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Research Article

Status at Discharge and Efficacy of Protocolized Medications for COVID-19 in Intensive Care

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ABSTRACT

Introduction: The use of certain medications in COVID-19 affects the discharge status of patients.

Objective: To relate the state of discharge, with age, condition and efficacy of protocolized medications in severe and critical patients with COVID-19.

Methods: An epidemiological, retrospective investigation was carried out in the intensive care unit of the provincial clinical surgical teaching hospital doctor León Cuervo Rubio, the universe and sample consisted of those admitted from March 2020 to July 2021, the variables were grouped in tables. According to affinity, the results were expressed by odds ratio, absolute risk reduction, in addition, the absolute and relative frequencies were estimated, the data were processed, using the statistical software MedCalc for Windows.

Results: Most of the patients were discharged alive 88 (66.67%), mortality was similar in the age groups of 70 to 79 and 80 to 89 years 12 (9.72%), the alive ones are serious 42 (34.15%), critically unstable deceased 22(17.8%), when relating the state at discharge with medications, those who receive Jusvinza have a high probability of being discharged alive 94(OR 389.400, CI-22.3484 to 6784.9271, P<0.0001), it also reduces mortality by 70.7% (CI-17.28, 694e), with a high sensitivity of 87.23% and specificity of 100%.

Conclusion: Most of the discharges are alive; the most effective medication used is Jusvinza peptide, as it increases the probability of life of patients and its positive effect on mortality.

Keywords: COVID-19, Sensitivity, Specificity

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INTRODUCTION

The current COVID-19 epidemic is produced by a type of coronavirus called SARS-CoV-2, which has a high aggressiveness and lethality and has also created a social and political crisis at the international level (Moh, 2020).

The SARS-CoV-2 infection was detected for the first time in the People's Republic of China in the province of Wuhan on December 20, 2019, from that moment the disease progressed rapidly so that in a short time it was considered by the WHO as the new pandemic (PAHO, 2020).

Many researchers such as Bhimraj A, *et al*., 2020 show that there is little scientific evidence of the different drugs used at the beginning of the pandemic, which has caused a constant evolution in action protocols at the international level.

Cuba has not been immune to this situation (Peña JP, 2020), it has presented a high number of positive cases as well as admissions and deaths since the beginning of the pandemic, for which it has had to make constant changes in its protocols and way of acting due to the high power mutant that presents the new coronavirus.

In Cuba, since January 2020, the Ministry of Public Health created a work strategy that involves all state agencies as well as the entire population (MOPH, 2020).

COVID-19 is a disease that presents 3 phases and in correspondence with them, different therapeutic alternatives have been proposed. The initial phase would be characterized by a high viral load, so it would be the ideal time to administer effective antiviral treatment. In a second phase, the inflammatory response would predominate, where anti-inflammatory drugs play the fundamental role and a third phase characterized by a state of hyper inflammation, for which the therapeutic alternative will be to inhibit or reduce this process of exaggerated response of the organism that could lead to the death.

The new pandemic represents a challenge for the governments of the world and the international scientific community in the search for alternatives and medicines for its control and eradication (Díaz E, *et al*., 2021; Tejeda GJJ, *et al*., 2020).

Researchers such as Tejeda GJJ, *et al*., 2020 show that there is no specific treatment for the disease, despite the fact that various medications are used with a certain degree of efficacy.

Román BR, *et al*., 2020 in a study carried out in Peru and Bolivia shows that the drugs used to treat COVID-19 have various side effects and are a danger to the health of the population.

Scientists such as Sánchez MLK, *et al*., 2021 in their research demonstrate the positive effect on mortality when high doses of steroids (methylprednisolone) and azithromycin are used for more than 5 days.

Cuba, since the emergence of the first cases of COVID-19, created a group of experts in charge of preparing a national action protocol for the prevention, control and eradication of the disease.

In the province of Pinar del Rio, Cuba, the Doctor León Cuervo Rubio Provincial Clinical Surgical Teaching Hospital was selected for the treatment of patients carrying the SARS-CoV-2 infection, in its intensive care units serious patients were admitted and Therefore, it is pertinent to carry out the following investigation with the objective of relating the discharge status, with age, condition and efficacy of protocolized medications in seriously and critically ill patients with COVID-19.

MATERIALS AND METHODS

Type of study

It is an epidemiological, analytical, observational (retrospective cohort).

Research period: March 2020 to July 2021.

Research site

Intensive care units belonging to the "Doctor León Cuervo Rubio" Clinical Surgical Teaching Provincial Hospital, in the city of Pinar del Rio, Cuba.

Participants

All serious and critical patients admitted to intensive care units

with SARS-CoV-2 (COVID-19) infection.

Inclusion criteria

Patients admitted to intensive care units with SARS-CoV-2 (COVID-19) infection, both sexes, older than 20 years with positive real-time PCR.

Exclusion criteria

Patients admitted to intensive care units with SARS-CoV-2 (COVID-19) infection, both sexes, older than 20 years with positive real-time PCR, deceased within 24 hours of admission.

Elimination criteria

Patients admitted to intensive care units that do not have SARS-CoV-2 (COVID-19) infection, negative real-time PCR.

Universe and sample

All patients admitted to intensive care units who meet the inclusion criteria (126 eligible patients, 123 evaluated for eligibility, 123 recruited). Time in which the variables were collected: for the collection of information, a clinical file supported in Excel 2013 was prepared, which contained all the variables necessary in the study.

Variables: Age, condition at discharge, patient's condition (severe, critically stable, critically unstable), medications used (steroids, Jusvinza, anticoagulants, Cimaher, antibiotics, recombinant erythropoietin).

Response variables: Status of patients at discharge (alive or deceased) according to age group, for the relationship of medications with status at discharge (alive, deceased), the adjusted Odds Ratio (OR) of each was determined variable. Confidence Intervals (CI) of 95% and level of significance (P) were also estimated. The percentage that the drug decreases mortality was calculated by calculating the Absolute Risk Reduction (ARR), in addition, the predictive value of the drugs used was estimated (Sensitivity, Specificity, Positive likelihood ratio, Negative likelihood ratio, and prevalence of the disease, predictive value positive, negative predictive value, and accuracy). For statistical analysis, the MEDCAL software was used.

Definitions

Status at discharge: Condition in which the patient is discharged (alive or deceased).

Serious: When there is a significant threat to your life or a high risk of death.

Stable critical: When multiple or sequential organ failures of vital functions occur during severity, vital signs are stable and death is a likely outcome. They are recoverable.

Unstable critical: When multiple or sequential organic failures of vital functions occur during its severity, its vital signs are not stable and in this case, death is an imminent result. They are not recoverable.

Absolute risk ratio: It is the lower the probability that the patient will die, after applying the medication.

Sensitivity: Probability that the patient will be discharged alive when the drug is used.

Specificity: Probability that the patient will be deceased when the drug is not used.

Positive likelihood ratio: Indicates at what point a person who is administered the medication is discharged alive.

Negative likelihood ratio: Indicates at what point a person who is not administered the medication is discharged deceased.

Positive predictive value: Probability that the patient will be discharged alive when the drug is administered.

Negative predictive value: Probability that the patient will be discharged deceased when the drug is not administered.

Precision: Overall probability that the drug is effective in the state at discharge alive.

RESULTS

Table 1 shows that the majority of patients were discharged alive 82 (66.67%) and mortality is higher and similar in the age groups of 70 to 79 and 80 to 89 years 12 (9.76%). *Table 2* states that the largest number of patients who were discharged alive had the serious condition 42 (34.15%) and the critically unstable deceased 22 (17.89%). *Table 3* shows that individuals receiving treatment with Jusvinza have the highest probability of being discharged alive 82 (66.67%), (OR 389.400, CI-22.3484 to 6784.9271, P<0.0001) and its use decreases mortality 70 .7% (CI-17.28 to 18.694) in absolute terms. *Table 4* shows that of the protocolized drugs used to treat severe and critical patients with COVID-19, jusvinza has the highest predictive value on survival (sensitivity of 87.23% and specificity 100%), with a predictive value positive of 100% and an accuracy of 90.24%.

Table 1: Discharge status of severely and critically ill patients according to age groups carriers of SARS-CoV-2 (COVID-19) infection admitted to the care units of the Doctor León Cuervo Rubio Teaching Provincial Clinical-Surgical Hospital in Pinar del Rio, Cuba

Age groups (years)	State at discharge				Total	
	Deceased		Alive			
	n	%	n	%	n	%
20-29	0	0	3	2.44	3	2.44
30-39	2	1.63	6	4.88	8	6.5
40-49	3	2.43	7	5.69	10	8.13
50-59	1	0.81	9	7.32	10	8.13
60-69	9	7.72	11	8.94	20	16.26
70-79	12	9.76	19	15.45	31	25.20
80-89	12	9.76	23	18.7	35	28.46
>90	2	1.63	4	3.25	6	4.88
Total	41	33.33	82	66.67	123	100

Table 2: Relationship between patient condition and discharge status

Patient condition	State at discharge				Total	
	Deceased		Alive			
	n	%	n	%	n	%
Critical, stable	11	8.94	32	26.02	43	34.96
Unstable, critical	22	17.89	8	6.50	30	24.39
Serious	8	6.5	42	34.15	50	40.65
Total	41	33.33	82	66.67	123	100

Table 3: Relationship between the use of medications and the discharge status of severe and critical patients with SARS-CoV-2 infection

Medicines	Status of patients at discharge						OR	IC (95%)	P	RAR	IC (95%)
	Vivos		Fallecidos		Total						
Jusvinza	n	%	n	%	n	%	389.4	22.3484	P<0.0001	70.70%	-17.28 and 18,694
Yes	82	66.67	12	9.75	94	76.42					
No	0	0	29	23.58	29	23.58					
Total	82	66.67	41	33.33	123	100					
Steroids											
Yes	72	58.54	41	33.33	113	91.87	0.0832	0.0048	P=0.0887	12.20%	-19.95 and 19,705
No	10	8.13	0	0	10	8.13					
Total	82	66.67	41	33.33	123	100					
Anticoagulants											
Yes	82	66.67	35	28.45	117	95.12	30.2113	1.6569	P=0.0214	14.60%	-19.95 and 20,704
No	0	0	6	4.88	6	4.88					
Total	82	66.67	41	33.33	123	100					
Antibiotics											
Yes	82	66.67	33		115	93.4	41.8657	2.3493	P=0.0110	19.50%	-20.06 and 20,446
No	0	0	8	6.5	8	6.5					
Total	82	66.67	41	33.33	123	100					
Cimaher											
Yes	9	7.72	9	7.72	18	15.44	0.4384	0.1592	P=0.1106	11%	-20.06 and 3.071
No	73	58.95	32	25.61	105	84.56					
Total	82	66.67	41	33.33	123	100					
Recombinant erythropoietin											
Yes	33	26.83	20	16.26	53	43.09	0.7071	0.3324	P=0.3683	8.50%	-9.31 and 9.139
No	49	39.84	21	17.07	70	56.91					
Total	82	66.67	41	33.33	123	100					

Table 4: Predictive value of the drugs used in the treatment of severe and critical patients with SARS-CoV-2 infection

Medicines	Value (%)	Confidence Interval (95%)
Jusvinza		
Sensitivity	87.23	78.76% and 93.23%
Specificity	100	88.06% and 100%
Positive likelihood ratio		
Negative likelihood ratio	0.13	0.08 and 0.22
Disease prevalence	76.42	67.93% and 83.61%
Positive predictive value	100	
Negative predictive value	70.73	58.76% and 80.39%
Accuracy	90.24	83.58% and 94.86%
Antibiotics		
Sensitivity	71.3	62.12% and 79.35%
Specificity	100	63.06% and 100.00%
Positive likelihood ratio		
Negative likelihood ratio	0.29	0.22 and 0.38
Disease prevalence	93.5	87.59% and 97.15%
Positive predictive value	100	
Negative predictive value	19.51	15.38% and 24,44%
Accuracy	73.17	64.43% and 80.76%
Anticoagulants		
Sensitivity	70.09	60.93% and 78.20%
Specificity	100	54.07% and 100%
Positive likelihood ratio		
Negative likelihood ratio	0.3	0.23 and 0.39
Disease prevalence	95.12	89.68% and 98.19%
Positive predictive value	100	
Negative predictive value	14.63	11.50% and 18.45%
Accuracy	71.54	62.71% and 79.31%
Steroids		
Sensitivity	63.72	54.14% and 72.55%
Specificity	0	0.00% and 30.85%
Positive likelihood ratio	0.64	0.55 and 0.73
Negative likelihood ratio		
Disease prevalence	91.87	85.56% and 96.03%
Positive predictive value	87.8	86.23% and 89.22%
Negative predictive value	0	
Accuracy	58.54	49.31% and 67.35%
Erythropoietin		
Sensitivity	40.24	29.56% and 51.66%
Specificity	30	19.62% and 42.13%
Positive likelihood ratio	0.57	0.42 and 0.78
Negative likelihood ratio	1.99	1.34 and 2.97
Disease prevalence	53.95	45.68% and 62.05%
Positive predictive value	40.24	33.17% and 47.75%
Negative predictive value	30	22.33% and 38.99%
Accuracy	35.53	27.94% and 43.69%

DISCUSSION

SARS-CoV-2 infection continues to be an important study problem in intensive care units due to its high morbidity and lethality at the national and provincial levels.

The study shows that the highest incidence of serious and critical cases occurs from the elderly, due to the lability that these people present in their health status.

The authors in their study state that the majority of patients are discharged alive as a result of multiple factors such as the existence of a properly conceived national protocol, the use of indigenous medicines with proven efficacy and effectiveness created by our scientists, in addition to having the necessary supplies and intensive care rooms duly equipped for the treatment of patients

The deceased are a minority and the elderly predominate, the result according to the authors is due to the fact that in this stage of life the organism undergoes transformations due to aging that make it more vulnerable as well as the appearance of chronic non-communicable diseases to do to the patient more labile, that is, their physical and health status facilitates the transition from serious to critical status and death.

The authors conclude that the low lethality could be attributed to the adequate follow-up of hospitalized patients, associated with constant advice by experts, as well as adherence to the diagnostic-therapeutic protocol, prepared by the Cuban Ministry of Public Health.

Zavaleta HM, *et al*., 2021 in their study factors associated with death from COVID-19 in patients admitted to a public hospital in Tacna, Peru shows that 32.9% died during follow-up and 67.1 were discharged alive and the main risk factors for death are increased age, lactic dehydrogenase and oxygen saturation below 90, a similar result to that shown by the authors but differs in terms of the number of living and deceased discharged patients.

Ferrando C, *et al*., 2021 in their investigation of characteristics, clinical course and factors associated with mortality in the ICU of critically ill patients infected with SARS-CoV-2 in Spain: A prospective, cohort and multicenter study shows that mortality in the ICU was of 31%. Complications are more frequent in non-survivors, such as acute respiratory distress Syndrome, acute renal failure, shock and arrhythmias, a result that differs from that shown in the present study and coincides only in low mortality.

Ferrando C, *et al*., 2021 in a study entitled clinical and epidemiological characterization of patients confirmed with COVID-19 in the province of Santiago de Cuba, concludes that 94.5% of those affected were discharged alive from the institution, a predominance was found male (52.7%), a result very different from that reported by the authors (Ferrer CJE, *et al*., 2020).

Patients admitted to the ICU have an order of priority: First priority is for unstable patients who require intensive help that cannot be offered outside the unit, priority two is for those who require intensive monitoring and who may require immediate intervention (César AGR and Torres MC, 2017), priority three is for patients who can receive intensive treatment to improve or stabilize exacerbations of chronic diseases, but it is possible to limit their treatment and support (Castro CJ, *et al*., 2021).

There are four basic characteristics that define the critical patient-

1. Serious illness.

2. Potential to reverse the disease.

3. Need for continuous nursing care and assistance.

4. Need for a technical area (ICU).

Sometimes critical patients due to the degree of condition and risk factors continue an unfavorable evolution characterized by hemodynamic instability, hence the term unstable critical, so the possibility of dying is high, as the study shows.

Castro CJ, *et al*., 2021 states that, in practical terms, a patient can be classified as serious when there is a significant threat to her life or a high risk of death. A patient will be in critical condition when multiple or sequential organic failures of their vital functions occur during its severity, a criterion with which the authors agree.

SARS-CoV-2 (COVID-19) infection has three stages-

- Early infection-Mild constitutional symptoms (Fever, dry cough, headache and diarrhea), lymphopenia, increased prothrombin time and slight increase in D-dimer and LDH, treatment is to promote immunosufficiency.
- Symptompatic hypoxia-Symptoms are dyspnea, hypoxia, PO_2/FO_2 ratio less than 300, abnormal chest radiological image, elevated transaminases, normal or low procalcitonin, treatment is to promote immunosufficiency
- Systemic hyperinflammation-SDMA, ARDS, SHOCK, heart failure, elevated markers of inflammation (CRP, LDH, Ferritin, elevation of troponin and NT-proBNP, treatment is immunosuppression (steroids, human immunoglobulin, IL-1 inhibitors, IL-G, IL-2, JAK cytokine inhibitors, Jusvinza).

In other words, the treatment guidelines for patients admitted to the intensive care unit when they are in phase 2-A and phase 3 of the disease where inflammation predominates, the treatment is immunomodulators, in our environment there is a national protocol to treat the same in which steroids, anticoagulants and jusvinza are prescribed mainly which has allowed obtaining favorable results as the authors express in their research.

Jusvinza is a peptide that inhibits the Janus or JAK cytokines, which are increased in the state of hyperinflammation as well as the decrease in the levels of proinflammatory cytokines: Tumor Necrosis Factor (TNF) and Interleukins (IL), 1,7,9 and 12. It is an indigenous drug which has shown good effectiveness and few adverse effects, a result that is evident in the authors' study where patients have a high probability of being discharged alive with the use of the drug, in addition to reducing mortality in 70.2% absolutely.

Horta MD, *et al*., 2022 in their study CIGB-258 (Jusvinza), hyperinflammation inhibitor peptide in patients with COVID-19, concludes that CIGB-258 induced clinical and radiological improvement in patients, in correspondence with its pharmacokinetic and biodistribution profile. This improvement was associated with a decrease in biomarkers of systemic inflammation, a result similar to that shown by the authors.

Rodríguez RV, *et al*., 2021 in their study, treatment with Jusvinza decreases hyperinflammation and hypercoagulation in critically ill patients with COVID-19, shows that treatment with Jusvinza induced clinical improvement in patients, associated with the decrease in several biomarkers of inflammation and coagulation. The survival of patients treated with Jusvinza was significantly higher than the survival of patients not treated with this peptide, a result that agrees with that shown by the authors.

One of the objectives to prevent the progression of severe pneumonia towards multi-organ dysfunction in SARS-CoV-2 infection is drug treatment, most patients received the main drug treatment guidelines: Steroids (Scolari MJ, 2020) at an immunomodulatory dose, heparins (Lazo PG, *et al*., 2021) to prevent thromboembolic phenomena, antibiotics to control superimposed nosocomial infections, Jusvinza (Rodríguez VR, *et al*., 2020; Oscar VC, 2020) a peptide inhibitor of Janus cytokines, which are increased in patients with severe forms of the disease, erythropoietin (Díaz POJ, *et al*., 2004) in patients with chronic kidney disease, which allowed a large number of severe and critical patients to survive the disease.

When the repercussion of medications on the discharge status of patients (alive or deceased) is measured, as the authors do, it is pertinent to carry

out the evaluation of its predictive value through the calculation of sensitivity, specificity, which allows determining if there is a proper relationship.

The analysis shows that the best predictive value among the drugs that guarantee the status at discharge alive is the use of Jusvinza with a sensitivity (87.23%) and specificity (100%), which means that severe and critical patients Carriers of the SARS-CoV-2 (COVID-19) infection when Jusvinza is administered have an 84% chance of being discharged alive and when it is not administered it has a 100% probability of being deceased.

CONCLUSION

When relating the state at discharge with medications, those who receive Jusvinza have a high probability of being discharged alive. Most of theft discharges are alive; the most effective drug used is Jusvinza peptide, as it increases the probability of life of patients and its positive effect on mortality. The results obtained by the authors show that despite the limitations to access state-of-the-art technology, Cuba has a group of scientists capable of creating drugs to treat complex and very aggressive diseases. As only patients over 20 years of age were included, it is possible that these findings cannot be extended to younger patients; however, it will help future research on the subject.

ETHICAL APPROVAL

The authors declare that this study was approved by the scientific council of the participating institutions. The research was conducted in accordance with the principles of medical ethics, the Declaration of Helsinki. We proceeded according to current institutional and national ethical standards. In the event that this manuscript contains images or personal information of patients, they authorized the disclosure of this information.

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