rate at the time for those receiving advanced airway support (52.4%) [6].

The study showed that age was a strongly prognostic factor in poor outcome, and especially in over aged 70 year olds [7]. Whilst it has been postulated that male gender is a risk factor for poor outcome in those with COVID-19 infection [8] (this is mirrored in the fact that over 75% of the patients admitted to ICU were male), once actually receiving advanced ventilatory support there was no difference in outcome between the genders.

Patient co-morbidities in the study group also mirrored national and international recognition that hypertension (seen in over 50% of the admitted patients) and diabetes mellitus (seen in over 25% of the admitted patients) are significant risk factors for severe covid-19 disease [8,9] However, once on advanced respiratory support there is no statistical difference in outcome with either of these co-morbidities or asthma, chronic obstructive pulmonary disease (COPD), ischaemic heart disease (IHD) or chronic kidney disease (CKD). Whilst these co-morbidities are present, the severity of the medical illness was not documented, for example whether patient had CKD stage 3 or stage 5. Additionally, the frailty score of the patients was not looked into or the APACHE II score or other scoring systems looking at premorbid state. Duration of symptoms pre-admission to ICU seemed to have no prognostic effect.

With covid-19 a novel infection with learning happening on a day by day basis, management of this disease changed over the period of 3 months of this study. One of the changes that came into effect later on during the pandemic was the use of CPAP for Covid-19. CPAP was something that was avoided at the start of the pandemic but later came into use on the medical wards and so the sample size of patients that had CPAP then came to ICU for advanced respiratory support was small compared to the total patient size 8 patients in survival group and 15 patients in mortality group). The number of days of CPAP pre intubation and ventilation was shown to have no effect on prognosis in this group of patients. Similarly, proning was something that was introduced later on during the pandemic on the medical wards to self-ventilating patients. Eight patients self-proned on the medical ward and were later admitted to ICU for advanced respiratory support. All these Eight had a bad outcome suggesting failure of self-proning has a strong prognostic characteristic.

Looking at in ICU investigations and treatments carried out, there was a number of test results and therapies that were strongly prognostic. Both a higher lactate on admission to ICU as well as a higher lactate during any point in the ICU stay were linked to increased mortality. This mirrored similar international studies [10]. Infact, during the course of the study, nobody with either an admission lactate above 4mmol/L or a in ICU lactate above 6mmol/L survived.

This trait was seen with a higher initial White cell count (WCC) on admission to ICU as well as a peak WCC and a peak neutrophil count in ICU [10]. Raised infection markers on laboratory test results being prognostic was also clinically backed-up with the amount of inotropic support being required as a prognostic factor. It was found that those requiring 2 or more inotropes was strongly suggestive of poor outcome. In this critical care unit in the study, noradrenaline is the first line inotrope used to support blood pressure in sepsis. A second agent is added when the noradrenaline infusion reaches the threshold of 0.5mcg/kg/min and is either vasopressin or adrenaline. This is suggestive that the presence of a septic sate, potentially secondary to a bacterial infection on-top of COVID-19 infection has a poor prognosis. The fluid balance at the end of 10 days was found to be statistically significantly higher in the mortality group which may also be an indicator of more severe septic state as increased amount of fluids may have been given due to the septic state to catch fluid losses.

C-Reactive protein was found to be raised in both group but showed to have no significant difference in the groups. This was also true of a low lymphocyte count which was thought to be characteristic of Covid-19 [11] but there seems to be no prognostic difference.

In relation to renal tests and treatment, renal markers on laboratory tests on admission to ICU seemed to have no prognostic value. This was also true of having renal support whilst in ICU in the form of hemofiltration or dialysis. This goes against other studies. However, a higher peak urea count during ICU stay was seen to be prognostic.

All of the patients admitted into ICU during this period required invasive ventilatory support. Admission pO2 on the blood gas investigation showed that a lower level was prognostic. During ICU stay a lower pH and a higher pCO2 was found to be prognostic. The oxygen requirements on admission to ICU and PEEP levels on admission to maintain oxygenation was found to be non-prognostic. However, a hight peak pressure on the ventilator on admission was found to be prognostic suggesting that poorly compliant lungs early on is prognostic for poor outcome. The number of times proning was needed was not prognostic but the requirement for early proning (i.e. proning within 24hours of admission to ICU) may be considered prognostic for poor outcome.

As already mentioned, the novel nature of the Covid-19 infection meant that management strategies changed during the period of the study based on new research and guidelines being introduced, for example the increased risk of thrombotic events in Covid-19 patients and management strategies implemented to counter this. The ICU mortality figures reduced month on month during this 3-month period which mirrored the national trend where mortality reduced month on month. However, in the scope of this study, the 3 month period has been looked at as a whole.

Key message

Sepsis markers and clinical findings were suggestive and hypothesised to be prognostic for a bad outcome but unfortunately it was not possible to determine whether this sepsis is due to Covid-19 in all cases or whether super-imposed bacterial infections were also had a part to play as not all these patients had positive cultures and markers such as Procalcitonin were not available at the centre. Other limitations of the study included the collection of thromboembolic complications which were not always able to be fully investigated and confirmed with imaging due to instability of the patients. Markers such as ferritin and vitamin D which may be a marker of prognosis was not collected in sufficient quantities on these patients to be able to make powerful conclusions from.

All the patients studied were from one centre, meaning the patient demographics may not be as fully representative as on a larger scale both nationally and internationally. Most of these patients represent the same socioeconomic background and so this may be a confounding factor in the results.

- Secondary sepsis or super-imposed infections are strong prognostic factors for a poor outcome.
- Use of multiple inotropes is a strong prognostic factor for a poor outcome.
- The longer the time requiring ventilation, the better the outcome – suggesting the infection and inflammatory process settles after a number of days.
- Late presentation and initial difficulty in oxygenation after intubation are suggestive of poor outcome.
- Patients that failed self-proning have a poor prognosis.

Declaration of Interest

The authors have no conflict of interests to declare.

Funding

No funding was requested or required for this study.

Bibliography

1. World Health Organization. Pneumonia of unknown cause-China (2020).
2. Centers for Disease Control and Prevention. 2019 Novel Coronavirus (2019-nCoV) Situation Summary (2020).
3. Worl dometer. Covd-19 Coronavirus Pandemic (2020).
4. Jang JG., *et al.* "Prognostic Factors for Severe Coronavirus Disease 2019 in Daegu, Korea". *Journal of Korean Medical Science* 35.23 (2020): e209.
5. ICNARC. "ICNARC report on COVID-19 in critical care (2020).
6. ICNARC. "ICNARC report on COVID-19 in critical care (2020).
7. Wang Z., *et al*. "Clinical Features of 69 Cases With Coronavirus Disease 2019 in Wuhan, China". *Clinical Infectious Diseases* 71.15 (2020): 769-777.
8. PD Wendel Garcia., *et al.* "Prognostic factors associated with mortality risk and disease progression in 639 critically ill patients with COVID-19 in Europe: Initial report of the international RISC-19-ICU prospective observational cohort". *EC linical Medicine* (2020).
9. Zhou F., *et al*. "Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study". *Lancet* 395.10229 (2020): 1054-1062.
10. Wu C., *et al*. "Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China". *JAMA Internal Medicine* 180.7 (2020): 934-943.
11. Guan WJ., *et al*. "China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China". *The New England Journal of Medicine* 382.18 (2020): 1708-1720.
12. Guo T., *et al*. "Cardiovascular Implications of Fatal Outcomes of Patients with Coronavirus Disease 2019 (COVID-19)". JAMA Cardiology 5.7 (2020): 811-818.
13. Gasparini M., *et al*. "Renal impairment and its impact on clinical outcomes in patients who are critically ill with COVID-19: a multicentre observational study". *Anaesthesia* (2020).

Volume 5 Issue 2 February 2021