Observational study on the assessment of prognostic factors for mortality in patients with SARS-CoV-2 pneumonia

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Research Article

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Abstract

Coronavirus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Infection can range from asymptomatic or paucisymptomatic to more severe forms with pneumonia and multiorgan dysfunction. Understanding the prognostic factors that influence the course of hospitalization and the onset of more severe forms of the disease has been one of the most important challenges of this pandemic. The main objective of this observational study is to establish some clinical and laboratory parameters useful for defining the prognosis of COVID-19 patients. The secondary end point is to understand how glycaemic changes affect the days of hospitalization. We observed how hypernatremia, hypocaliamia, newly diagnosed renal insufficiency and altered glycemic values were the main complications that arose during hospitalization, especially in patients staying in high-intensity units. Interestingly, we also noted how the altered glycemic values correlated with a longer length of hospital stay. We hope this study will help to better understand what the most important factors to be aware of for COVID-19 patients.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially called novel coronavirus (CoV) 2019 is responsible for Coronavirus disease 2019 (COVID-19), current pneumonia outbreak that began in early December 2019 near the Wuhan city, Hubei province, China. From the phylogenetic analysis carried out with complete genomic sequences, bats appear to be the reservoir of the SARS-CoV-2, but the host or intermediate hosts have not been detected so far, although three main areas of work are already underway in China to investigate.

It is also believed that mammals can act as intermediate hosts in which, as a result of recombination and mutations, genetic variants are generated that may be responsible for the "species jump" to humans.

Coronaviruses primarily cause infections of the gastrointestinal and respiratory tract and are inherently classified into four main types: Gammacoronavirus, Deltacoronavirus, Betacoronavirus, and Alphacoronavirus.

Coronaviruses have long been regarded as commonplace seasonal respiratory viruses. However, in the last 18 years, they have been responsible for diseases burdened by high mortality: the SARS (severe acute respiratory syndrome) of 2002, an epidemic apparently resolved in 2003, and the Middle East respiratory syndrome (MERS), which occurred in 2012 and still present with sporadic cases.

COVID-19 involves not only the lungs but a multiplicity of organs and leaves as relics the possibility of disabling sequelae, primarily neurological, pulmonary, cardiovascular, and nephrological. Furthermore, it involves serious social repercussions since the most vulnerable populations cannot avoid exposing themselves to the risk of contagion and more often have comorbidities [diabetes, obesity, chronic obstructive pulmonary disease (COPD), etc.]. This is without counting the economic repercussions, documented by a fall in gross domestic product (GDP) in the world, greater not only than the banking crisis of 2008 but also the great depression of 1929.

COVID-19 pandemic has completely destabilized patient management in healthcare. In a short time, entire hospitals and public and private health structures have been forced to revolutionize the diagnostic-therapeutic process. Based on the natural evolution of the disease and its clinical presentation, specific departments have been created from scratch at various intensities of care.

In COVID – 19 wards, patient prototype is characterized by comorbid subjects, therefore more difficult to manage clinically, as well as elderly or defunct. This needs a holistic, mainly internistic approach, to be able to manage the complexity of treatments that these patients require in order to obtain favorable prognostic outcomes.

COVID – 19 subjects often need non-invasive ventilatory assistance, with possible evolutions to invasive treatments.

Objectives Of The Study

Primary end point

The main objective of this observational study is to establish some clinical and laboratory parameters useful for defining the prognosis of COVID-19 patients, hospitalized in wards with high and low intensity of care.

Secondary end point

The secondary objective is to understand how glycemic changes affect the days of hospitalization (LoS) and the patient's clinical course, in terms of major and minor complications during hospitalization. Furthermore, by monitoring the blood gas analytical profile, it is outlined as a further outcome whether the use of non-invasive mechanical ventilation affects the improvement of gas exchange and, indirectly, the average hospital stay.

Study Design

Experimental Plan

This is a single-center observational clinical study investigating evaluable prognostic factors among patients with COVID-19 syndrome.

The data of all adult patients who passed through the high and low intensity COVID-19 wards in the period between November 2020 and January 2021 were analyzed.

An important stratification of the population is linked to the type of patient, whether acute or critical, based on the intensity of care and assistance provided. Subsequently, the set of comorbidities presented by single individuals was considered, using the Charlson Comorbidity Index (CCI) as a score.

From a metabolic point of view, the type of nutrition in place was highlighted, the insulin schemes used (in terms of hypoglycemic effects), and the variations in the entry and exit of the main electrolytes (Sodium (Na +) and Potassium (K +).

Finally, the blood gas collection, during non-invasive ventilation or oxygen therapy delivery, further allowed the implementation of prognostic knowledge.

POPULATION STUDIED

A sample of n.= 100 patients (63 male, 37 female), divided into two homogeneous groups based on the intensity of care (n. = 50 in high-intensity care (HIC), and n. = 50 in low-intensity care (LIC) unit), was analyzed to obtain a significance level of 0.05 and a power of 0.90. The average age of the low-intensity care population is 74.06 ± 16.05 years, the high-intensity patients' average age is 81 ± 13.21 years. All patients have radiological signs of COVID-19 related pneumonia. Of these 100 patients, 67 are affected by type 2 diabetes mellitus (49 in the HIC group, 18 in the LIC group), 72% under oral hypoglycemic treatment while 28% under insulin therapy. Further pathologies most represented are obesity (60% in the HIC group, 40% in the LIC group), chronic obstructive pneumonia (75% in the HIC, of which 50% under home oxygen therapy, 55% in the LIC group, of which 20% with home oxygen therapy), arterial hypertension (80% in the high-intensity group, of which 40% with a history of ischemic heart disease and 20% with a history of major cerebrovascular events , 60% in the LIC group, of which 30% with a history of ischemic heart disease and 15% with a history of major cerebrovascular events), solid neoplasms (40% in the HIC group, 15% in the LIC group) and haematological (30% in the HIC group, 10% in the LIC one), chronic renal failure with evolution to acute (75% in the HIC group, 55% in the LIC group).

Patients were recruited from St. Andrea Hospital (Rome), in "COVID-19 unit". The study has been subjected to review and approval by the Ethics Committee of the same hospital, in accordance with the guidelines of the Ministry of Health and the Declaration of Helsinki with revision of 2000.

All study participants have read and approved the informed consent for the processing of personal data.

Subjects included in the study are over 18 years of age, are able to intend and have tested positive for SARS COV2 infection at the time of enrollment.

EFFECTIVENESS EVALUATION

In order to understand which is the most correct prognostic evaluation of patients with COVID - 19 syndrome, parameters and timing were analyzed as listed below.

Demographics

• Date of birth

• Gender

<u>Medical history</u>

<u>District and general physical examination</u>

• Physical state

• Skin

• Head and neck

• Lymph node

• Thyroid

• Cardiovascular system

• Respiratory System

• Abdomen

• Other

• Cardiovascular parameters

• Blood pressure and heart rate

• ECG

<u>Biochemical analysis</u>

• Fasting blood sugar

• Glycated hemoglobin (for diabetic patients)

• Hematological profile

• Electrolytic profile

• Glycemic profile during the hospital stay (from the first day of hospitalization to the seventh day, not including the first 24 hours of transit in the ward)

• Blood gas analysis profile

<u>Drug history</u>

Days of hospitalization

DIRECT ACCESS TO THE ORIGINAL DOCUMENTATION

The investigator must allow the National Regulatory Authority, and the staff designated by the Independent Ethics Committee or the coordinating investigator, direct access to the complete original documentation - and its verification - including informed consent, signed by enrolled patients or their Legal Representatives, and medical records or outpatient records. Persons who have direct access to this documentation should take all reasonable precautions to maintain the patient's identity and all information that is owned by the Coordinating Investigator, in accordance with applicable laws.

QUALITY ASSURANCE PROCEDURES

The organization, monitoring and quality assurance of this study will be the responsibility of the coordinating investigator.

Clinical monitoring

Clinical monitoring will be carried out by qualified persons appointed by the Coordinating Investigator and will be conducted according to the guidelines of the ISO 14155-1 Standard. Furthermore, the monitoring activities will include verifying the correct compilation of the CRFs and, where applicable, the consistency between the source documents and the electronic archived data used for the randomization procedures. The coordinating investigator will ensure the practical training of the personnel involved in the study on surgical and medical techniques and on the filling of CRFs.

Data review and audit

Data review and audits will be performed by qualified persons appointed by the coordinating investigator.

STATISTIC ANALYSIS

There are two analysis populations that will be used in the assessment of treatment differences: intent-to-treat (coinciding with the analysable population for safety) and evaluable efficacy.

The intent-to-treat (ITT) population consists of all patients who received medical treatment. The population evaluable for efficacy consists of all ITT patients who completed the study, i.e. all patients in whom the primary endpoint was measured.

Effectiveness analysis

All categorical variables (binary or with more than two modalities) will be analyzed using a Chi-Square test or Fisher Exact test when appropriate. For continuous variables the relative deltas will be calculated as the difference between the 1-year values and the baseline values over the baseline values and will be analyzed by means of a t-test for independent samples. Differences between groups and trends over time will also be analyzed using the Analysis of Variance for Repeated Measurements.

Safety and tolerability analysis

All patients who have undergone surgical treatment will be included in the safety analysis. Safety analyzes will include tabulation of the type and frequency of any adverse events recorded. Between-group differences in the percentage of patients reporting an adverse event will be analyzed using Fisher's exact test, while all ongoing laboratory safety assessments will be summarized using descriptive statistics and related deltas calculated. The deltas will be analyzed by the Mann-Whitney U test or the T test as appropriate.

ETHICAL ASPECTS

All parties involved in the study agree and verify that the experimental study is conducted in compliance with the ethical principles deriving from the Helsinky Declaration, the guidelines of Good Clinical Practice (GPC) and applicable laws.

Ethical permissions

The coordinating investigator is responsible for submitting this clinical protocol to the local Independent Ethics Committee (IEC) for approval prior to enrolling patients. The coordinating investigator will need to provide the IEC with all documents necessary to obtain approval. Such study will be notified or submitted for approval by the Health Authority in accordance with applicable laws.

Informed consent

Prior to the start of the study, the Informed Consent forms to be provided to patients and / or their Legal Representatives must be submitted to the Independent Ethics Committee for review and approval, along with the protocol.

Results

Primary end point

The low-care-intensity patient group had an average CCI of 5 ± 4.

40% of this group had major and/or minor complications during their hospital stay

including (see Graphic 1):

- Bacterial pneumonia (37%), of which 9% complicated by severe respiratory failure, which required transfer to intensive care units

- Exitus (19%)

- Sepsis (19%)

- Acute renal failure (13%)

- Acute ischemic heart disease (3%)

It is interesting to note that the subjects included in the latter group show alterations in the hydro electrolytic profile and common laboratory values (see Graphic 2):

- Hyponatremia (32%)

- Hypernatremia (5%)

- Hypokalemia (21%)

- Newly diagnosed acute renal failure (10%) with a mean creatinine level within this group of 1.8 mg / dl ± 0.3

- Altered glycemic values (32%) - considering that in this group 70% of patients were suffering from type 2 diabetes mellitus already before entering the ward - with a daily average blood glucose level of 204 mg / dl ± 43.

As foreseeable, in the group of patients with hospital complications, an increase of almost 50% in the average hospital stay (LoS 21 ± 3) was observed compared to the group of subjects without intra-hospital complications (Los 11 ± 2) (p <0.05) (see Graphic 3).

The HIC group had a CCI of 7 ± 2.

70% of this group had major and/or minor complications during their hospital stay

including (see Graphic 4):

- Bacterial pneumonia (22%), of which 25% complicated by severe respiratory failure

- Exitus (18%)

- Sepsis (16%)

- Acute renal failure (19%)

Common hydro electrolytic alterations found in this group were: (see Graphic 5):

- Hyponatremia (22%) with a mean of Na + 122 mEq / L ± 6

- Hypernatremia (5%) with a mean of Na + 152 mEq / L ± 2.7

- Hypokalemia (17%) with a mean of K + 2.4 mEq / L ± 0.4

- Newly diagnosed acute renal failure (26%) with a mean creatinine level in this group of 2.4 mg / dl ± 0.7

- Altered glycemic values (30%) - considering that in this group 90% of patients were suffering from type 2 diabetes mellitus already before entering the ward - with a daily average blood glucose level of 221 mg / dl ± 47

Similarly to LIC group, in patients with hospital complications, an increase of almost 30% in the average hospital stay was observed (LoS 24 ± 2) compared to the group of subjects who did not show intra-hospital complications. (Los 17 ± 3) with (p <0.05) (see Graphic 6)

Secondary end point

Analyzing data we can observe that in both HIC and LIC group the average hospital stay is longer within the population with poor glycemic control and significant changes in the glycemic profile (see Graphics 7 and 8).

In particular:

- In the LIC group, there is an average lengthening of hospital stay of about 5 ± 2 days within the subpopulation with decompensated diabetes mellitus or with iatrogenic hyperglycemia, compared to the group with compensated diabetes mellitus (p <0.05);- In the HIC group, there was also an increase in average days of hospitalization of 8 ± 3 days within the subpopulation with decompensated diabetes mellitus or with iatrogenic hyperglycemia, compared to the group with compensated diabetes mellitus (p <0.05).

By analyzing the data from the blood gas analysis performed during the hospitalization we can observe a positive trend of partial pressure levels of oxygen (PaO2) during the hospital stay (p <0.05). On the contrary, there was no positive trend of serum lactate levels (see Graphic 9).

In detail:

- In the LIC group, 40% of the population required non-invasive mechanical ventilation (NIV). Almost all patients of this group (about 90%) showed a marked clinical improvement already after a few hours from the start of NIV, with an increase in pO2 values of about 45% on the 5th day (mean initial pO2 58 ± 6 mmHg vs mean final pO2 84.1 ± 3 mmHg). Against this, the serum lactate profile did not show statistically significant decreases during intensive treatment (mean initial Lac 2.1 ± 0.3 mmol / L vs mean final Lac 2.7 ± 0.4 mmol / L);

- In the HIC group, 100% of patients underwent NIV cycles during their hospital stay. Of these, only 50% showed partial clinical improvement after a few hours from the start of ventilatory therapy (initial mean pO2 48.3 ± 4 mmHg vs final mean pO2 71.5 ± 6 mmHg). The profile of serum lactates, on the other hand, progressively worsened (average initial Lac 3.2 ± 0.5 mmol / L vd average final Lac 4.7 ± 1.1 mmol / L)

Discussion

The data collected from this study confirm what has already been partially described in the scientific literature. In a 2021 review, it was observed how hyponatremia may be one of the first laboratory signs of SARS-CoV-2 infection: the mechanisms, still only partially known, could be correlated with inappropriate antidiuretic hormone (ADH) secretion, with tubular - glomerular damage caused by viral infection or with a greater dispersion of electrolytes in the gastro - intestinal tract.

In an original paper of 2020, a multicenter study showed how the same hydro electrolytic variations, connected to the COVID-19 infection, negatively affect the prognosis of the patients involved, with an increase in mortality rates and with a notable impact on the average hospital stays.

Regarding glycemic fluctuations, however, numerous studies had already emphasized the importance of proper glycemic control during hospitalization to avoid the onset of complications. Similar results were obtained within the populations of SARS-CoV-2 patients.

The use of early NIV in patients susceptible to sub-intensive or intensive treatment, as well as the choice of using high-flow oxygen nasal canula (HFNC) in the early stages of respiratory failure, are winning strategies to counter the negative effects of restrictive respiratory diseases caused by SARS. -CoV-2. However, satisfactory outcomes have not always been obtained from the use of these respiratory devices. One of the main reasons is attributable to the fact that COVID-19 is a multi-organ disease: the main causes of therapeutic failure, and therefore of mortality, are due to the irreversible damage caused to the cardiovascular and renal systems. This study has several limitations: firstly thee small sample of patient, the lack of a longer observation period, as well as the impossibility of being able to continue the follow-up even at the time of discharge. The latter could have highlighted any late complications, including the now well-known Long Covid Disease, with which clinicians will have to interface over the next few years.

Conclusions

The SARS-CoV-2 infection has completely disrupted the health and clinical management of hospitals. The virulence achieved, the impact on the world economy and society are unprecedented in anthropological history. Multidisciplinary and multiparametric management of these patients is necessary to ensure better clinical outcomes. The commitment of the health personnel has made it possible to considerably deepen their knowledge. Despite this, infection can range from asymptomatic to more severe forms with pneumonia and multiorgan dysfunction the prognostic factors that influence the course of hospitalization and the onset of more severe forms of the disease have not been fully clarified. Hopefully the results obtained with this study will help to better understand what the most important factors to be aware of for COVID-19 patients.

Declarations

1. No funding for this paper has been taken

2. Conflicts of interest/Competing interests: not applicable
3. Ethics approval has been got by Sant'Andrea Hospital ethical committee
4. Consent to participate: not applicable
5. Consent for publication: not applicable
6. Availability of data and material: not applicable
7. Code availability: not applicable
8. Authors' contributions: all authors collected and elaborated data. Martelletti Paolo was the supervisor.

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Figures

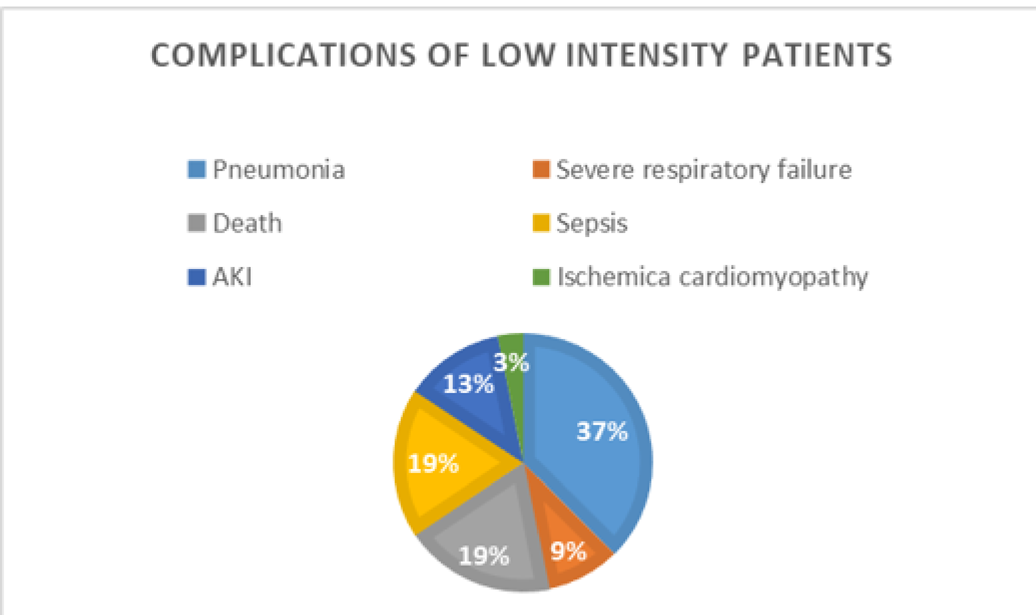

Figure 1

Graphic 1 - Complications of patients with low intensity of care

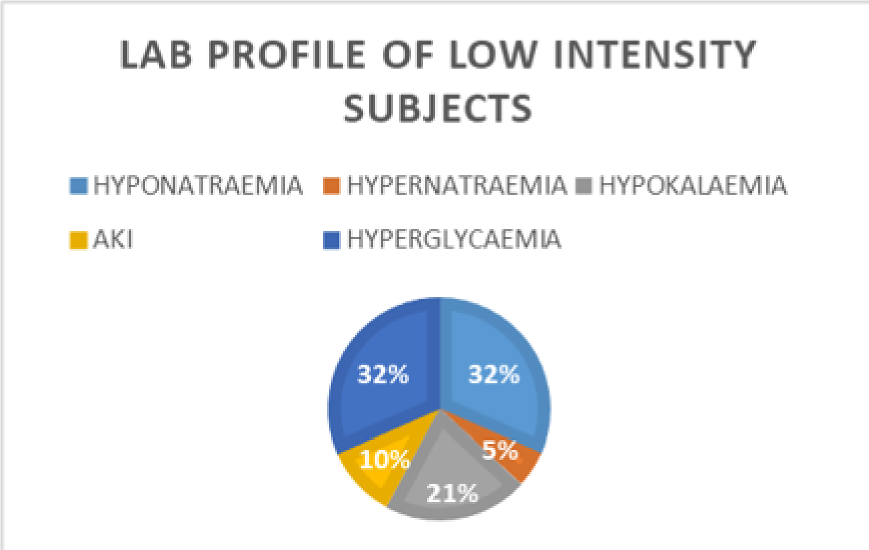

Figure 2

Graphic 2 - Low intensity laboratory panel

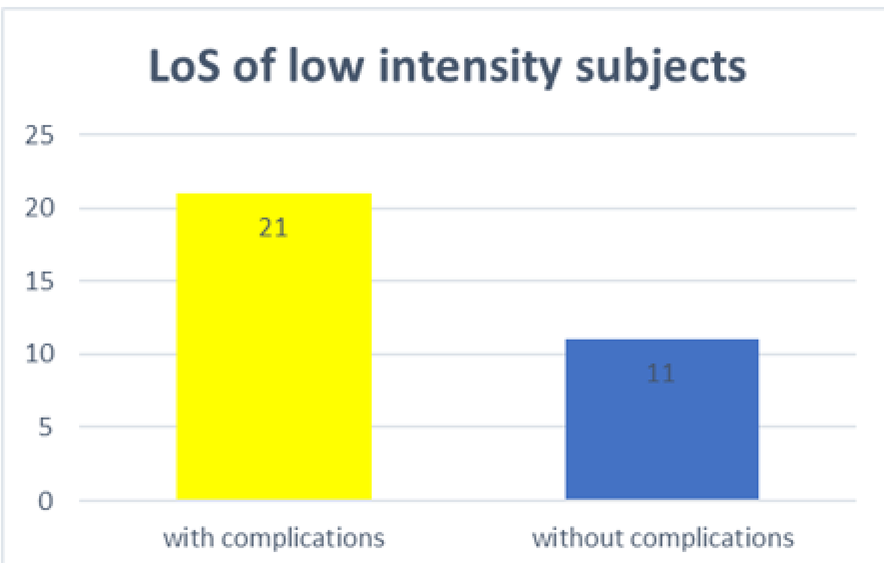

Figure 3

Graphic 3 - LoS Low intensity hospitalization

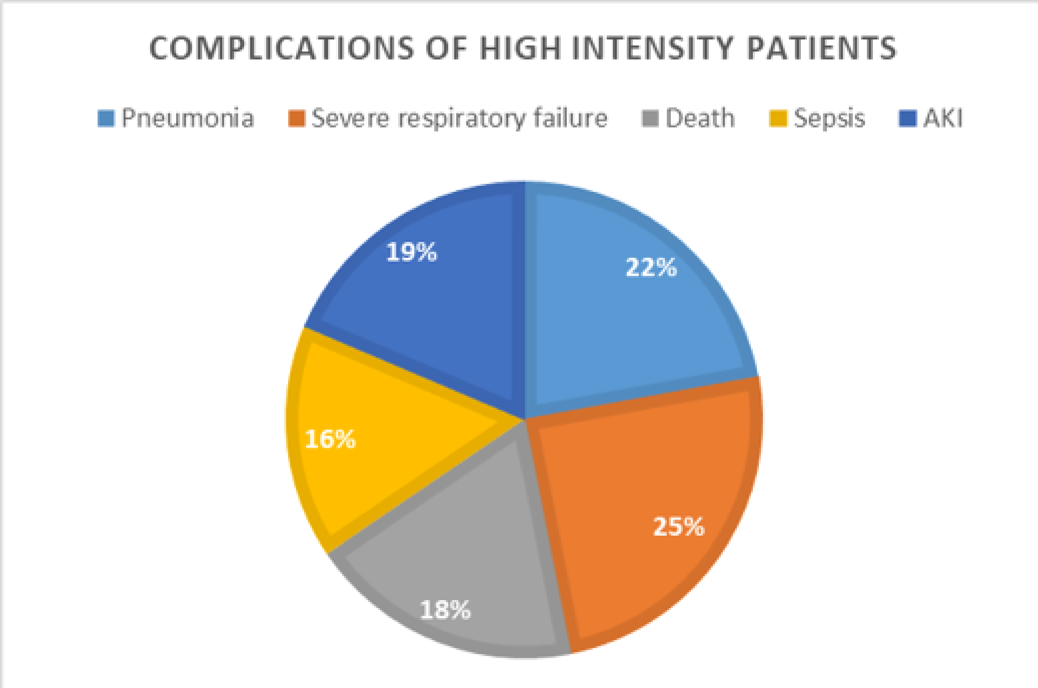

Figure 4

Graphic 4 - Complications of hospitalizations with high intensity of care

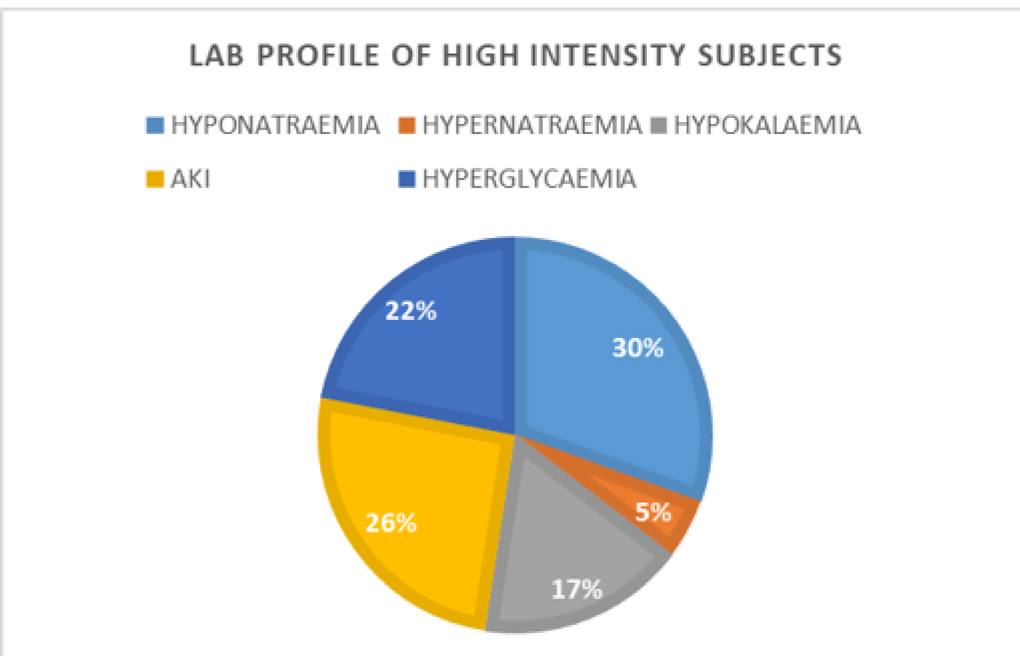

Figure 5

Graphic 5 – Laboratory profile of high - intensity care patients

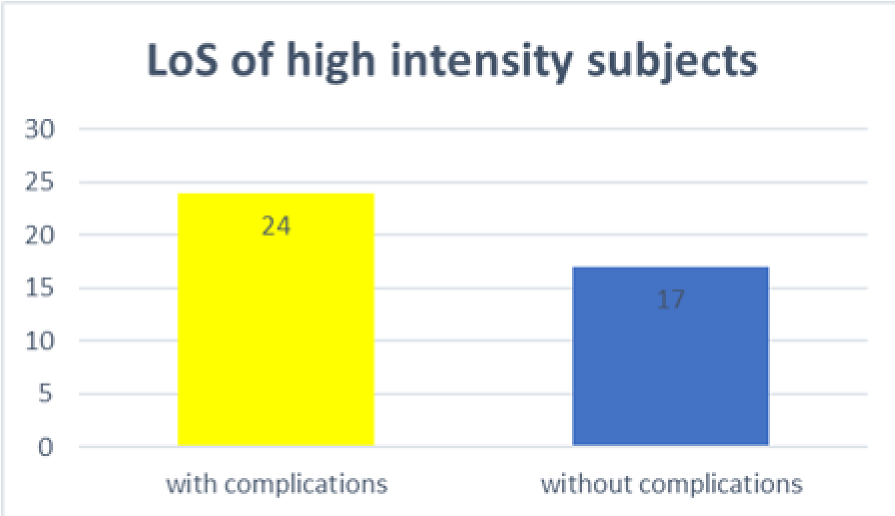

Figure 6

Graphic 6 - LoS High intensity of care

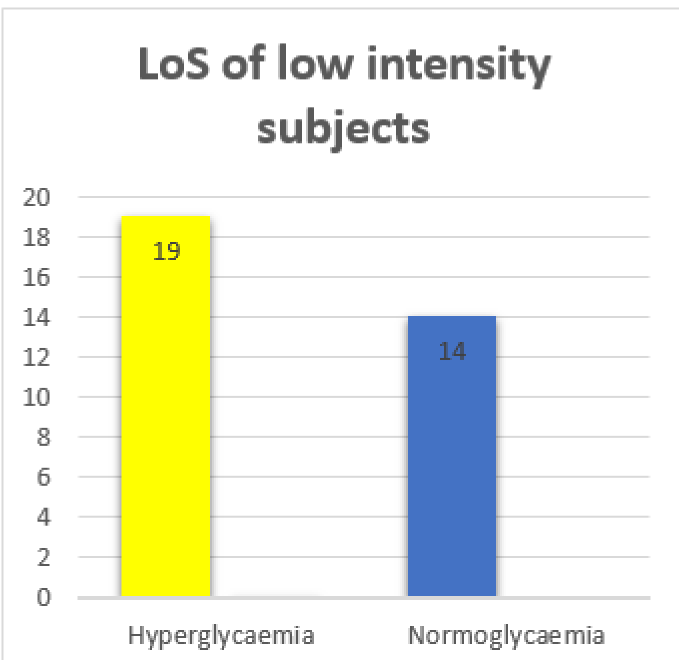

Figure 7

Graphic 7 - LoS comparison of diabetic patients of both groups

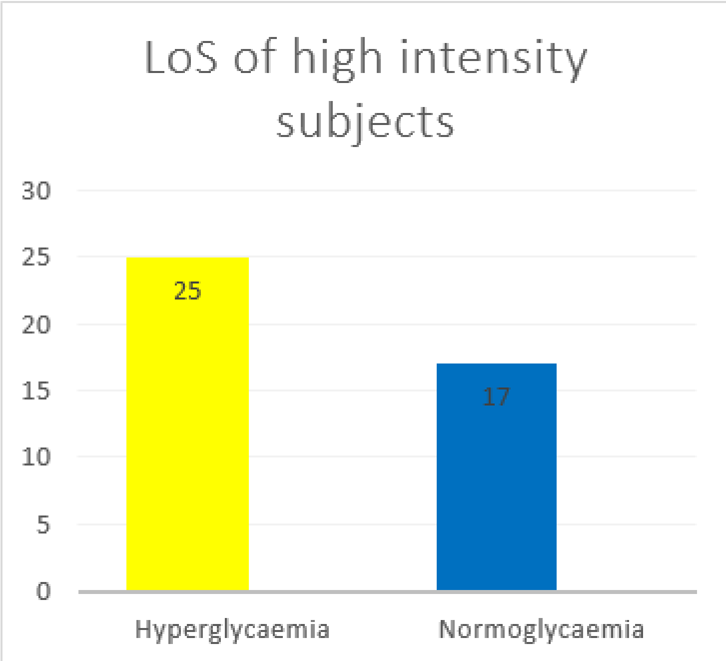

Figure 8

Graphic 8 - LoS comparison of diabetic patients of both groups

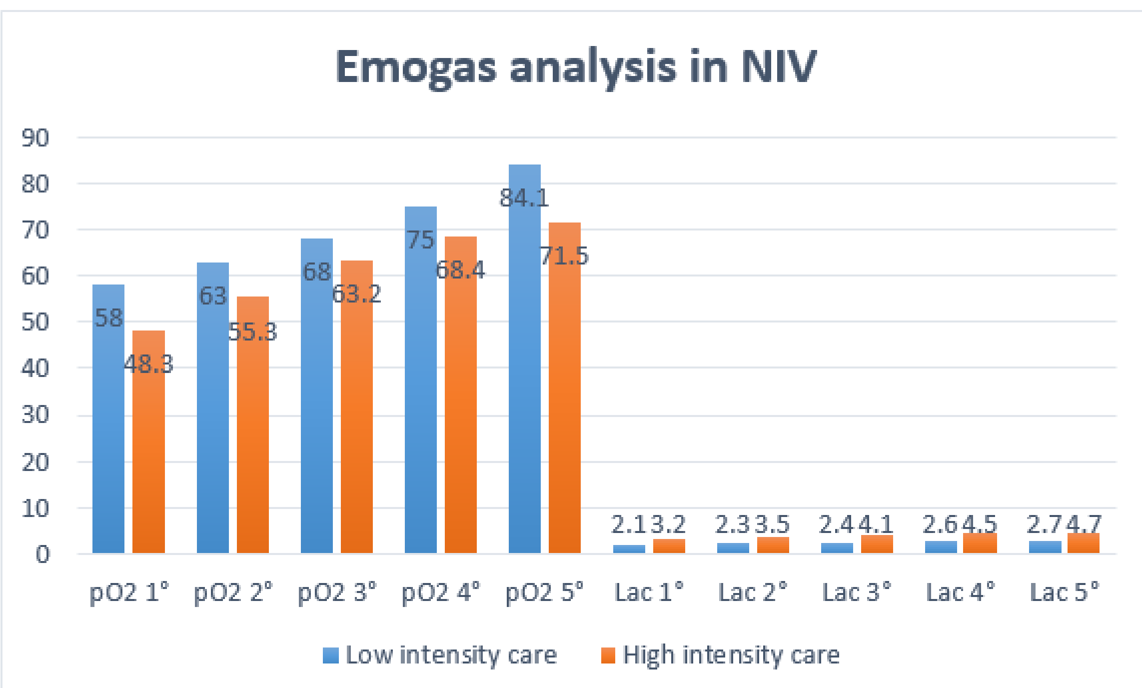

Figure 9

Graphic 9 - Blood gas analysis profile of both groups