

## **Section 1: Data Collection**

### **1.1 Main comorbidities**

We collected data about the following comorbidities:

- Hypertension;
- Moderate/Severe Chronic Obstructive Pulmonary Disease (COPD);
- Congestive Heart Failure;
- Diabetes, treated or not with insulin;
- Cerebral Vascular Disease;
- Chronic Kidney disease, defined as moderate/severe or end stage renal disease (ESRD);
- Arrhythmia;
- Obesity, defined as BMI  $\geq 30.0$  kg/m<sup>2</sup>;
- History of myocardial infarction;
- Localized or metastatic solid tumor;
- Peripheral vascular disease;
- Hemiplegia;
- Liver disease, defined as mild or moderate/severe;
- Dementia;
- Neurodegenerative disease;
- Hematological malignancy;
- Drug/alcohol addiction;
- Peptic ulcer;
- Connective tissue disease.

### **1.2 Clinical conditions and procedures**

We reported the following variables:

- Admission for trauma;
- Sepsis or septic shock on ICU admission;
- Surgery performed before ICU admission, defined as none, neurosurgical, and others;
- Non-surgical procedure before ICU admission, defined as none, neuro-interventist, and others.

**1.3 Laboratory Tests and indexes computation**

During specific time points (on the same PDT day, 24, 48, 72, and 96 hours post-PDT), we collected the following values obtained from venous blood samples: white blood cells (WBC), hemoglobin (Hb), platelets (PLT), neutrophils, lymphocytes, and monocytes.

Using these data, we computed the following indexes:

- 1) Neutrophil-to-Lymphocyte Ratio (NLR) [1]:

$$NLR = \frac{Neutrophil}{Lymphocyte}$$

- 2) Platelet-to-Lymphocyte Ratio (PLR) [2]:

$$PLR = \frac{Platelets}{Lymphocyte}$$

- 3) Monocyte-to-Lymphocyte Ratio (MLR) [3]:

$$MLR = \frac{Monocyte}{Lymphocyte}$$

- 4) Systemic Inflammation Response Index (SIRI) [4]:

$$SIRI = \frac{Neutrophil \times Monocyte}{Lymphocyte}$$

- 5) Systemic Immune-Inflammation Index (SII) [5]:

$$SII = \frac{Neutrophil \times Platelets}{Lymphocyte}$$

- 6) Aggregate Index of Systemic Inflammation (AISI) [6]:

$$AISI = \frac{Neutrophil \times Platelets \times Monocyte}{Lymphocyte}$$

**Section 2: Statistics**

**2.1 Pairwise comparison for trends**

According to the results of ANOVA for repeated measures or non-parametric Friedman test, pairwise comparisons were performed with paired Student t-test or paired Wilcoxon signed rank (W) test. Time<sub>0</sub> was considered as the baseline. P-values were corrected using the False Discovery Rate (FDR) method.

**2.2 Tertile groups trend analysis**

Descriptive statistics were computed for every tertile (low, medium, and high groups). To analyze the difference between groups and within time, we performed two-way ANOVA for repeated measures or, in the case of skewed data, the Aligned Rank Transform (ART) method. The ART allows a nonparametric analysis of variance to be conducted on factorial models with fixed and random effects (or repeated measures) and numeric or ordinal responses. This is done by aligning and ranking the fixed effects using this function and then conducting an analysis of variance on linear models built from the transformed data using ANOVA. [7]

For significant interaction between time and tertile distribution, one-way ANOVA for repeated measures or Friedman test was performed for every tertile (low, medium, high). Pairwise comparisons were performed with the Student t-test or W test. P-values were corrected using the FDR method.

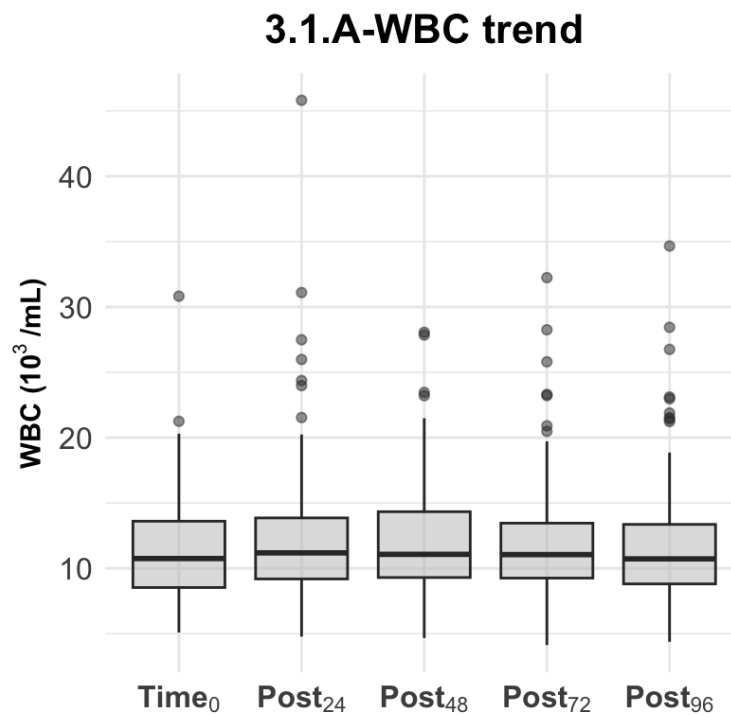
**Section 3: Results**

**3.1 Friedman test and pairwise comparison results**

**3.1.1 WBC**

WBC values during considering time points were:

- Time<sub>0</sub>: 10.7x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 8.5-13.6, min 5.1, max 30.8);
- Post<sub>24</sub>: 11.2x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 9.2-13.8, min 4.8, max 45.8);
- Post<sub>48</sub>: 11.1x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 9.3-14.3, min 4.7, max 28.1);
- Post<sub>72</sub>: 11.0x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 9.2-13.4, min 4.1, max 32.2);
- Post<sub>96</sub>: 10.7 x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 8.8-13.4, min 4.4, max 34.7).



*Figure 3.1.A: Boxplot for WBC values measured during specific time points. The grey circles represent outliers.*

Friedman test was statistically significant [ $\chi^2=16.912$ , degree of freedom (df)=4,  $p=0.002$ , Figure 3.1.A].

Pairwise analysis with the W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>:  $p=0.056$ ;

- Time<sub>0</sub> vs Post<sub>48</sub>: p=0.044;
- Time<sub>0</sub> vs Post<sub>72</sub>: p=0.612;
- Time<sub>0</sub> vs Post<sub>96</sub>: p=0.684.

### 3.1.2 Neutrophils

Neutrophils values during considering time points were:

- Time<sub>0</sub>:  $8.5 \times 10^3$  units/mL (Q<sub>1</sub>-Q<sub>3</sub> 6.8-10.9, min 3.3, max 26.3);
- Post<sub>24</sub>:  $9.0 \times 10^3$  units/mL (Q<sub>1</sub>-Q<sub>3</sub> 7.2-11.3, min 3.1, max 44.6);
- Post<sub>48</sub>:  $9.1 \times 10^3$  units/mL (Q<sub>1</sub>-Q<sub>3</sub> 7.5-11.4, min 3.1, max 26.8);
- Post<sub>72</sub>:  $8.8 \times 10^3$  units/mL (Q<sub>1</sub>-Q<sub>3</sub> 7.0-11.5, min 2.5, max 29.5);
- Post<sub>96</sub>:  $8.5 \times 10^3$  units/mL (Q<sub>1</sub>-Q<sub>3</sub> 6.7-11.0, min 2.9, max 29.2).

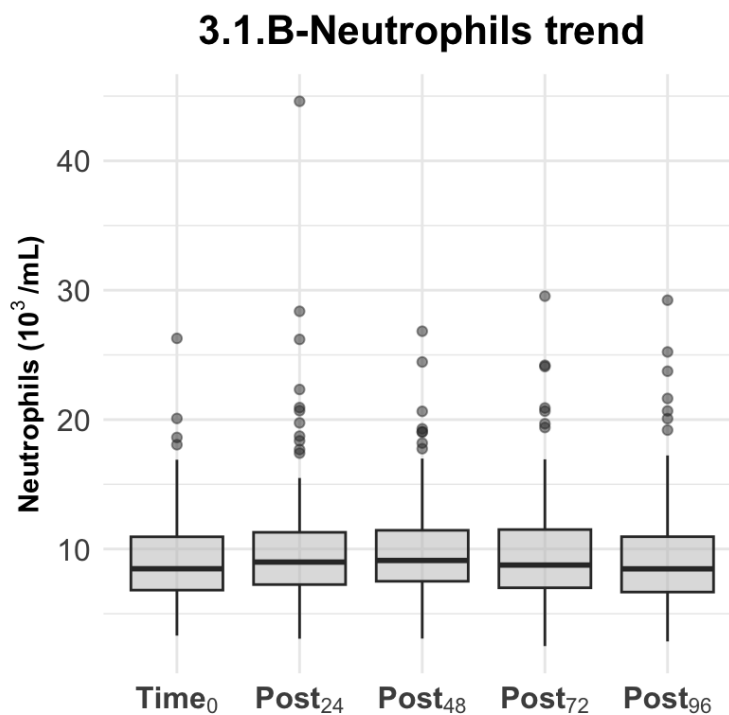


Figure 3.1.B: Boxplot for neutrophils values measured during specific time points. The grey circles represent outliers.

Friedman test was statistically significant ( $\chi^2=14.623$ ,  $df=4$ ,  $p=0.005$ , Figure 3.1.B). Pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>: p= 0.168;
- Time<sub>0</sub> vs Post<sub>48</sub>: p= 0.088;
- Time<sub>0</sub> vs Post<sub>72</sub>: p=0.712;
- Time<sub>0</sub> vs Post<sub>96</sub>: p=0.836.

### 3.1.3 Lymphocytes

Lymphocyte values during considering time points were:

- Time<sub>0</sub>: 1030 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 776-1388, min 340, max 3330);
- Post<sub>24</sub>: 1080 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 812-1376, min 240, max 3230);
- Post<sub>48</sub>: 1020 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 772-1448, min 350, max 3540);
- Post<sub>72</sub>: 1068 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 810-1450, min 360, max 3320);
- Post<sub>96</sub>: 1132 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 866-1424, min 230, max 3270).

Friedman test was not statistically significant ( $\chi^2=4.436$ , df=4, p=0.350).

### 3.1.4 Monocytes

Monocyte values during considering time points were:

- Time<sub>0</sub>: 680 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 512-880, min 60, max 2340);
- Post<sub>24</sub>: 720 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 540-896, min 250, max 2260);
- Post<sub>48</sub>: 745 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 578-910, min 150, max 1890);
- Post<sub>72</sub>: 716 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 547-958, min 80, max 2038);
- Post<sub>96</sub>: 705 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 540-905, min 265, max 3080).

Friedman test was not statistically significant ( $\chi^2=6.111$ , df=4, p=0.191).

### 3.1.5 Hemoglobin

Hemoglobin values during considering time points were:

- Time<sub>0</sub>: 9.2 g/dL (Q<sub>1</sub>-Q<sub>3</sub> 8.8-10.0, min 7.5, max 13.3);
- Post<sub>24</sub>: 9.4 g/dL (Q<sub>1</sub>-Q<sub>3</sub> 8.5-10.0, min 7.5, max 13.9);
- Post<sub>48</sub>: 9.4 g/dL (Q<sub>1</sub>-Q<sub>3</sub> 8.7-10.1, min 7.3, max 13.2);
- Post<sub>72</sub>: 9.3 g/dL (Q<sub>1</sub>-Q<sub>3</sub> 8.7-10.0, min 7.4, max 14.0);

- Post<sub>96</sub>: 9.5 g/dL (Q<sub>1</sub>-Q<sub>3</sub> 8.8-10.2, min 7.5, max 12.5).

Friedman test was not statistically significant ( $\chi^2=1.506$ , df=4, p=0.826).

### 3.1.6 Platelets

Platelets values during considering time points were:

- Time<sub>0</sub>: 280.5x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 201.2-382.1, min 64.0, max 725.0);
- Post<sub>24</sub>: 289.5x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 217.5-364.2, min 84.0, max 747.0);
- Post<sub>48</sub>: 286.6x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 216.4-369.8, min 74.0, max 740.0);
- Post<sub>72</sub>: 294.0x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 234.0-391.4, min 77.0, max 754.0);
- Post<sub>96</sub>: 307.4x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 224.9-388.3, min 72.0, max 764.0).

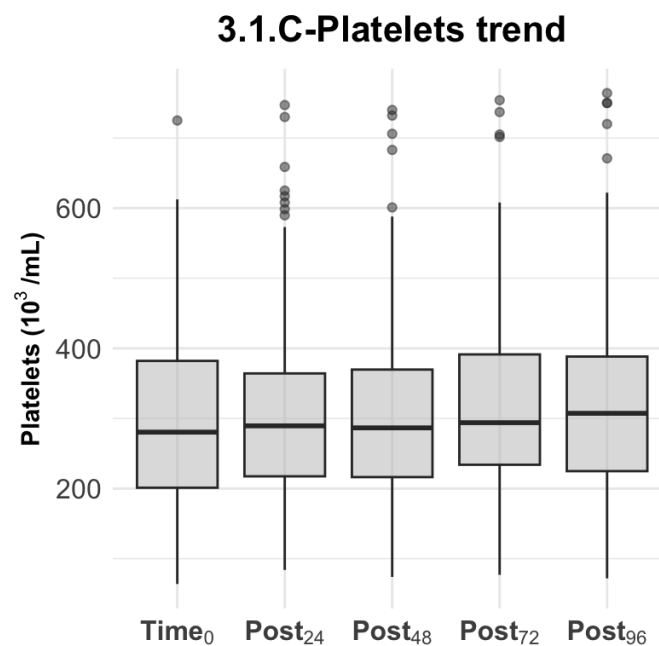


Figure 3.1.C: Boxplot for platelets values measured during specific time points. The grey circles represent outliers.

Friedman test was statistically significant ( $\chi^2=15.124$ , df=4, p=0.004, Figure 3.1.C). Pairwise analysis with paired W test reported the following results:

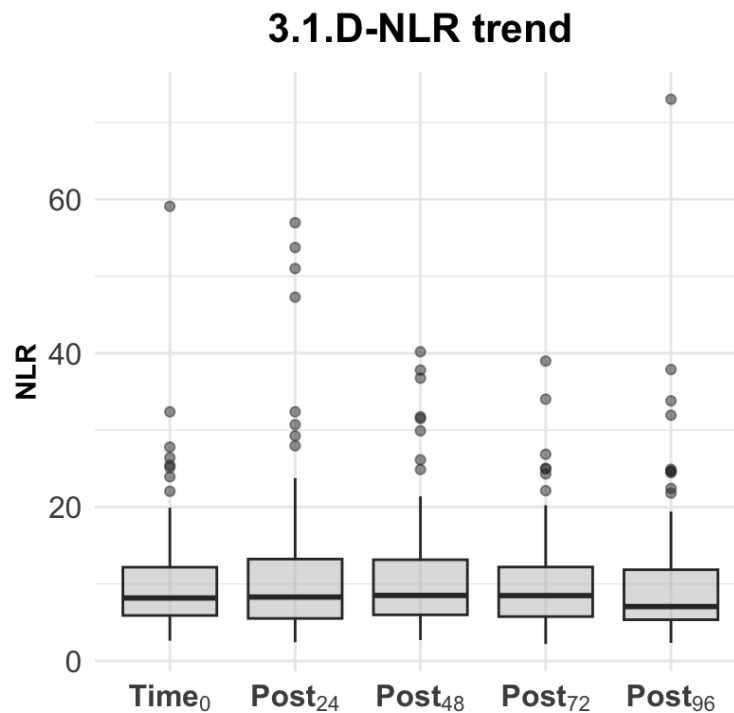
- Time<sub>0</sub> vs Post<sub>24</sub>: p=0.041;
- Time<sub>0</sub> vs Post<sub>48</sub>: p=0.056;

- Time<sub>0</sub> vs Post<sub>72</sub>: p=0.032;
- Time<sub>0</sub> vs Post<sub>96</sub>: p=0.036.

### 3.1.7 NLR

NLR values during considering time points were:

- Time<sub>0</sub>: 8.2 (Q<sub>1</sub>-Q<sub>3</sub> 5.9-12.2, min 2.6, max 59.1);
- Post<sub>24</sub>: 8.3 (Q<sub>1</sub>-Q<sub>3</sub> 5.5-13.2, min 2.4, max 57.0);
- Post<sub>48</sub>: 8.5 (Q<sub>1</sub>-Q<sub>3</sub> 6.0-13.1, min 2.7, max 40.2);
- Post<sub>72</sub>: 8.5 (Q<sub>1</sub>-Q<sub>3</sub> 5.8-12.2, min 2.2, max 39.0);
- Post<sub>96</sub>: 7.1 (Q<sub>1</sub>-Q<sub>3</sub> 5.3-11.8, min 2.3, max 73.0).



*Figure 3.1.D: Boxplot for NLR values measured during specific time points. The grey circles represent outliers.*

Friedman test was statistically significant ( $\chi^2=9.673$ ,  $df=4$ ,  $p=0.046$ , Figure 3.1.D). Pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>: p=0.695;

- Time<sub>0</sub> vs Post<sub>48</sub>: p=0.518;
- Time<sub>0</sub> vs Post<sub>72</sub>: p=0.834;
- Time<sub>0</sub> vs Post<sub>96</sub>: p=0.675.

### 3.1.8 PLR

PLR values during considering time points were:

- Time<sub>0</sub>: 275.4 (Q<sub>1</sub>-Q<sub>3</sub> 191.9-400.3, min 43.5, max 867.4);
- Post<sub>24</sub>: 270.8 (Q<sub>1</sub>-Q<sub>3</sub> 184.9-398.9, min 44.3, max 1041.5);
- Post<sub>48</sub>: 287.2 (Q<sub>1</sub>-Q<sub>3</sub> 191.5-411.2, min 47.0, max 1260.7);
- Post<sub>72</sub>: 283.1 (Q<sub>1</sub>-Q<sub>3</sub> 194.1-411.8, min 49.7, max 954.4);
- Post<sub>96</sub>: 282.5 (Q<sub>1</sub>-Q<sub>3</sub> 199.0-376.9, min 55.0, max 1078.3).

Friedman test was not statistically significant ( $\chi^2=4.037$ , df=4, p=0.401).

### 3.1.9 MLR

MLR values during considering time points were:

- Time<sub>0</sub>: 0.69 (Q<sub>1</sub>-Q<sub>3</sub> 0.50-0.93, min 0.06, max 2.15);
- Post<sub>24</sub>: 0.65 (Q<sub>1</sub>-Q<sub>3</sub> 0.49-0.92, min 0.17, max 2.87);
- Post<sub>48</sub>: 0.72 (Q<sub>1</sub>-Q<sub>3</sub> 0.52-0.94, min 0.27, max 2.06);
- Post<sub>72</sub>: 0.66 (Q<sub>1</sub>-Q<sub>3</sub> 0.51-0.91, min 0.10, max 2.47);
- Post<sub>96</sub>: 0.64 (Q<sub>1</sub>-Q<sub>3</sub> 0.49-0.90, min 0.24, max 3.21).

Friedman test was statistically significant ( $\chi^2=10.988$ , df=4, p=0.027, Figure 3.1.E). Pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>: p=1.000;
- Time<sub>0</sub> vs Post<sub>48</sub>: p=0.632;
- Time<sub>0</sub> vs Post<sub>72</sub>: p=1.000;
- Time<sub>0</sub> vs Post<sub>96</sub>: p=0.859.

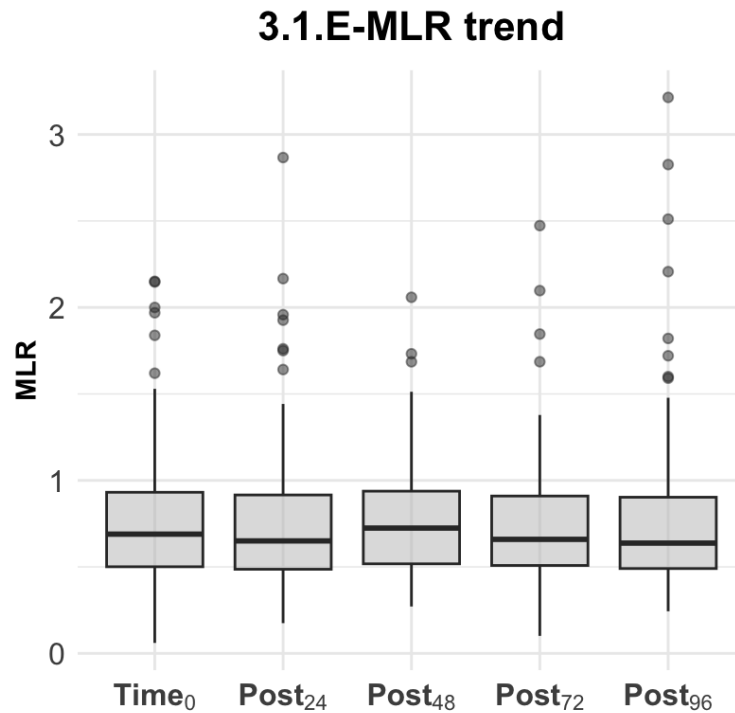


Figure 3.1.E: Boxplot for MLR values measured during specific time points. The grey circles represent outliers.

#### 3.1.10 SIRI

SIRI values during considering time points were:

- Time<sub>0</sub>: 5.5 (Q<sub>1</sub>-Q<sub>3</sub> 3.4-9.1, min 0.9, max 43.1);
- Post<sub>24</sub>: 5.9 (Q<sub>1</sub>-Q<sub>3</sub> 4.0-9.7, min 0.9, max 81.3);
- Post<sub>48</sub>: 6.3 (Q<sub>1</sub>-Q<sub>3</sub> 4.3-9.5, min 1.2, max 34.8);
- Post<sub>72</sub>: 5.7 (Q<sub>1</sub>-Q<sub>3</sub> 3.8-9.5, min 0.9, max 35.2);
- Post<sub>96</sub>: 5.3 (Q<sub>1</sub>-Q<sub>3</sub> 3.4-8.5, min 1.0, max 50.3).

Friedman test was statistically significant ( $\chi^2=12.708$ ,  $df=4$ ,  $p=0.013$ , Figure 3.1.F). Pairwise analysis with paired

W test reported the followign results:

- Time<sub>0</sub> vs Post<sub>24</sub>:  $p=0.674$ ;
- Time<sub>0</sub> vs Post<sub>48</sub>:  $p=0.260$ ;
- Time<sub>0</sub> vs Post<sub>72</sub>:  $p=0.730$ ;
- Time<sub>0</sub> vs Post<sub>96</sub>:  $p=0.907$ .

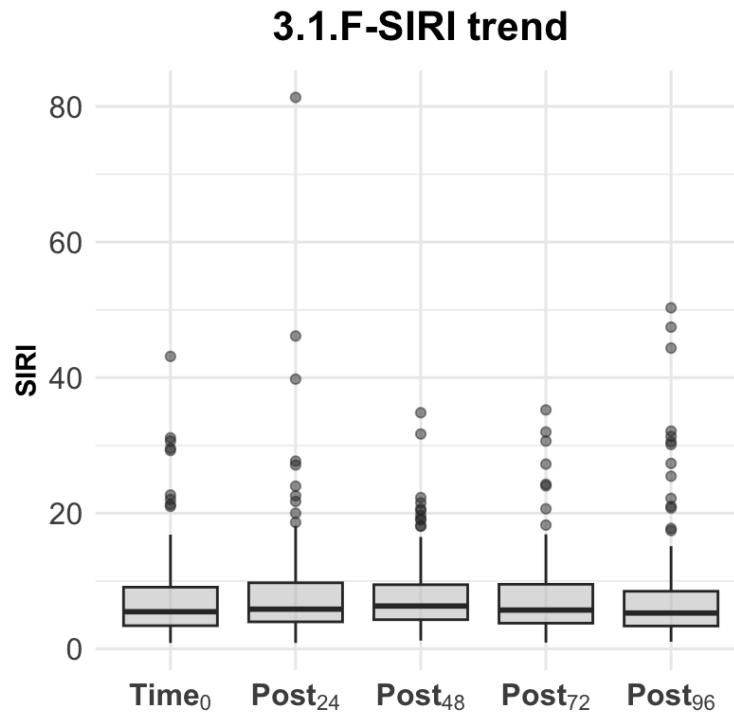


Figure 3.1.F: Boxplot for SIRI values measured during specific time points. The grey circles represent outliers.

#### 3.1.11 SII

SII values during considering time points were:

- Time<sub>0</sub>: 2346.7 (Q<sub>1</sub>-Q<sub>3</sub> 1648.2-3595.3, min 461.1, max 16150.5);
- Post<sub>24</sub>: 2465.3 (Q<sub>1</sub>-Q<sub>3</sub> 1465.8-4331.6, min 401.2, max 22042.2);
- Post<sub>48</sub>: 2733.4 (Q<sub>1</sub>-Q<sub>3</sub> 1706.9-4231.8, min 476.0, max 21117.0);
- Post<sub>72</sub>: 2572.4 (Q<sub>1</sub>-Q<sub>3</sub> 1667.3-3970.9, min 380.4, max 12846.6);
- Post<sub>96</sub>: 2344.4 (Q<sub>1</sub>-Q<sub>3</sub> 1540.0-3809.9, min 433.6, max 18104.0).

Friedman test was statistically significant ( $\chi^2=5.979$ ,  $df=4$ ,  $p=0.201$ ).

#### 3.1.12 AISI

AISI values during considering time points were:

- Time<sub>0</sub>: 1626.6 (Q<sub>1</sub>-Q<sub>3</sub> 1027.3-3034.0, min 248.9, max 13485.7);
- Post<sub>24</sub>: 1764.9 (Q<sub>1</sub>-Q<sub>3</sub> 1023.5-2893.7, min 260.8, max 28871.2);
- Post<sub>48</sub>: 1694.7 (Q<sub>1</sub>-Q<sub>3</sub> 1176.4-3004.0, min 252.3, max 15204.2);

- Post<sub>72</sub>: 1861.2 (Q<sub>1</sub>-Q<sub>3</sub> 1057.4-2854.9, min 197.8, max 13496.3);
- Post<sub>96</sub>: 1667.9 (Q<sub>1</sub>-Q<sub>3</sub> 1046.3-2555.7, min 210.4, max 33748.1).

Friedman test was statistically significant ( $\chi^2=10.091$ ,  $df=4$ ,  $p=0.039$ , Figure 3.1.G). Pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>:  $p=0.202$ ;
- Time<sub>0</sub> vs Post<sub>48</sub>:  $p=0.024$ ;
- Time<sub>0</sub> vs Post<sub>72</sub>:  $p=0.437$ ;
- Time<sub>0</sub> vs Post<sub>96</sub>:  $p=0.726$ .

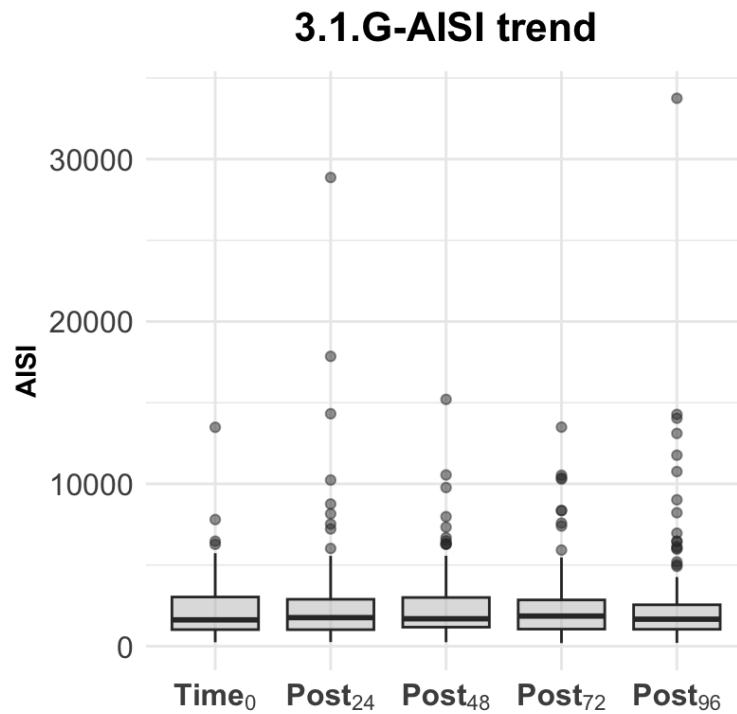


Figure 3.1.G: Boxplot for AISI values measured during specific time points. The grey circles represent outliers.

### **3.2 Terzile distribution analysis**

#### **3.2.1 WBC**

The group Low (n=38) showed the following trend:

- T<sub>0</sub>: median 7.6x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 7.1-8.5, min 5.1, max 9.0 x10<sup>3</sup> units/mL);
- Post<sub>24</sub>: median 8.7x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 7.7-10.5, min 4.8, max 13.6 x10<sup>3</sup> units/mL);
- Post<sub>48</sub>: median 10.0x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 8.5-11.0, min 4.7, max 15.9 x10<sup>3</sup> units/mL);
- Post<sub>72</sub>: median 9.8x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 8.2-11.4, min 4.1, max 14.8 x10<sup>3</sup> units/mL);
- Post<sub>96</sub>: median 9.5x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 7.8-11.0, min 4.4, max 17.9 x10<sup>3</sup> units/mL).

The group Medium (n=38) showed the following trend:

- T<sub>0</sub>: median 10.7x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 9.9-11.8, min 9.0, max 12.7 x10<sup>3</sup> units/mL);
- Post<sub>24</sub>: median 11.0x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 10.0-12.4, min 7.2, max 27.5 x10<sup>3</sup> units/mL);
- Post<sub>48</sub>: median 10.9x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 9.5-13.0, min 6.4, max 18.2 x10<sup>3</sup> units/mL);
- Post<sub>72</sub>: median 11.0x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 8.7-12.8, min 5.1, max 23.3 x10<sup>3</sup> units/mL);
- Post<sub>96</sub>: median 10.2x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 9.0-12.2, min 7.2, max 21.9 x10<sup>3</sup> units/mL).

The group High (n=38) showed the following trend:

- T<sub>0</sub>: median 15.1x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 13.7-17.6, min 12.8, max 30.8 x10<sup>3</sup> units/mL);
- Post<sub>24</sub>: median 15.4x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 13.2-19.2, min 8.1, max 45.8 x10<sup>3</sup> units/mL);
- Post<sub>48</sub>: median 14.9x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 11.5-19.2, min 7.3, max 28.1 x10<sup>3</sup> units/mL);
- Post<sub>72</sub>: median 14.0x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 10.7-16.9, min 6.8, max 32.2 x10<sup>3</sup> units/mL);
- Post<sub>96</sub>: median 12.4x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 10.5-16.7, min 5.9, max 34.7 x10<sup>3</sup> units/mL).

The ART analysis showed the following results:

- Main Effect of tertiles distribution: F = 65.545, p<0.001, indicating a strong and statistically significant difference in WBC values between the tertiles;
- Main Effect of time: F = 4.211, p=0.002, suggesting that time has a statistically significant impact on the WBC values;
- Interaction effect tertiles:time: F = 6.121, p<0.001, indicating that the effect of time differs across the tertiles.

Figure 3.2.1 illustrates the trends in WBC counts over time, stratified by tertiles.

## 3.2.1-Tertiles Trends WBC

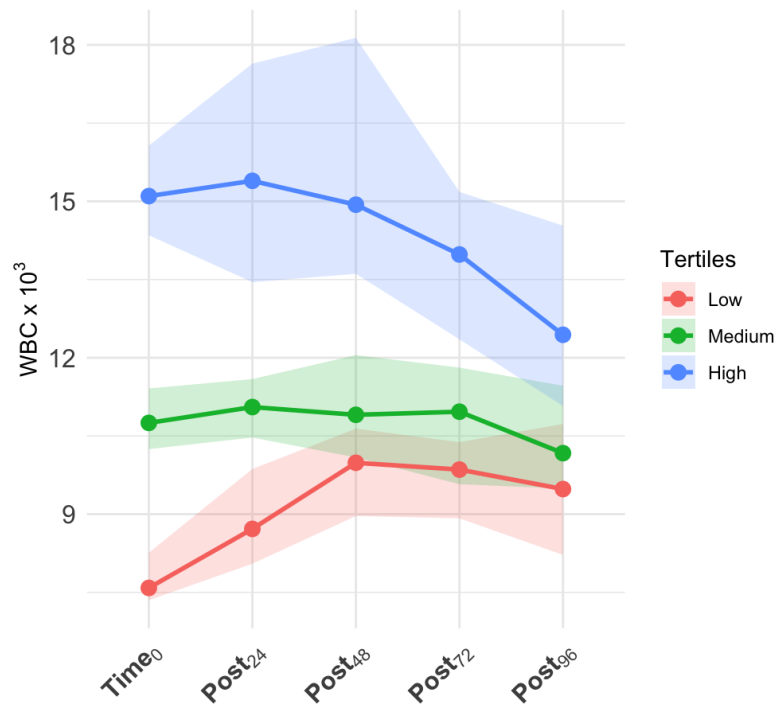


Figure 3.2.1 Tertiles trends for WBC. The lines represent the median WBC values for each tertile, while the shaded areas indicate the CI<sub>95%</sub>.

Post-hoc analysis with Friedman test showed that only trends in Low ( $\chi^2=29.300$ ,  $df=4$ ,  $p<0.001$ ) and High ( $\chi^2=27.400$ ,  $df=4$ ,  $p<0.001$ ) were statistically significant, but not in Medium tertile ( $\chi^2=1.230$ ,  $df=4$ ,  $p=0.872$ ).

In Low tertile, the pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>:  $p<0.001$ ;
- Time<sub>0</sub> vs Post<sub>48</sub>:  $p<0.001$ ;
- Time<sub>0</sub> vs Post<sub>72</sub>:  $p<0.001$ ;
- Time<sub>0</sub> vs Post<sub>96</sub>:  $p<0.001$ .

In High tertile, the pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>:  $p=0.922$ ;
- Time<sub>0</sub> vs Post<sub>48</sub>:  $p=0.698$ ;
- Time<sub>0</sub> vs Post<sub>72</sub>:  $p=0.110$ ;
- Time<sub>0</sub> vs Post<sub>96</sub>:  $p=0.099$ .

Death rates in tertiles were 31.6% (12 patients) in Low, 18.4% (7 patients) in medium, and 21.0% (8 patients) in High. Frequencies were not statistically significant ( $\chi^2=2.038$ ,  $p=0.361$ ).

Table 3.2.1 showed the results for univariate and multivariate logistic regression analysis. Univariate and multivariate logistic regression showed that WBC tertiles were not related to outcome.

Variables		Univariate		Multivariate	
		OR (CI <sub>95%</sub> )	p-value	OR (CI <sub>95%</sub> )	p-value
WBC Tertile	Low	Ref.	-	Ref.	-
	Medium	0.489 (0.161-1.397)	0.189	0.409 (0.128-1.210)	0.115
	High	0.578 (0.198-1.613)	0.300	0.452 (0.145-1.327)	0.156
CCI		-	-	1.119 (0.899-1.389)	0.403
SOFA		-	-	1.109 (0.954-1.297)	0.276

### 3.2.2 Neutrophils

The group Low (n=38) showed the following trend:

- T<sub>0</sub>: median 5.8x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 5.3-6.7, min 3.3, max 7.1 x10<sup>3</sup> units/mL);
- Post<sub>24</sub>: median 7.1x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 5.7-8.3, min 3.1, max 10.4 x10<sup>3</sup> units/mL);
- Post<sub>48</sub>: median 7.4x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 6.5-9.1, min 3.1, max 12.7 x10<sup>3</sup> units/mL);
- Post<sub>72</sub>: median 7.6x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 6.0-8.8, min 2.5, max 14.2 x10<sup>3</sup> units/mL);
- Post<sub>96</sub>: median 6.9x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 5.2-8.5, min 2.9, max 15.7x10<sup>3</sup> units/mL).

The group Medium (n=38) showed the following trend:

- T<sub>0</sub>: median 8.5x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 7.8-9.3, min 7.2, max 10.5 x10<sup>3</sup> units/mL);
- Post<sub>24</sub>: median 9.0x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 8.0-10.7, min 5.0, max 26.2 x10<sup>3</sup> units/mL);
- Post<sub>48</sub>: median 9.3x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 8.0-11.3, min 5.7, max 20.6 x10<sup>3</sup> units/mL);
- Post<sub>72</sub>: median 9.0x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 7.6-10.4, min 3.1, max 20.9 x10<sup>3</sup> units/mL);
- Post<sub>96</sub>: median 8.3x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 7.1-11.6, min 5.8, max 20.7 x10<sup>3</sup> units/mL).

The group High (n=38) showed the following trend:

- T<sub>0</sub>: median 12.7x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 11.0-15.1, min 10.5, max 26.3 x10<sup>3</sup> units/mL);
- Post<sub>24</sub>: median 11.7x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 10.0-15.5, min 7.2, max 44.6 x10<sup>3</sup> units/mL);
- Post<sub>48</sub>: median 11.3x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 8.9-16.7, min 5.8, max 26.8 x10<sup>3</sup> units/mL);

- Post<sub>72</sub>: median  $11.6 \times 10^3$  units/mL (Q<sub>1</sub>-Q<sub>3</sub> 8.1-13.0, min 5.5, max  $29.5 \times 10^3$  units/mL);
- Post<sub>96</sub>: median  $10.2 \times 10^3$  units/mL (Q<sub>1</sub>-Q<sub>3</sub> 8.5-13.7, min 5.3, max  $29.2 \times 10^3$  units/mL).

The ART analysis showed the following results:

- Main Effect of tertiles distribution:  $F = 59.737$ ,  $p < 0.001$ , indicating a strong and statistically significant difference in neutrophils values between the tertiles;
- Main Effect of time:  $F = 3.104$ ,  $p = 0.015$ , suggesting that time has a statistically significant impact on the neutrophils values;
- Interaction effect tertiles:time:  $F = 5.203$ ,  $p < 0.001$ , indicating that the effect of time differs across the tertiles.

Figure 3.2.2 illustrates the trends in neutrophils counts over time, stratified by tertiles.

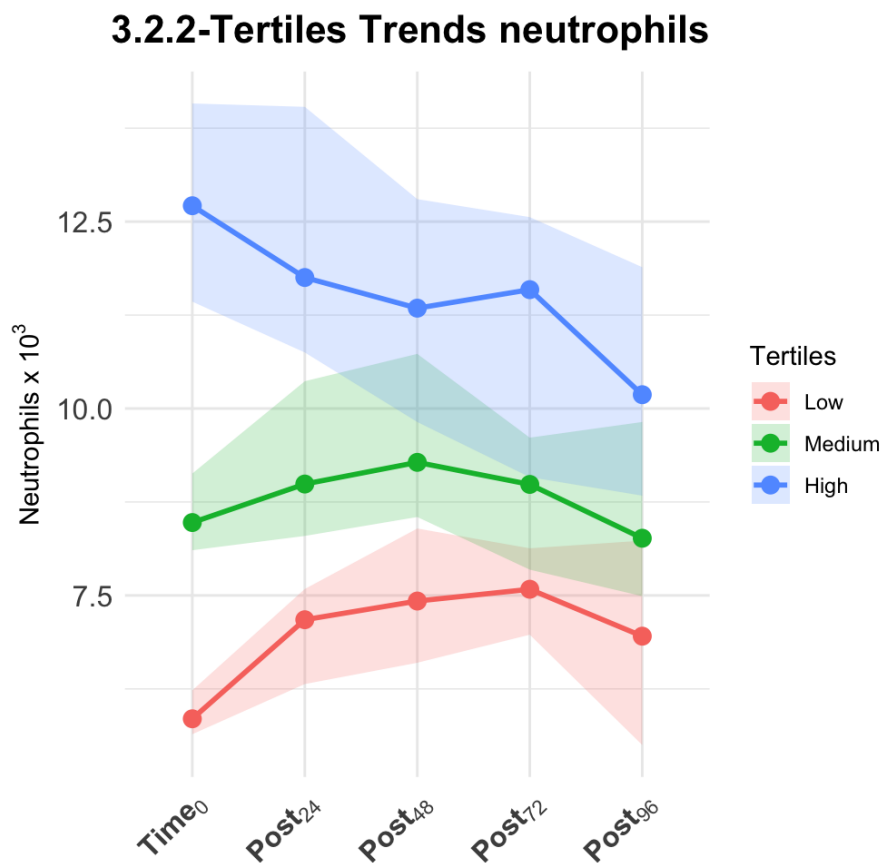


Figure 3.2.2 *Tertiles trends for neutrophils. The lines represent the median neutrophils values for each tertile, while the shaded areas indicate the CI<sub>95%</sub>.*

Post-hoc analysis with Friedman test showed that only trends in Low ( $\chi^2=25.100$ ,  $df=4$ ,  $p < 0.001$ ) and High ( $\chi^2=26.400$ ,  $df=4$ ,  $p < 0.001$ ) were statistically significant, but not in Medium tertile ( $\chi^2=3.680$ ,  $df=4$ ,  $p = 0.450$ ).

In Low tertile, the pairwise analysis with paired W test reported the followign results:

- Time<sub>0</sub> vs Post<sub>24</sub>: p<0.001;
- Time<sub>0</sub> vs Post<sub>48</sub>: p<0.001;
- Time<sub>0</sub> vs Post<sub>72</sub>: p<0.001;
- Time<sub>0</sub> vs Post<sub>96</sub>: p=0.003.

In High tertile, the pairwise analysis with paired W test reported the followign results:

- Time<sub>0</sub> vs Post<sub>24</sub>: p=0.258;
- Time<sub>0</sub> vs Post<sub>48</sub>: p=0.157;
- Time<sub>0</sub> vs Post<sub>72</sub>: p=0.031;
- Time<sub>0</sub> vs Post<sub>96</sub>: p=0.043.

Death rates in tertiles were 28.9% (11 patients) in Low, 15.8% (6 patients) in medium, and 26.3% (10 patients) in High. Frequences were not statistically significant ( $\chi^2=2.038$ , p=0.361).

Table 3.2.2 showed the results for univariate and multivariate logistic regression analysis. Univariate and multivariate logistic regression showed that WBC tertiles were not related to outcome.

Variables		Univariate		Multivariate	
		OR (CI <sub>95%</sub> )	p-value	OR (CI <sub>95%</sub> )	p-value
Neutrophils Tertile	Low	Ref.	-	Ref.	-
	Medium	0.460 (0.142-1.375)	0.174	0.420 (0.127-1.276)	0.135
	High	0.877 (0.316-2.408)	0.798	0.726 (0.248-2.078)	0.552
CCI		-	-	1.095 (0.877-1.358)	0.410
SOFA		-	-	1.090 (0.942-1.268)	0.249

### 3.2.3 Lymphocytes

The group Low (n=38) showed the following trend:

- T<sub>0</sub>: median 665 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 554-774, min 340, max 820 units/mL);
- Post<sub>24</sub>: median 780 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 601-909, min 240, max 2980 units/mL);
- Post<sub>48</sub>: median 750 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 594-877, min 350, max 2345 units/mL);
- Post<sub>72</sub>: median 820 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 611-1060, min 360, max 1710 units/mL);
- Post<sub>96</sub>: median 977 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 677-1187, min 250, max 2270 units/mL).

The group Medium (n=38) showed the following trend:

- T<sub>0</sub>: median 1030 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 962-1150, min 840, max 1255 units/mL);
- Post<sub>24</sub>: median 1035 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 860-1222, min 500, max 2250 units/mL);
- Post<sub>48</sub>: median 1045 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 856-1209, min 430, max 1790 units/mL);
- Post<sub>72</sub>: median 965 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 812-1262, min 650, max 1860 units/mL);
- Post<sub>96</sub>: median 1121 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 869-1277, min 230, max 2160 units/mL).

The group High (n=38) showed the following trend:

- T<sub>0</sub>: median 1560 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 1400-1920, min 1260, max 3330 units/mL);
- Post<sub>24</sub>: median 1505 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 1275-1825, min 600, max 3230 units/mL);
- Post<sub>48</sub>: median 1475 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 1268-1708, min 600, max 3540 units/mL);
- Post<sub>72</sub>: median 1475 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 1290-1608, min 700, max 3320 units/mL);
- Post<sub>96</sub>: median 1475 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 1108-1730, min 740, max 3270 units/mL).

The ART analysis showed the following results:

- Main Effect of tertiles distribution:  $F = 78.537$ ,  $p < 0.001$ , indicating a strong and statistically significant difference in lymphocytes values between the tertiles;
- Main Effect of time:  $F = 0.729$ ,  $p = 0.572$ , suggesting that time did not have a statistically significant impact on the lymphocytes values;
- Interaction effect tertiles:time:  $F = 6.378$ ,  $p < 0.001$ , indicating that the effect of time differs across the tertiles.

Figure 3.2.3 illustrates the trends in lymphocytes counts over time, stratified by tertiles.

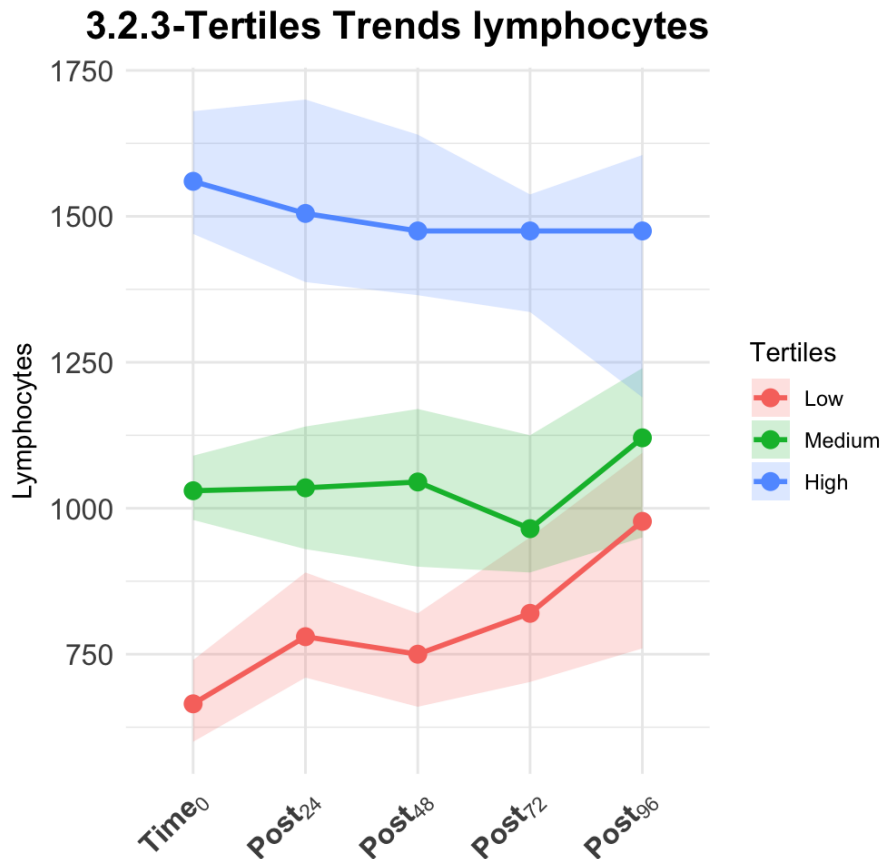


Figure 3.2.3 Tertiles trends for lymphocytes. The lines represent the median lymphocytes values for each tertile, while the shaded areas indicate the  $CI_{95\%}$ .

Post-hoc analysis with Friedman test showed that only trends in Low ( $\chi^2=28.800$ ,  $df=4$ ,  $p<0.001$ ) and High ( $\chi^2=14.900$ ,  $df=4$ ,  $p\text{-value } 0.005$ ) were statistically significant, but not in Medium tertile ( $\chi^2=1.430$ ,  $df=4$ ,  $p=0.838$ ).

In Low tertile, the pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>:  $p=0.005$ ;
- Time<sub>0</sub> vs Post<sub>48</sub>:  $p=0.009$ ;
- Time<sub>0</sub> vs Post<sub>72</sub>:  $p<0.001$ ;
- Time<sub>0</sub> vs Post<sub>96</sub>:  $p<0.001$ .

In High tertile, the pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>:  $p=0.491$ ;
- Time<sub>0</sub> vs Post<sub>48</sub>:  $p=0.161$ ;

- Time<sub>0</sub> vs Post<sub>72</sub>: p=0.010;
- Time<sub>0</sub> vs Post<sub>96</sub>: p=0.009.

Death rates in tertiles were 26.3% (10 patients) in Low, 21.0% (8 patients) in medium, and 23.7% (9 patients) in High. Frequencies were not statistically significant ( $\chi^2=0.291$ , p=0.864).

Table 3.2.3 showed the results for univariate and multivariate logistic regression analysis. Univariate and multivariate logistic regression showed that lymphocytes tertiles were not related to outcome.

<b>Table 3.2.3: Logistic Regression Analyses Results</b>					
<b>Variables</b>		<b>Univariate</b>		<b>Multivariate</b>	
		<b>OR (CI<sub>95%</sub>)</b>	<b>p-value</b>	<b>OR (CI<sub>95%</sub>)</b>	<b>p-value</b>
Lymphocytes Tertile	Low	Ref.	-	Ref.	-
	Medium	0.747 (0.252-2.159)	0.590	0.683 (0.221-2.031)	0.496
	High	0.869 (0.302-2.469)	0.791	0.942 (0.324-2.730)	0.913
CCI		-	-	1.103 (0.885-1.371)	0.376
SOFA		-	-	1.084 (0.939-1.257)	0.270

### 3.2.4 Monocytes

The group Low (n=38) showed the following trend:

- T<sub>0</sub>: median 470 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 400-507, min 60, max 535 units/mL);
- Post<sub>24</sub>: median 530 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 444-560, min 250, max 890 units/mL);
- Post<sub>48</sub>: median 600 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 492-732, min 250, max 1100 units/mL);
- Post<sub>72</sub>: median 605 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 440-764, min 250, max 1130 units/mL);
- Post<sub>96</sub>: median 655 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 460-727, min 265, max 940 units/mL).

The group Medium (n=38) showed the following trend:

- T<sub>0</sub>: median 680 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 612-730, min 550, max 800 units/mL);
- Post<sub>24</sub>: median 690 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 621-747, min 390, max 970 units/mL);
- Post<sub>48</sub>: median 685 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 578-809, min 150, max 1320 units/mL);
- Post<sub>72</sub>: median 655 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 540-835, min 80, max 1490 units/mL);
- Post<sub>96</sub>: median 630 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 515-816, min 270, max 1420 units/mL).

The group High (n=38) showed the following trend:

- T<sub>0</sub>: median 1010 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 885-1202, min 820, max 2340 units/mL);

- Post<sub>24</sub>: median 955 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 861-1217, min 470, max 2260 units/mL);
- Post<sub>48</sub>: median 965 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 825-1209, min 360, max 1890 units/mL);
- Post<sub>72</sub>: median 985 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 714-1245, min 450, max 2037 units/mL);
- Post<sub>96</sub>: median 905 units/mL (Q<sub>1</sub>-Q<sub>3</sub> 665-1208, min 470, max 3080 units/mL).

The ART analysis showed the following results:

- Main Effect of tertiles distribution:  $F = 72.552$ ,  $p < 0.001$ , indicating a strong and statistically significant difference in lymphocytes values between the tertiles;
- Main Effect of time:  $F = 1.093$ ,  $p = 0.359$ , suggesting that time did not have a statistically significant impact on the lymphocytes values;
- Interaction effect tertiles:time:  $F = 4.882$ ,  $p < 0.001$ , indicating that the effect of time differs across the tertiles.

Figure 3.2.4 illustrates the trends in monocytes counts over time, stratified by tertiles.

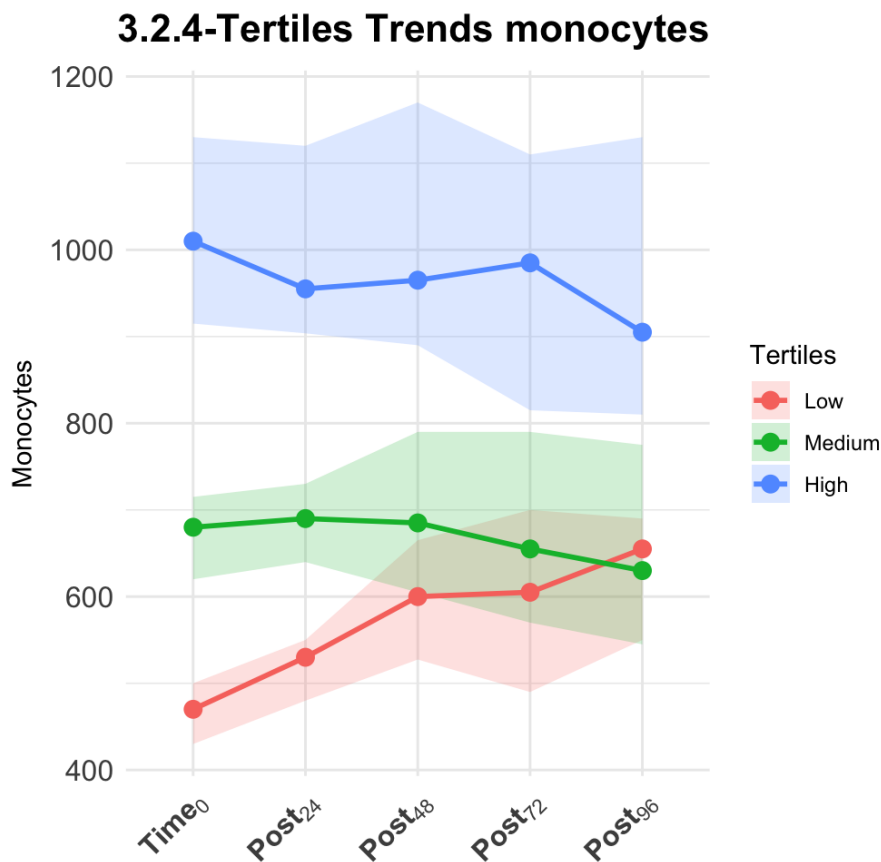


Figure 3.2.4 Tertiles trends for monocytes. The lines represent the median lymphocytes values for each tertile, while the shaded areas indicate the CI<sub>95%</sub>.

Post-hoc analysis with Friedman test showed that only trend in Low ( $\chi^2=32.600$ ,  $df=4$ ,  $p<0.001$ ) was statistically significant, but not in Medium ( $\chi^2=2.220$ ,  $df=4$ ,  $p=0.696$ ) and High ( $\chi^2=9.370$ ,  $df=4$ ,  $p=0.052$ ).

In Low tertile, the pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>:  $p<0.001$ ;
- Time<sub>0</sub> vs Post<sub>48</sub>:  $p<0.001$ ;
- Time<sub>0</sub> vs Post<sub>72</sub>:  $p<0.001$ ;
- Time<sub>0</sub> vs Post<sub>96</sub>:  $p<0.001$ .

Death rates in tertiles were 36.8% (14 patients) in Low, 18.4% (7 patients) in medium, and 15.8% (6 patients) in High. Frequencies were not statistically significant ( $\chi^2=5.534$ ,  $p=0.063$ ).

Table 3.2.4 showed the results for univariate and multivariate logistic regression analysis.

<b>Table 3.2.4: Logistic Regression Analyses Results</b>					
<b>Variables</b>		<b>Univariate</b>		<b>Multivariate</b>	
		<b>OR (CI<sub>95%</sub>)</b>	<b>p-value</b>	<b>OR (CI<sub>95%</sub>)</b>	<b>p-value</b>
Monocytes Tertile	Low	Ref.	-	Ref.	-
	Medium	0.387 (0.129-1.081)	0.077	0.323 (0.101-0.937)	0.044
	High	0.321 (0.302-0.925)	0.042	0.287 (0.087-0.847)	0.029
CCI		-	-	1.126 (0.903-1.400)	0.345
SOFA		-	-	1.102 (0.947-1.289)	0.269

In the univariate logistic regression analysis, patients in the High tertiles showed a reduced death probability compared to Low tertiles (OR 0.321, CI<sub>95%</sub> 0.302-0.925,  $p=0.042$ ). In the multivariate model, Medium (OR 0.323, CI<sub>95%</sub> 0.101-0.937,  $p=0.044$ ) and High (OR 0.287, CI<sub>95%</sub> 0.087-0.847,  $p=0.029$ ) showed a reduced death probability compared to Low tertile.

The 30-days survival probabilities were 71.0% (CI<sub>95%</sub> 55.6-90.6%) for Low, 87.1% (CI<sub>95%</sub> 76.0-99.9%) for Medium, and 92.1% (CI<sub>95%</sub> 83.9-100.0%) for High. The median survival times could not be determined for any group, as less than 50% of patients experienced the event within the study period. The log-rank test showed that differences in survival probabilities were not statistically significant ( $\chi^2=5.600$ ,  $df=2$ ,  $p=0.061$ ). The Figure 3.2.5 shows the Kaplan-Meier curves stratified for monocytes tertiles.

### 3.2.5 Kaplan-Meier Survival Curves by Monocytes Tertiles

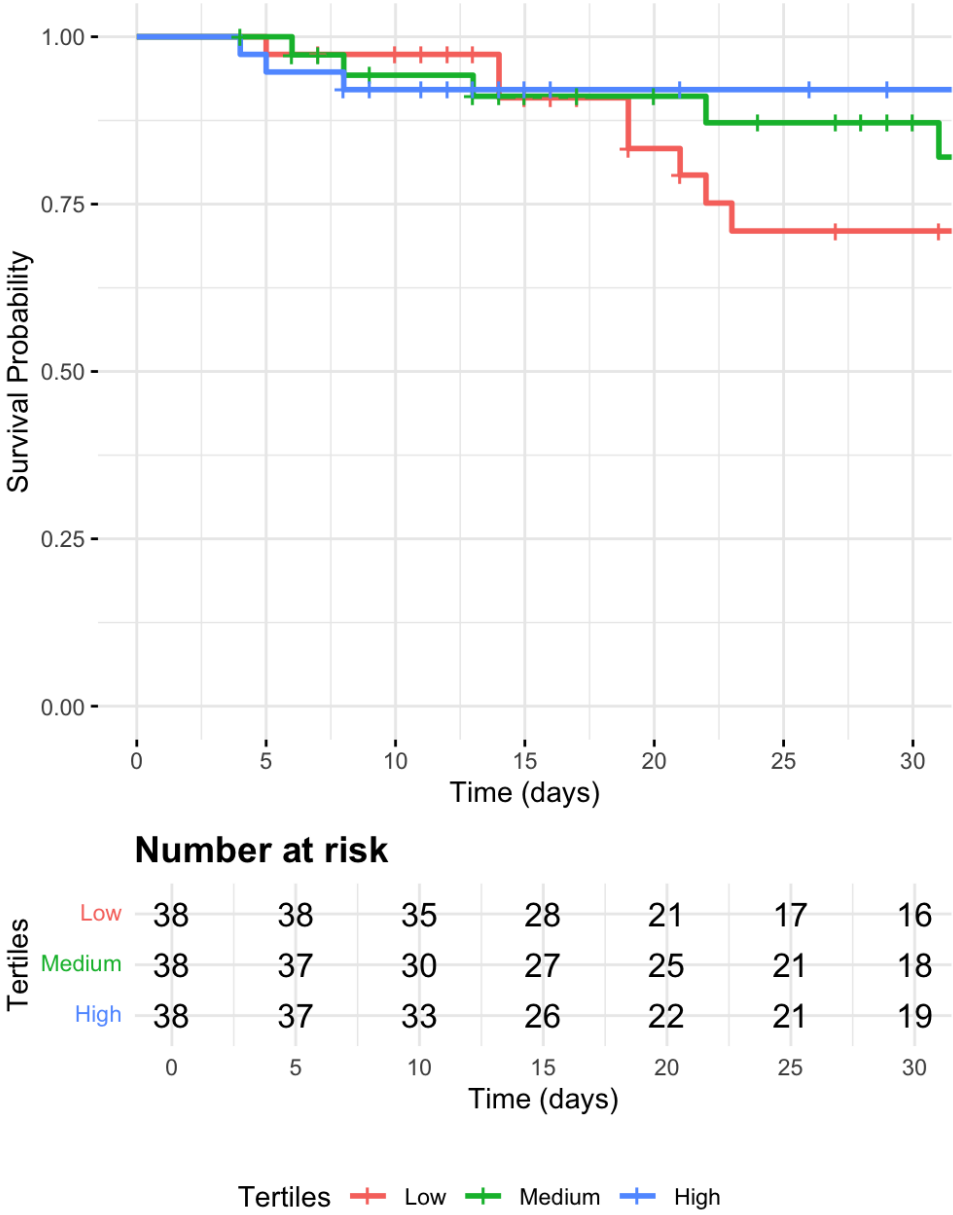


Figure 3.2.5 Kaplan-Meier survival curves stratified by monocyte tertiles (Low, Medium, High). The plot shows the survival probability over the first 30 days, with the number of patients at risk reported in the table below. No statistically significant differences were observed between groups (log-rank test  $\chi^2=5.600$ ,  $df=2$ ,  $p=0.061$ ).

### 3.2.5 Hemoglobin

The group Low (n=40) showed the following trend:

- T<sub>0</sub>: median 8.6 g/dL (Q<sub>1</sub>-Q<sub>3</sub> 8.2-8.8, min 7.5, max 8.9 g/dL);
- Post<sub>24</sub>: median 8.5 g/dL (Q<sub>1</sub>-Q<sub>3</sub> 8.1-9.0, min 7.5, max 10.2 g/dL);
- Post<sub>48</sub>: median 8.5 g/dL (Q<sub>1</sub>-Q<sub>3</sub> 8.4-9.4, min 7.3, max 10.3 g/dL);
- Post<sub>72</sub>: median 9.0 g/dL (Q<sub>1</sub>-Q<sub>3</sub> 8.5-9.5, min 7.4, max 10.8 g/dL);
- Post<sub>96</sub>: median 8.9 g/dL (Q<sub>1</sub>-Q<sub>3</sub> 8.5-9.9, min 7.5, max 10.9 g/dL).

The group Medium (n=36) showed the following trend:

- T<sub>0</sub>: median 9.2 g/dL (Q<sub>1</sub>-Q<sub>3</sub> 9.1-9.4, min 8.9, max 9.8 g/dL);
- Post<sub>24</sub>: median 9.2 g/dL (Q<sub>1</sub>-Q<sub>3</sub> 8.9-9.5, min 8.0, max 10.5 g/dL);
- Post<sub>48</sub>: median 9.3 g/dL (Q<sub>1</sub>-Q<sub>3</sub> 8.7-9.7, min 7.7, max 10.8 g/dL);
- Post<sub>72</sub>: median 9.2 g/dL (Q<sub>1</sub>-Q<sub>3</sub> 8.5-9.7, min 8.0, max 10.8 g/dL);
- Post 96: median 9.2 g/dL (Q<sub>1</sub>-Q<sub>3</sub> 8.7-9.9, min 7.7, max 10.9 g/dL).

The group High (n=38) showed the following trend:

- T<sub>0</sub>: median 10.5 g/dL (Q<sub>1</sub>-Q<sub>3</sub> 10.1-11.0, min 9.9, max 13.3 g/dL);
- Post<sub>24</sub>: median 10.3 g/dL (Q<sub>1</sub>-Q<sub>3</sub> 9.7-11.0, min 9.0, max 13.9 g/dL);
- Post<sub>48</sub>: median 10.2 g/dL (Q<sub>1</sub>-Q<sub>3</sub> 9.6-11.0, min 8.5, max 13.2 g/dL);
- Post<sub>72</sub>: median 10.6 g/dL (Q<sub>1</sub>-Q<sub>3</sub> 9.3-11.1, min 8.3, max 14.0 g/dL);
- Post<sub>96</sub>: median 10.1 g/dL (Q<sub>1</sub>-Q<sub>3</sub> 9.5-10.8, min 8.0, max 12.5 g/dL).

The ART analysis showed the following results:

- Main Effect of tertiles distribution: F = 83.958, p<0.001, indicating a strong and statistically significant difference in hemoglobin values between the tertiles;
- Main Effect of time: F = 0.755, p=0.555, suggesting that time did not have a statistically significant impact on the hemoglobin values;
- Interaction effect tertiles:time: F = 5.308, p<0.001, indicating that the effect of time differs across the tertiles.

Figure 3.2.6 illustrates the trends in lymphocytes counts over time, stratified by tertiles.

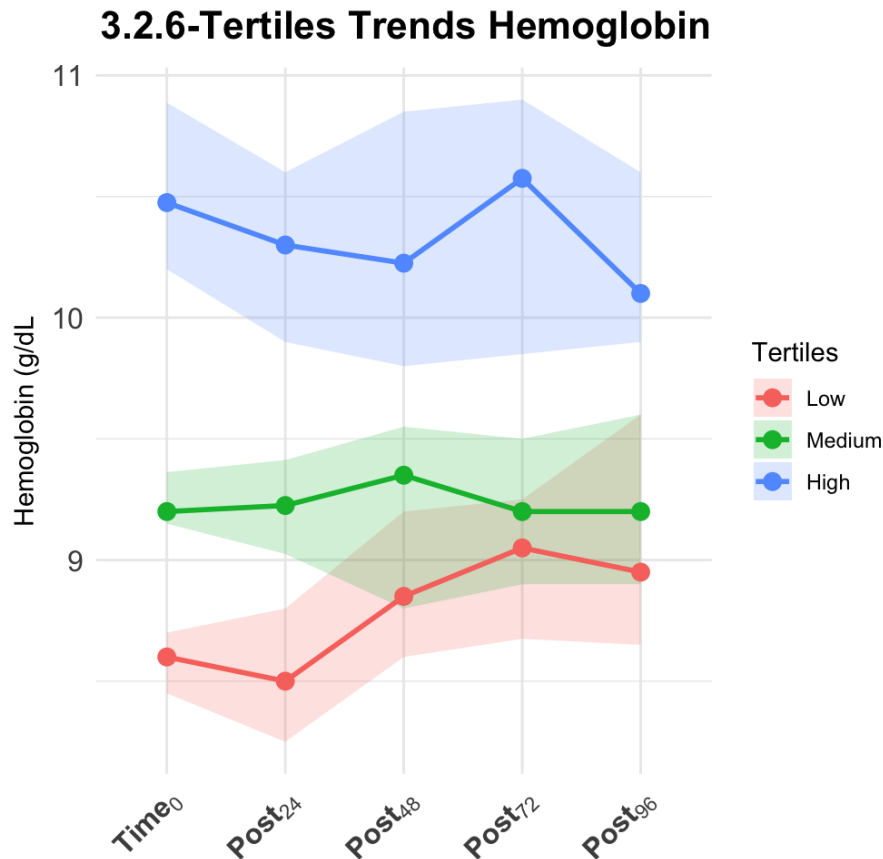


Figure 3.2.6 Tertiles trends for hemoglobin. The lines represent the median lymphocytes values for each tertile, while the shaded areas indicate the CI<sub>95%</sub>.

Post-hoc analysis with Friedman test showed that only trends in Low ( $\chi^2=17.100$ ,  $df=4$ ,  $p$ -value 0.002) and High ( $\chi^2=20.600$ ,  $df=4$ ,  $p<0.001$ ) were statistically significant, but not in Medium tertile ( $\chi^2=1.430$ ,  $df=4$ ,  $p=0.839$ ).

In Low tertile, the pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>:  $p=0.567$ ;
- Time<sub>0</sub> vs Post<sub>48</sub>:  $p=0.005$ ;
- Time<sub>0</sub> vs Post<sub>72</sub>:  $p=0.007$ ;
- Time<sub>0</sub> vs Post<sub>96</sub>:  $p=0.001$ .

In High tertile, the pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>:  $p=0.046$ ;
- Time<sub>0</sub> vs Post<sub>48</sub>:  $p=0.020$ ;
- Time<sub>0</sub> vs Post<sub>72</sub>:  $p=0.051$ ;

- Time<sub>0</sub> vs Post<sub>96</sub>: p=0.006.

Death rates in tertiles were 27.5% (11 patients) in Low, 22.2% (8 patients) in medium, and 21.0% (8 patients) in High. Frequencies were not statistically significant ( $\chi^2=0.510$ , p=0.775).

Table 3.2.5 showed the results for univariate and multivariate logistic regression analysis. Univariate and multivariate logistic regression showed that hemoglobin tertiles were not related to outcome.

Variables		Univariate		Multivariate	
		OR (CI <sub>95%</sub> )	p-value	OR (CI <sub>95%</sub> )	p-value
Hemoglobin Tertile	Low	Ref.	-	Ref.	-
	Medium	0.753 (0.257-2.137)	0.596	0.750 (0.253-2.152)	0.595
	High	0.703 (0.240-1.985)	0.508	0.775 (0.260-2.251)	0.640
CCI		-	-	1.080 (0.872-1.330)	0.472
SOFA		-	-	1.081 (0.932-1.257)	0.303

### 3.2.6 Platelet

The group Low (n=38) showed the following trend:

- T<sub>0</sub>: median 177.5x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 152.8-200.0, min 64.0, max 218.0 x10<sup>3</sup> units/mL);
- Post<sub>24</sub>: median 189.8x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 151.2-222.8, min 84.0, max 282.0 x10<sup>3</sup> units/mL);
- Post<sub>48</sub>: median 209.5x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 170.2-235.8, min 94.0, max 321.8 x10<sup>3</sup> units/mL);
- Post<sub>72</sub>: median 219.8x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 162.0-261.2, min 86.0, max 360.0 x10<sup>3</sup> units/mL);
- Post<sub>96</sub>: median 234.5x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 180.2-312.0, min 72.0, max 427.0x10<sup>3</sup> units/mL).

The group Medium (n=38) showed the following trend:

- T<sub>0</sub>: median 280.5x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 249.8-299.0, min 223.5, max 318.0 x10<sup>3</sup> units/mL);
- Post<sub>24</sub>: median 295.5x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 262.5-311.8, min 156.0, max 387.0 x10<sup>3</sup> units/mL);
- Post<sub>48</sub>: median 297.0x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 260.9-334.0, min 100.0, max 374.0 x10<sup>3</sup> units/mL);
- Post<sub>72</sub>: median 291.5x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 254.4-338.0, min 112.5, max 455.5 x10<sup>3</sup> units/mL);
- Post<sub>96</sub>: median 287.5x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 232.8-342.2, min 82.0, max 671.0 x10<sup>3</sup> units/mL).

The group High (n=38) showed the following trend:

- T<sub>0</sub>: median 437.5x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 385.5-518.5, min 319.0, max 725.0 x10<sup>3</sup> units/mL);
- Post<sub>24</sub>: median 411.0x10<sup>3</sup> units/mL (Q<sub>1</sub>-Q<sub>3</sub> 351.6-531.0, min 200.0, max 747.0 x10<sup>3</sup> units/mL);

- Post<sub>48</sub>: median  $432.0 \times 10^3$  units/mL (Q<sub>1</sub>-Q<sub>3</sub> 342.5-531.8, min 74.0, max  $740.0 \times 10^3$  units/mL);
- Post<sub>72</sub>: median  $430.9 \times 10^3$  units/mL (Q<sub>1</sub>-Q<sub>3</sub> 352.2-529.0, min 77.0, max  $754.0 \times 10^3$  units/mL);
- Post<sub>96</sub>: median  $411.8 \times 10^3$  units/mL (Q<sub>1</sub>-Q<sub>3</sub> 319.2-553.2, min 95.0, max  $764.0 \times 10^3$  units/mL).

The ART analysis showed the following results:

- Main Effect of tertiles distribution:  $F = 114.752$ ,  $p < 0.001$ , indicating a strong and statistically significant difference in platelets values between the tertiles;
- Main Effect of time:  $F = 3.235$ ,  $p = 0.012$ , suggesting that time have a statistically significant impact on the platelets values;
- Interaction effect tertiles:time:  $F = 3.851$ ,  $p < 0.001$ , indicating that the effect of time differs across the tertiles.

Figure 3.2.7 illustrates the trends in lymphocytes counts over time, stratified by tertiles.

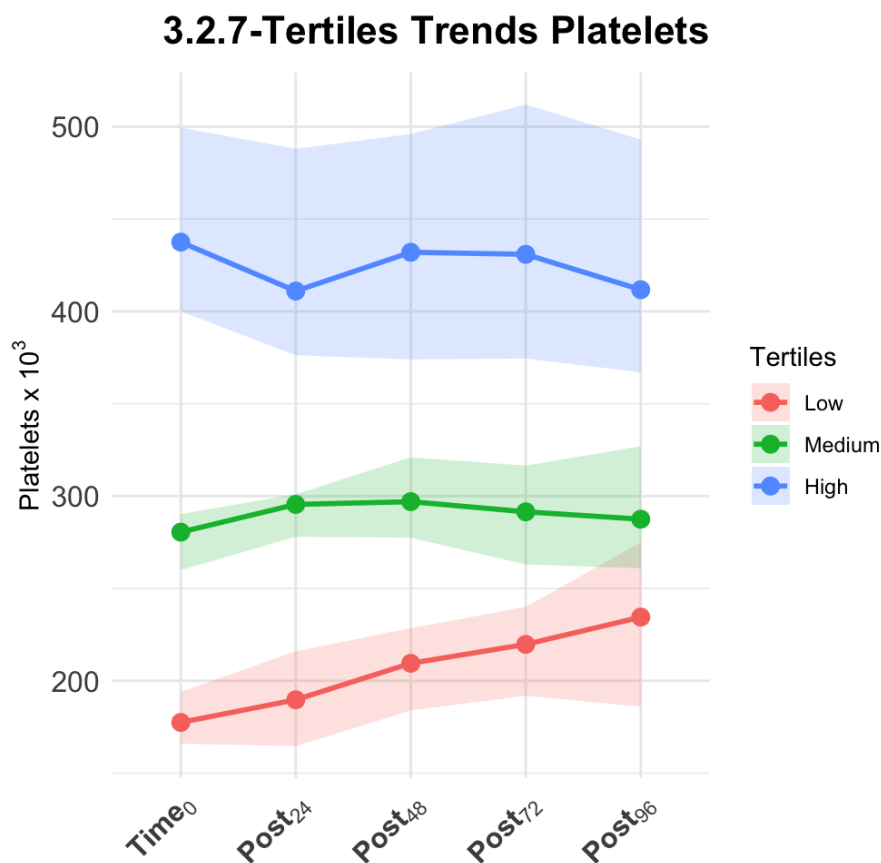


Figure 3.2.7 Tertiles trends for platelets. The lines represent the median lymphocytes values for each tertile, while the shaded areas indicate the  $CI_{95\%}$ .

Post-hoc analysis with Friedman test showed that only trend in Low ( $\chi^2=44.500$ ,  $df=4$ ,  $p<0.001$ ) was statistically significant, but not in Medium ( $\chi^2=5.840$ ,  $df=4$ ,  $p=0.211$ ) and High ( $\chi^2=2.930$ ,  $df=4$ ,  $p=0.570$ ) tertiles.

In Low tertile, the pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>:  $p=0.013$ ;
- Time<sub>0</sub> vs Post<sub>48</sub>:  $p<0.001$ ;
- Time<sub>0</sub> vs Post<sub>72</sub>:  $p<0.001$ ;
- Time<sub>0</sub> vs Post<sub>96</sub>:  $p<0.001$ .

Death rates in tertiles were 31.6% (12 patients) in Low, 26.3% (10 patients) in medium, and 13.1% (5 patients) in High. Frequencies were not statistically significant ( $\chi^2=3.785$ ,  $p=0.151$ ).

Table 3.2.6 showed the results for univariate and multivariate logistic regression analysis. Univariate and multivariate logistic regression showed that platelets tertiles were not related to outcome.

Variables		Univariate		Multivariate	
		OR (CI <sub>95%</sub> )	p-value	OR (CI <sub>95%</sub> )	p-value
Platelets Tertile	Low	Ref.	-	Ref.	-
	Medium	0.774 (0.281-2.091)	0.613	0.726 (0.258-1.994)	0.536
	High	0.328 (0.094-1.005)	0.060	0.333 (0.095-1.031)	0.066
CCI		-	-	1.095 (0.883-1.353)	0.397
SOFA		-	-	1.067 (0.919-1.240)	0.393

### 3.2.7 NLR

The group Low (n=38) showed the following trend:

- T<sub>0</sub>: median 5.0 (Q<sub>1</sub>-Q<sub>3</sub> 3.7-5.8, min 2.6, max 6.5);
- Post<sub>24</sub>: median 5.0 (Q<sub>1</sub>-Q<sub>3</sub> 4.3-7.1, min 2.7, max 47.3);
- Post<sub>48</sub>: median 5.4 (Q<sub>1</sub>-Q<sub>3</sub> 4.5-7.0, min 2.7, max 17.8);
- Post<sub>72</sub>: median 5.9 (Q<sub>1</sub>-Q<sub>3</sub> 4.4-8.7, min 2.7, max 20.2);
- Post<sub>96</sub>: median 6.1 (Q<sub>1</sub>-Q<sub>3</sub> 3.9-8.5, min 2.4, max 24.9).

The group Medium (n=38) showed the following trend:

- T<sub>0</sub>: median 8.2 (Q<sub>1</sub>-Q<sub>3</sub> 7.3-9.2, min 6.5, max 10.0);
- Post<sub>24</sub>: median 8.4 (Q<sub>1</sub>-Q<sub>3</sub> 7.0-10.7, min 3.8, max 22.0);

- Post<sub>48</sub>: median 8.8 (Q<sub>1</sub>-Q<sub>3</sub> 7.3-12.6, min 4.8, max 26.1);
- Post<sub>72</sub>: median 8.5 (Q<sub>1</sub>-Q<sub>3</sub> 6.2-11.6, min 2.2, max 24.3);
- Post<sub>96</sub>: median 6.9 (Q<sub>1</sub>-Q<sub>3</sub> 5.8-10.0, min 2.3, max 73.0).

The group High (n=38) showed the following trend:

- T<sub>0</sub>: median 14.9 (Q<sub>1</sub>-Q<sub>3</sub> 12.2-19.1, min 10.3, max 59.1);
- Post<sub>24</sub>: median 14.4 (Q<sub>1</sub>-Q<sub>3</sub> 8.8-21.0, min 2.4, max 56.9);
- Post<sub>48</sub>: median 13.0 (Q<sub>1</sub>-Q<sub>3</sub> 8.8-16.3, min 4.7, max 40.2);
- Post<sub>72</sub>: median 10.3 (Q<sub>1</sub>-Q<sub>3</sub> 8.1-15.7, min 4.4, max 39.0);
- Post<sub>96</sub>: median 10.7 (Q<sub>1</sub>-Q<sub>3</sub> 6.5-16.2, min 3.5, max 37.9).

The ART analysis showed the following results:

- Main Effect of tertiles distribution:  $F = 53.459$ ,  $p < 0.001$ , indicating a strong and statistically significant difference in NLR values between the tertiles;
- Main Effect of time:  $F = 5.338$ ,  $p < 0.001$ , suggesting that time had a statistically significant impact on the NLR values;
- Interaction effect tertiles:time:  $F = 6.333$ ,  $p < 0.001$ , indicating that the effect of time differs across the tertiles.

Figure 3.2.8 illustrates the trends in NLR over time, stratified by tertiles.

## 3.2.8-Tertiles Trends NLR

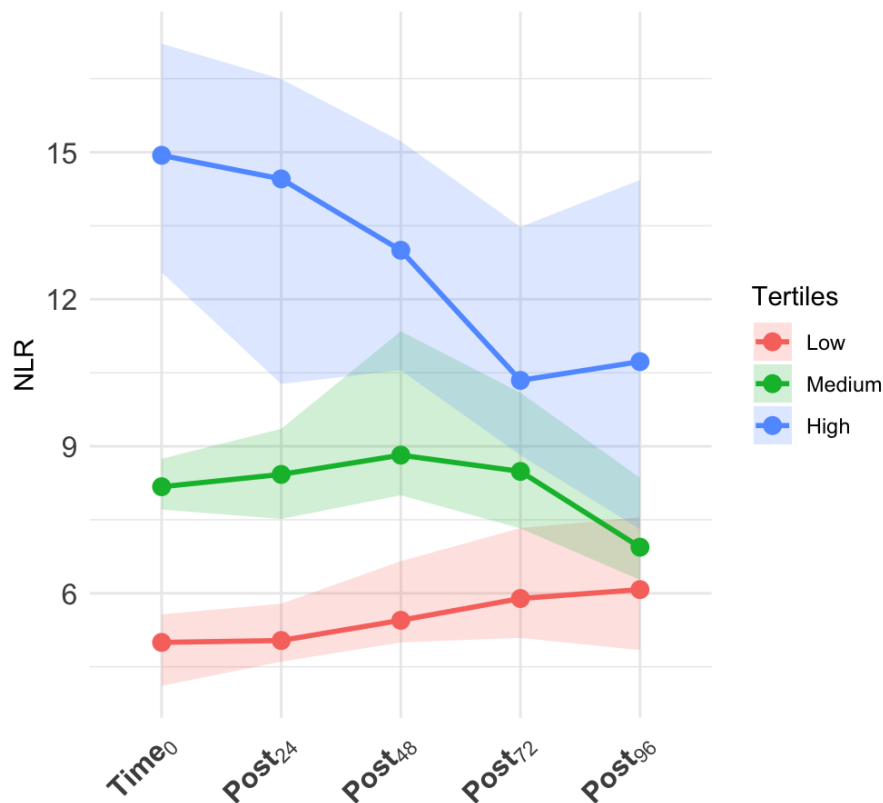


Figure 3.2.8 Tertiles trends for NLR. The lines represent the median lymphocytes values for each tertile, while the shaded areas indicate the  $CI_{95\%}$ .

Post-hoc analysis with Friedman test showed that only trends in Low ( $\chi^2=14.800$ ,  $df=4$ ,  $p=0.005$ ) and High ( $\chi^2=19.900$ ,  $df=4$ ,  $p=0.005$ ) were statistically significant, but not in Medium tertile ( $\chi^2=8.910$ ,  $df=4$ ,  $p=0.063$ ).

In Low tertile, the pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>:  $p=0.007$ ;
- Time<sub>0</sub> vs Post<sub>48</sub>:  $p=0.003$ ;
- Time<sub>0</sub> vs Post<sub>72</sub>:  $p<0.001$ ;
- Time<sub>0</sub> vs Post<sub>96</sub>:  $p<0.001$ .

In High tertile, the pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>:  $p=0.321$ ;
- Time<sub>0</sub> vs Post<sub>48</sub>:  $p=0.144$ ;
- Time<sub>0</sub> vs Post<sub>72</sub>:  $p=0.002$ ;
- Time<sub>0</sub> vs Post<sub>96</sub>:  $p=0.008$ .

Death rates in tertiles were 15.8% (6 patients) in Low, 34.2% (13 patients) in medium, and 21.0% (8 patients) in High. Frequencies were not statistically significant ( $\chi^2=3.785$ ,  $p=0.151$ ).

Table 3.2.7 showed the results for univariate and multivariate logistic regression analysis. Univariate and multivariate logistic regression showed that NLR tertiles were not related to outcome.

Variables		Univariate		Multivariate	
		OR (CI <sub>95%</sub> )	p-value	OR (CI <sub>95%</sub> )	p-value
NLR Tertile	Low	Ref.	-	Ref.	-
	Medium	2.773 (0.954-8.864)	0.069	2.725 (0.929-8.772)	0.076
	High	1.422 (0.443-4.779)	0.555	1.176 (0.346-4.097)	0.794
CCI		-	-	1.084 (0.876-1.342)	0.452
SOFA		-	-	1.099 (0.943-1.290)	0.233

### 3.2.8 PLR

The group Low (n=38) showed the following trend:

- T<sub>0</sub>: median 152.8 (Q<sub>1</sub>-Q<sub>3</sub> 124.5-188.1, min 43.5, max 217.1);
- Post<sub>24</sub>: median 155.7 (Q<sub>1</sub>-Q<sub>3</sub> 129.6-198.8, min 44.3, max 495.8);
- Post<sub>48</sub>: median 164.8 (Q<sub>1</sub>-Q<sub>3</sub> 141.4-221.1, min 47.0, max 336.6);
- Post<sub>72</sub>: median 191.0 (Q<sub>1</sub>-Q<sub>3</sub> 151.2-261.9, min 49.7, max 376.3);
- Post<sub>96</sub>: median 221.7 (Q<sub>1</sub>-Q<sub>3</sub> 157.9-288.6, min 55.0, max 524.1).

The group Medium (n=38) showed the following trend:

- T<sub>0</sub>: median 275.4 (Q<sub>1</sub>-Q<sub>3</sub> 242.8-300.7, min 225.8, max 341.1);
- Post<sub>24</sub>: median 275.8 (Q<sub>1</sub>-Q<sub>3</sub> 225.7-341.0, min 91.6, max 591.7);
- Post<sub>48</sub>: median 295.6 (Q<sub>1</sub>-Q<sub>3</sub> 237.4-350.2, min 109.2, max 556.2);
- Post<sub>72</sub>: median 264.1 (Q<sub>1</sub>-Q<sub>3</sub> 206.7-405.7, min 89.6, max 551.6);
- Post 96: median 275.7 (Q<sub>1</sub>-Q<sub>3</sub> 215.3-342.6, min 59.0, max 633.3).

The group High (n=38) showed the following trend:

- T<sub>0</sub>: median 447.6 (Q<sub>1</sub>-Q<sub>3</sub> 402.8-569.6, min 345.2, max 867.4);
- Post<sub>24</sub>: median 452.5 (Q<sub>1</sub>-Q<sub>3</sub> 347.5-589.7, min 234.0, max 1041.5);
- Post<sub>48</sub>: median 449.6 (Q<sub>1</sub>-Q<sub>3</sub> 363.3-600.5, min 101.4, max 1260.7);

- Post<sub>72</sub>: median 415.0 (Q<sub>1</sub>-Q<sub>3</sub> 322.9-540.0, min 79.4, max 954.4);
- Post<sub>96</sub>: median 338.2 (Q<sub>1</sub>-Q<sub>3</sub> 283.0-569.1, min 82.6, max 1078.3).

The ART analysis showed the following results:

- Main Effect of tertiles distribution:  $F = 101.203$ ,  $p < 0.001$ , indicating a strong and statistically significant difference in PLR values between the tertiles;
- Main Effect of time:  $F = 0.640$ ,  $p = 0.634$ , suggesting that time did not have a statistically significant impact on the PLR values;
- Interaction effect tertiles:time:  $F = 4.657$ ,  $p < 0.001$ , indicating that the effect of time differs across the tertiles.

Figure 3.2.9 illustrates the trends in PLR over time, stratified by tertiles.

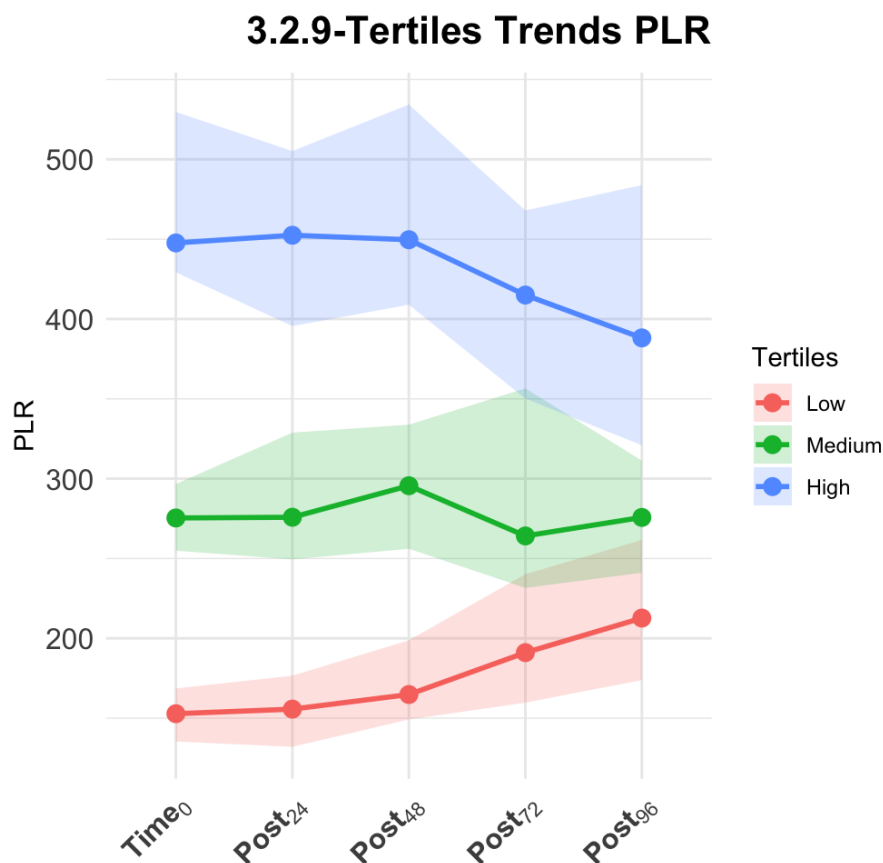


Figure 3.2.9 Tertiles trends for PLR. The lines represent the median lymphocytes values for each tertile, while the shaded areas indicate the CI<sub>95%</sub>.

Post-hoc analysis with Friedman test showed that only trends in Low ( $\chi^2=24.400$ ,  $df=4$ ,  $p < 0.001$ ) and High ( $\chi^2=15.200$ ,  $df=4$ ,  $p = 0.004$ ) were statistically significant, but not in Medium tertile ( $\chi^2=5.960$ ,  $df=4$ ,  $p = 0.202$ ).

In Low tertile, the pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>: p-value<sub>Adj</sub> 0.113;
- Time<sub>0</sub> vs Post<sub>48</sub>: p-value<sub>Adj</sub> 0.018;
- Time<sub>0</sub> vs Post<sub>72</sub>: p-value<sub>Adj</sub> <0.001;
- Time<sub>0</sub> vs Post<sub>96</sub>: p-value<sub>Adj</sub> <0.001.

In High tertile, the pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>: p-value<sub>Adj</sub> 0.609;
- Time<sub>0</sub> vs Post<sub>48</sub>: p-value<sub>Adj</sub> 0.605;
- Time<sub>0</sub> vs Post<sub>72</sub>: p-value<sub>Adj</sub> 0.083;
- Time<sub>0</sub> vs Post<sub>96</sub>: p-value<sub>Adj</sub> 0.040.

Death rates in tertiles were 28.9% (11 patients) in Low, 21.0% (8 patients) in medium, and 21.0% (8 patients) in High. Frequencies were not statistically significant ( $\chi^2=0.873$ ,  $p=0.646$ ).

Table 3.2.8 showed the results for univariate and multivariate logistic regression analysis. Univariate and multivariate logistic regression showed that PLR tertiles were not related to outcome.

Variables		Univariate		Multivariate	
		OR (CI <sub>95%</sub> )	p-value	OR (CI <sub>95%</sub> )	p-value
PLR Tertile	Low	Ref.	-	Ref.	-
	Medium	0.654 (0.223-1.856)	0.428	0.580 (0.191-1.683)	0.322
	High	0.654 (0.223-1.856)	0.428	0.679 (0.229-1.948)	0.474
CCI		-	-	1.089 (0.879-1.343)	0.424
SOFA		-	-	1.092 (0.941-1.271)	0.246

### 3.2.9 MLR

The group Low (n=38) showed the following trend:

- T<sub>0</sub>: median 0.42 (Q<sub>1</sub>-Q<sub>3</sub> 0.31-0.50, min 0.06, max 0.53);
- Post<sub>24</sub>: median 0.44 (Q<sub>1</sub>-Q<sub>3</sub> 0.35-0.56, min 0.17, max 0.82);
- Post<sub>48</sub>: median 0.52 (Q<sub>1</sub>-Q<sub>3</sub> 0.40-0.73, min 0.28, max 1.04);
- Post<sub>72</sub>: median 0.52 (Q<sub>1</sub>-Q<sub>3</sub> 0.39-0.59, min 0.26, max 1.38);
- Post<sub>96</sub>: median 0.48 (Q<sub>1</sub>-Q<sub>3</sub> 0.37-0.59, min 0.26, max 2.83).

The group Medium (n=38) showed the following trend:

- T<sub>0</sub>: median 0.69 (Q<sub>1</sub>-Q<sub>3</sub> 0.59-0.75, min 0.54, max 0.85);
- Post<sub>24</sub>: median 0.64 (Q<sub>1</sub>-Q<sub>3</sub> 0.56-0.79, min 0.25, max 2.87);
- Post<sub>48</sub>: median 0.70 (Q<sub>1</sub>-Q<sub>3</sub> 0.57-0.88, min 0.27, max 1.38);
- Post<sub>72</sub>: median 0.66 (Q<sub>1</sub>-Q<sub>3</sub> 0.54-0.85, min 0.10, max 1.33);
- Post 96: median 0.66 (Q<sub>1</sub>-Q<sub>3</sub> 0.55-0.92, min 0.24, max 2.21).

The group High (n=38) showed the following trend:

- T<sub>0</sub>: median 1.03 (Q<sub>1</sub>-Q<sub>3</sub> 0.94-1.31, min 0.88, max 2.15);
- Post<sub>24</sub>: median 1.01 (Q<sub>1</sub>-Q<sub>3</sub> 0.84-1.27, min 0.29, max 2.17);
- Post<sub>48</sub>: median 1.01 (Q<sub>1</sub>-Q<sub>3</sub> 0.80-1.29, min 0.48, max 2.06);
- Post<sub>72</sub>: median 0.87 (Q<sub>1</sub>-Q<sub>3</sub> 0.70-1.10, min 0.32, max 2.47);
- Post<sub>96</sub>: median 0.83 (Q<sub>1</sub>-Q<sub>3</sub> 0.60-1.03, min 0.33, max 3.21).

The ART analysis showed the following results:

- Main Effect of tertiles distribution:  $F = 88.943$ ,  $p < 0.001$ , indicating a strong and statistically significant difference in MLR values between the tertiles;
- Main Effect of time:  $F = 2.596$ ,  $p = 0.036$ , suggesting that time had a statistically significant impact on the MLR values;
- Interaction effect tertiles:time:  $F = 7.413$ ,  $p < 0.001$ , indicating that the effect of time differs across the tertiles.

Figure 3.2.10 illustrates the trends in MLR over time, stratified by tertiles.

**3.2.10-Tertiles Trends MLR**

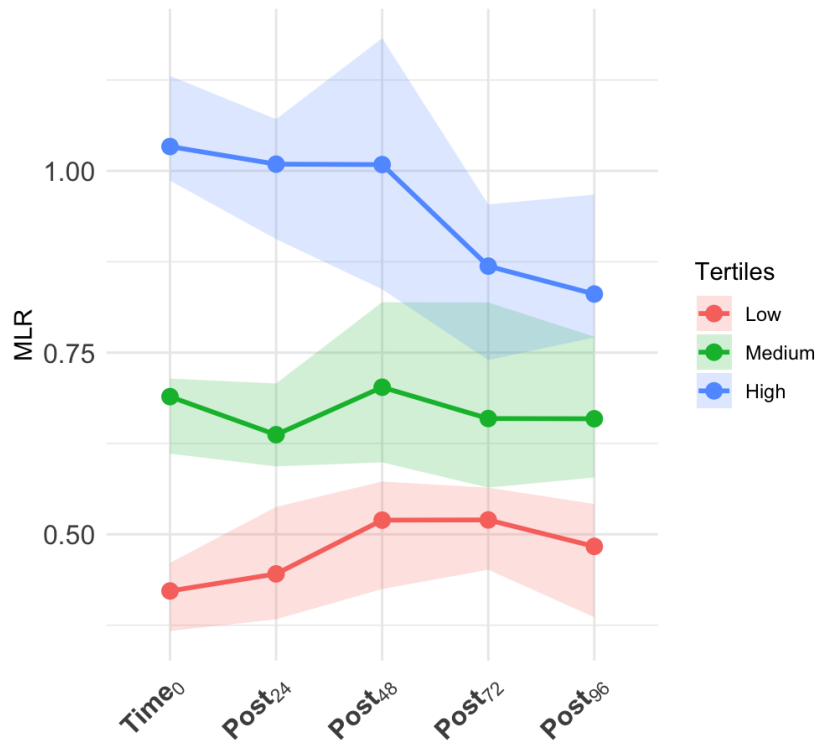


Figure 3.2.10 Tertiles trends for MLR. The lines represent the median lymphocytes values for each tertile, while the shaded areas indicate the CI<sub>95%</sub>.

Post-hoc analysis with Friedman test showed that only trends in Low ( $\chi^2=26.200$ ,  $df=4$ ,  $p$ -value  $<0.001$ ) and High ( $\chi^2=26.700$ ,  $df=4$ ,  $p<0.001$ ) were statistically significant, but not in Medium tertile ( $\chi^2=4.270$ ,  $df=4$ ,  $p=0.370$ ).

In Low tertile, the pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>:  $p=0.009$ ;
- Time<sub>0</sub> vs Post<sub>48</sub>:  $p<0.001$ ;
- Time<sub>0</sub> vs Post<sub>72</sub>:  $p<0.001$ ;
- Time<sub>0</sub> vs Post<sub>96</sub>:  $p=0.001$ .

In High tertile, the pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>:  $p=0.300$ ;
- Time<sub>0</sub> vs Post<sub>48</sub>:  $p=0.099$ ;
- Time<sub>0</sub> vs Post<sub>72</sub>:  $p=0.010$ ;
- Time<sub>0</sub> vs Post<sub>96</sub>:  $p=0.007$ .

Death rates in tertiles were 31.6% (12 patients) in Low, 23.7% (9 patients) in medium, and 15.8% (6 patients) in High. Frequencies were not statistically significant ( $\chi^2=2.621$ ,  $p=0.270$ ).

Table 3.2.9 showed the results for univariate and multivariate logistic regression analysis. Univariate and multivariate logistic regression showed that PLR tertiles were not related to outcome.

Variables		Univariate		Multivariate	
		OR (CI <sub>95%</sub> )	p-value	OR (CI <sub>95%</sub> )	p-value
MLR Tertile	Low	Ref.	-	Ref.	-
	Medium	0.672 (0.238-1.843)	0.443	0.597 (0.204-1.676)	0.332
	High	0.406 (0.126-1.195)	0.111	0.381 (0.117-1.139)	0.093
CCI		-	-	1.082 (0.874-1.335)	0.460
SOFA		-	-	1.098 (0.947-1.279)	0.218

### 3.2.10 SIRI

The group Low (n=38) showed the following trend:

- T<sub>0</sub>: median 3.0 (Q<sub>1</sub>-Q<sub>3</sub> 1.9-3.4, min 0.9, max 3.9);
- Post<sub>24</sub>: median 4.1 (Q<sub>1</sub>-Q<sub>3</sub> 2.4-5.0, min 0.9, max 13.4);
- Post<sub>48</sub>: median 4.8 (Q<sub>1</sub>-Q<sub>3</sub> 3.4-6.9, min 1.2, max 11.4);
- Post<sub>72</sub>: median 4.4 (Q<sub>1</sub>-Q<sub>3</sub> 3.3-5.6, min 1.4, max 15.5);
- Post<sub>96</sub>: median 4.1 (Q<sub>1</sub>-Q<sub>3</sub> 2.3-5.1, min 1.0, max 47.4).

The group Medium (n=38) showed the following trend:

- T<sub>0</sub>: median 5.5 (Q<sub>1</sub>-Q<sub>3</sub> 4.8-6.9, min 4.1, max 8.2);
- Post<sub>24</sub>: median 5.3 (Q<sub>1</sub>-Q<sub>3</sub> 3.9-7.6, min 1.7, max 20.0);
- Post<sub>48</sub>: median 5.6 (Q<sub>1</sub>-Q<sub>3</sub> 4.2-8.6, min 2.0, max 18.1);
- Post<sub>72</sub>: median 6.5 (Q<sub>1</sub>-Q<sub>3</sub> 3.4-8.3, min 0.9, max 24.3);
- Post 96: median 5.4 (Q<sub>1</sub>-Q<sub>3</sub> 3.6-6.7, min 2.0, max 31.3).

The group High (n=38) showed the following trend:

- T<sub>0</sub>: median 10.7 (Q<sub>1</sub>-Q<sub>3</sub> 9.1-16.5, min 8.3, max 43.1);
- Post<sub>24</sub>: median 11.2 (Q<sub>1</sub>-Q<sub>3</sub> 7.9-17.8, min 2.1, max 81.3);
- Post<sub>48</sub>: median 9.3 (Q<sub>1</sub>-Q<sub>3</sub> 6.3-17.4, min 4.0, max 34.8);

- Post<sub>72</sub>: median 8.5 (Q<sub>1</sub>-Q<sub>3</sub> 4.9-13.9, min 2.5, max 35.2);
- Post<sub>96</sub>: median 8.0 (Q<sub>1</sub>-Q<sub>3</sub> 5.4-17.1, min 1.6, max 50.3).

The ART analysis showed the following results:

- Main Effect of tertiles distribution:  $F = 55.811$ ,  $p < 0.001$ , indicating a strong and statistically significant difference in SIRI values between the tertiles;
- Main Effect of time:  $F = 2.993$ ,  $p = 0.018$ , suggesting that time had a statistically significant impact on the SIRI values;
- Interaction effect tertiles:time:  $F = 4.554$ ,  $p < 0.001$ , indicating that the effect of time differs across the tertiles.

Figure 3.2.11 illustrates the trends in SIRI over time, stratified by tertiles.

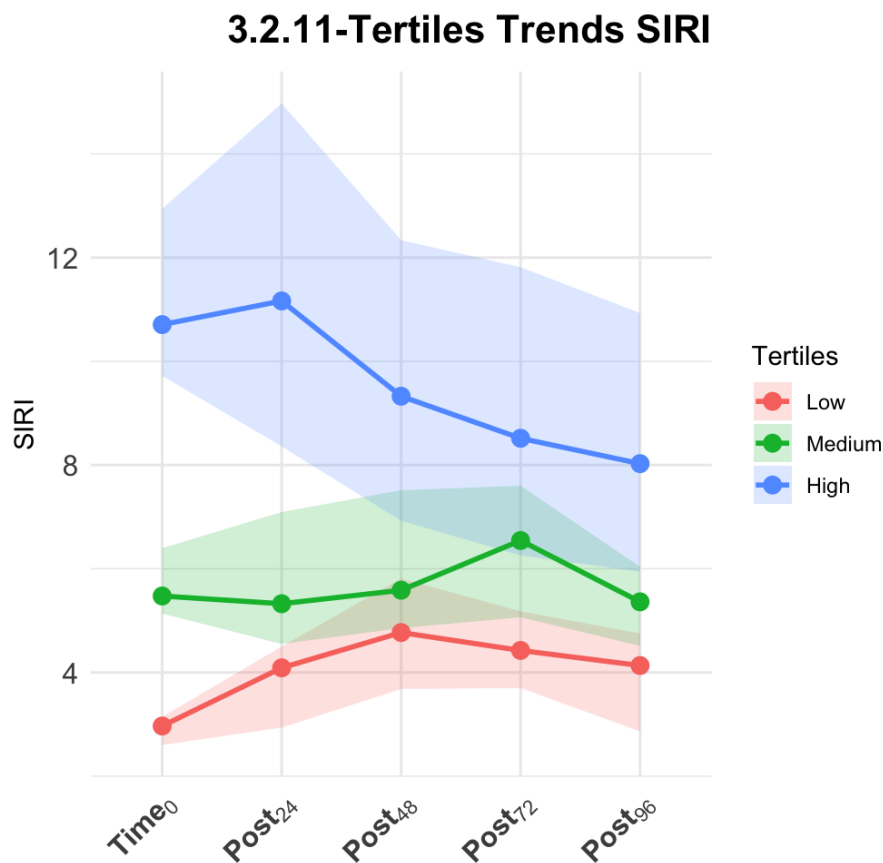


Figure 3.2.11 Tertiles trends for SIRI. The lines represent the median lymphocytes values for each tertile, while the shaded areas indicate the CI<sub>95%</sub>.

Post-hoc analysis with Friedman test showed that only trends in Low ( $\chi^2=41.600$ ,  $df=4$ ,  $p\text{-value} < 0.001$ ) and High ( $\chi^2=26.100$ ,  $df=4$ ,  $p < 0.001$ ) were statistically significant, but not in Medium tertile ( $\chi^2=1.770$ ,  $df=4$ ,  $p=0.779$ ).

In Low tertile, the pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>:  $p < 0.001$ ;
- Time<sub>0</sub> vs Post<sub>48</sub>:  $p < 0.001$ ;
- Time<sub>0</sub> vs Post<sub>72</sub>:  $p < 0.001$ ;
- Time<sub>0</sub> vs Post<sub>96</sub>:  $p < 0.001$ .

In High tertile, the pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>:  $p=0.405$ ;
- Time<sub>0</sub> vs Post<sub>48</sub>:  $p=0.148$ ;
- Time<sub>0</sub> vs Post<sub>72</sub>:  $p=0.019$ ;
- Time<sub>0</sub> vs Post<sub>96</sub>:  $p=0.057$ .

Death rates in tertiles were 28.9% (11 patients) in Low, 26.3% (10 patients) in medium, and 15.8% (6 patients) in High. Frequencies were not statistically significant ( $\chi^2=2.038$ ,  $p=0.361$ ).

Table 3.2.10 showed the results for univariate and multivariate logistic regression analysis. Univariate and multivariate logistic regression showed that SIRS tertiles were not related to outcome.

Variables		Univariate		Multivariate	
		OR (CI <sub>95%</sub> )	p-value	OR (CI <sub>95%</sub> )	p-value
SIRS Tertile	Low	Ref.	-	Ref.	-
	Medium	0.877 (0.316-2.408)	0.798	0.884 (0.312-2.480)	0.815
	High	0.460 (0.142-1.374)	0.174	0.350 (0.100-1.108)	0.083
CCI		-	-	1.087 (0.880-1.341)	0.432
SOFA		-	-	1.135 (0.971-1.336)	0.116

### 3.2.11 SII

The group Low (n=38) showed the following trend:

- T<sub>0</sub>: median 1253.1 (Q<sub>1</sub>-Q<sub>3</sub> 796.9-1638.7, min 461.1, max 1889.0);
- Post<sub>24</sub>: median 1270.1 (Q<sub>1</sub>-Q<sub>3</sub> 835.5-1850.5, min 401.3, max 3797.3);

- Post<sub>48</sub>: median 1336.1 (Q<sub>1</sub>-Q<sub>3</sub> 950.6-2271.8, min 476.0, max 3883.7);
- Post<sub>72</sub>: median 1542.5 (Q<sub>1</sub>-Q<sub>3</sub> 970.6-2492.0, min 380.4, max 6171.0);
- Post<sub>96</sub>: median 1325.9 (Q<sub>1</sub>-Q<sub>3</sub> 1009.5-2165.9, min 433.6, max 7612.3).

The group Medium (n=38) showed the following trend:

- T<sub>0</sub>: median 2347.0 (Q<sub>1</sub>-Q<sub>3</sub> 2106.0-2827.0, min 1912.0, max 3173.0);
- Post<sub>24</sub>: median 2450.2 (Q<sub>1</sub>-Q<sub>3</sub> 1715.6-3591.5, min 663.3, max 16785.6);
- Post<sub>48</sub>: median 2865.0 (Q<sub>1</sub>-Q<sub>3</sub> 1967.0-3845.0, min 1205.0, max 5848.0);
- Post<sub>72</sub>: median 2703.9 (Q<sub>1</sub>-Q<sub>3</sub> 1967.3-3642.7, min 559.5, max 9307.8);
- Post 96: median 2619.0 (Q<sub>1</sub>-Q<sub>3</sub> 1838.0-3831.0, min 1241.0, max 18104.0).

The group High (n=38) showed the following trend:

- T<sub>0</sub>: median 4394.0 (Q<sub>1</sub>-Q<sub>3</sub> 3606.0-5381.0, min 3248.0, max 16151.0);
- Post<sub>24</sub>: median 4596.0 (Q<sub>1</sub>-Q<sub>3</sub> 3197.0-6069.0, min 1627.0, max 22042.0);
- Post<sub>48</sub>: median 4572.0 (Q<sub>1</sub>-Q<sub>3</sub> 2989.0-6395.0, min 1310.0, max 21117.0);
- Post<sub>72</sub>: median 3692.0 (Q<sub>1</sub>-Q<sub>3</sub> 2649.0-4720.0, min 1207.0, max 12847.0);
- Post<sub>96</sub>: median 3275.9 (Q<sub>1</sub>-Q<sub>3</sub> 2246.2-4607.7, min 693.5, max 11156.3).

The ART analysis showed the following results:

- Main Effect of tertiles distribution:  $F = 76.654$ ,  $p < 0.001$ , indicating a strong and statistically significant difference in SII values between the tertiles;
- Main Effect of time:  $F = 3.283$ ,  $p = 0.011$ , suggesting that time had a statistically significant impact on the SII values;
- Interaction effect tertiles:time:  $F = 5.263$ ,  $p < 0.001$ , indicating that the effect of time differs across the tertiles.

Figure 3.2.12 illustrates the trends in SII over time, stratified by tertiles.

## 3.2.12-Tertiles Trends SII

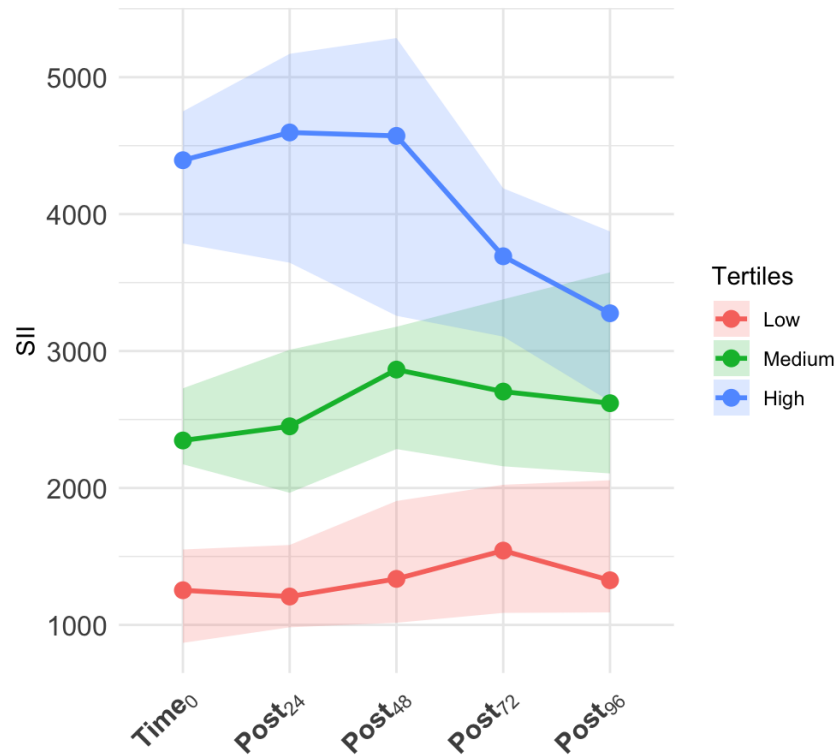


Figure 3.2.12 Tertiles trends for SII. The lines represent the median lymphocytes values for each tertile, while the shaded areas indicate the  $CI_{95\%}$ .

Post-hoc analysis with Friedman test showed that only trends in Low ( $\chi^2=20.800$ ,  $df=4$ ,  $p<0.001$ ) and High ( $\chi^2=25.900$ ,  $df=4$ ,  $p<0.001$ ) were statistically significant, but not in Medium tertile ( $\chi^2=4.080$ ,  $df=4$ ,  $p=0.395$ ).

In Low tertile, the pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>:  $p=0.063$ ;
- Time<sub>0</sub> vs Post<sub>48</sub>:  $p=0.009$ ;
- Time<sub>0</sub> vs Post<sub>72</sub>:  $p=0.006$ ;
- Time<sub>0</sub> vs Post<sub>96</sub>:  $p=0.007$ .

In High tertile, the pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>:  $p=0.875$ ;
- Time<sub>0</sub> vs Post<sub>48</sub>:  $p=0.875$ ;
- Time<sub>0</sub> vs Post<sub>72</sub>:  $p=0.005$ ;
- Time<sub>0</sub> vs Post<sub>96</sub>:  $p=0.003$ .

Death rates in tertiles were 34.2% (13 patients) in Low, 18.4% (7 patients) in medium, and 18.4% (7 patients) in High. Frequencies were not statistically significant ( $\chi^2=3.494$ ,  $p=0.174$ ).

Table 3.2.11 showed the results for univariate and multivariate logistic regression analysis. Univariate and multivariate logistic regression showed that PLR tertiles were not related to outcome.

Variables		Univariate		Multivariate	
		OR (CI <sub>95%</sub> )	p-value	OR (CI <sub>95%</sub> )	p-value
SII Tertile	Low	Ref.	-	Ref.	-
	Medium	0.434 (0.144-1.225)	0.123	0.417 (0.136-1.191)	0.110
	High	0.434 (0.144-1.225)	0.123	0.384 (0.123-1.112)	0.086
CCI		-	-	1.094 (0.882-1.351)	0.404
SOFA		-	-	1.101 (0.948-1.285)	0.210

### 3.2.12 AISI

The group Low (n=38) showed the following trend:

- T<sub>0</sub>: median 683.0 (Q<sub>1</sub>-Q<sub>3</sub> 361.0-1022.7, min 248.9, max 1146.5);
- Post<sub>24</sub>: median 846.3 (Q<sub>1</sub>-Q<sub>3</sub> 587.5-1281.0, min 260.8, max 2815.7);
- Post<sub>48</sub>: median 979.7 (Q<sub>1</sub>-Q<sub>3</sub> 691.2-1490.5, min 252.3, max 5126.4);
- Post<sub>72</sub>: median 1226.5 (Q<sub>1</sub>-Q<sub>3</sub> 581.7-1766.1, min 197.8, max 3921.9);
- Post<sub>96</sub>: median 1072.2 (Q<sub>1</sub>-Q<sub>3</sub> 594.6-1701.0, min 210.4, max 2657.8).

The group Medium (n=38) showed the following trend:

- T<sub>0</sub>: median 1627.0 (Q<sub>1</sub>-Q<sub>3</sub> 1386.0-1861.0, min 1197.0, max 2342.0);
- Post<sub>24</sub>: median 1672.6 (Q<sub>1</sub>-Q<sub>3</sub> 1090.9-2262.1, min 534.3, max 5016.6);
- Post<sub>48</sub>: median 2047.0 (Q<sub>1</sub>-Q<sub>3</sub> 1493.4-2993.4, min 614.6, max 6688.9);
- Post<sub>72</sub>: median 1875.6 (Q<sub>1</sub>-Q<sub>3</sub> 1237.7-3101.6, min 251.8, max 13496.3);
- Post 96: median 1706.0 (Q<sub>1</sub>-Q<sub>3</sub> 1221.9-2688.0, min 260.9, max 14043.6).

The group High (n=38) showed the following trend:

- T<sub>0</sub>: median 3670.0 (Q<sub>1</sub>-Q<sub>3</sub> 3050.0-4817.0, min 2350.0, max 13486.0);
- Post<sub>24</sub>: median 3655.1 (Q<sub>1</sub>-Q<sub>3</sub> 2456.2-5565.7, min 566.3, max 28871.2);
- Post<sub>48</sub>: median 2879.0 (Q<sub>1</sub>-Q<sub>3</sub> 1645.0-5307.0, min 1090.0, max 15204.0);

- Post<sub>72</sub>: median 2458.3 (Q<sub>1</sub>-Q<sub>3</sub> 1877.8-3976.9, min 759.1, max 10534.2);
- Post<sub>96</sub>: median 2228.6 (Q<sub>1</sub>-Q<sub>3</sub> 1570.9-5153.9, min 752.9, max 33748.1).

The ART analysis showed the following results:

- Main Effect of tertiles distribution:  $F = 71.279$ ,  $p < 0.001$ , indicating a strong and statistically significant difference in AISI values between the tertiles;
- Main Effect of time:  $F = 3.009$ ,  $p = 0.018$ , suggesting that time had a statistically significant impact on the AISI values;
- Interaction effect tertiles:time:  $F = 4.994$ ,  $p < 0.001$ , indicating that the effect of time differs across the tertiles.

Figure 3.2.13 illustrates the trends in SII over time, stratified by tertiles.

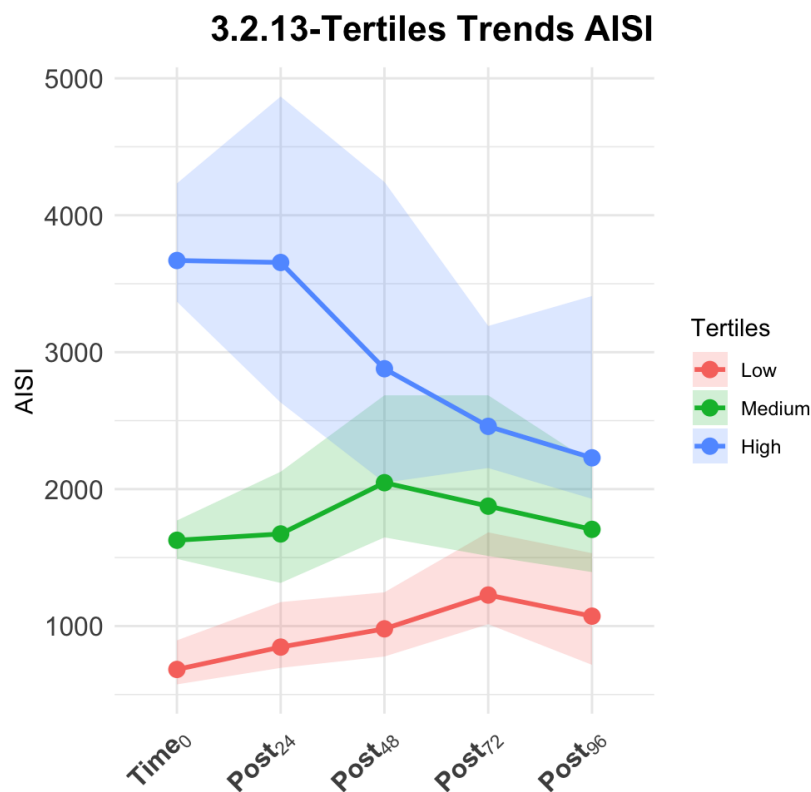


Figure 3.2.13 *Tertiles trends for AISI. The lines represent the median lymphocytes values for each tertile, while the shaded areas indicate the CI<sub>95%</sub>.*

Post-hoc analysis with Friedman test showed that trends in Low ( $\chi^2=22.600$ ,  $df=4$ ,  $p < 0.001$ ), Medium ( $\chi^2=11.900$ ,  $df=4$ ,  $p = 0.018$ ), and High ( $\chi^2=20.700$ ,  $df=4$ ,  $p < 0.001$ ) were statistically significant.

In Low tertile, the pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>: p=0.013;
- Time<sub>0</sub> vs Post<sub>48</sub>: p<0.001;
- Time<sub>0</sub> vs Post<sub>72</sub>: p<0.001;
- Time<sub>0</sub> vs Post<sub>96</sub>: p<0.001.

In Medium tertile, the pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>: p=0.473;
- Time<sub>0</sub> vs Post<sub>48</sub>: p=0.006;
- Time<sub>0</sub> vs Post<sub>72</sub>: p=0.071;
- Time<sub>0</sub> vs Post<sub>96</sub>: p=0.192.

In High tertile, the pairwise analysis with paired W test reported the following results:

- Time<sub>0</sub> vs Post<sub>24</sub>: p=0.657;
- Time<sub>0</sub> vs Post<sub>48</sub>: p=0.607;
- Time<sub>0</sub> vs Post<sub>72</sub>: p=0.042;
- Time<sub>0</sub> vs Post<sub>96</sub>: p=0.080.

Death rates in tertiles were 31.6% (12 patients) in Low, 26.3% (10 patients) in medium, and 13.1% (5 patients) in High. Frequencies were not statistically significant ( $\chi^2=3.785$ , p=0.151).

Table 3.2.12 showed the results for univariate and multivariate logistic regression analysis.

<b>Table 3.2.12: Logistic Regression Analyses Results</b>					
<b>Variables</b>		<b>Univariate</b>		<b>Multivariate</b>	
		<b>OR (CI<sub>95%</sub>)</b>	<b>p-value</b>	<b>OR (CI<sub>95%</sub>)</b>	<b>p-value</b>
WBC Tertile	Low	Ref.	-	Ref.	-
	Medium	0.774 (0.281-2.091)	0.613	0.757 (0.269-2.090)	0.592
	High	0.328 (0.094-1.005)	0.060	0.270 (0.074-0.861)	0.034
CCI		-	-	1.107 (0.892-1.369)	0.348
SOFA		-	-	1.119 (0.959-1.314)	0.155

In the multivariate logistic regression analysis, AISI values in High tertile (OR 0.270, CI<sub>95%</sub> 0.074-0.861, p=0.034) was related to the outcome, but not in the univariate analysis (OR 0.328, CI<sub>95%</sub> 0.094-1.005, p=0.060).

The 30-days survival probabilities were 77.7% (CI<sub>95%</sub> 64.3-93.7%) for Low, 83.9% (CI<sub>95%</sub> 71.7-98.2%) for Medium, and 90.5% (CI<sub>95%</sub> 80.5-100.0%) for High. The median survival times could not be determined for any group, as less than 50% of patients experienced the event within the study period. The log-rank test showed

that differences in survival probabilities were not statistically significant ( $\chi^2=3.000$ ,  $df=2$ ,  $p=0.200$ ). The Figure 3.2.14 shows the Kaplan-Meier curves stratified for AISI tertiles.

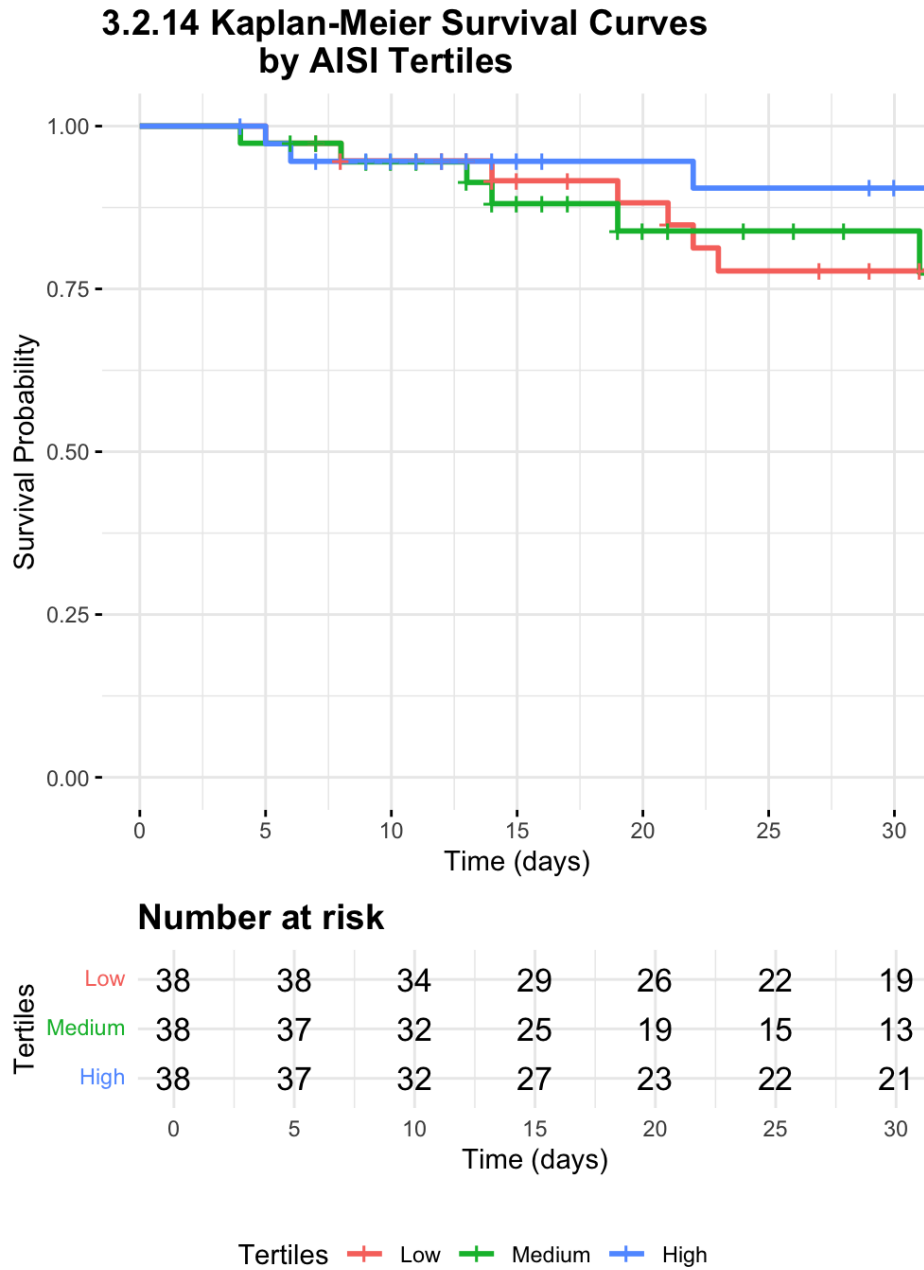


Figure 3.2.14 Kaplan-Meier survival curves stratified by AISI tertiles (Low, Medium, High). The plot shows the survival probability over the first 30 days, with the number of patients at risk reported in the table below. No statistically significant differences were observed between groups (log-rank test  $\chi^2=3.000$ ,  $df=2$ ,  $p=0.200$ ).

**Reference**

1. Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. *Int Immunopharmacol.* 2020;84:106504.
2. Sun YY, Wang MQ, Wang Y, Sun X, Qu Y, Zhu HJ, et al. Platelet-to-lymphocyte ratio at 24h after thrombolysis is a prognostic marker in acute ischemic stroke patients. *Front Immunol.* 2022;13:1000626.
3. Yang L, Gao C, Li F, Yang L, Chen J, Guo S, et al. Monocyte-to-lymphocyte ratio is associated with 28-day mortality in patients with acute respiratory distress syndrome: a retrospective study. *J Intensive Care.* 2021;9(1):49.
4. Wang X, Tian W, Zhao Y, Yang Y, Deng L. Systemic immune inflammation index and system inflammation response index on the third postoperative day predict poor prognosis of aneurysmal subarachnoid hemorrhage patients. *Medicine (Baltimore).* 2024;103(16):e37818.
5. Wang S, Zhang G. Association Between Systemic Immune-Inflammation Index and Adverse Outcomes in Patients With Acute Coronary Syndrome: A Meta-Analysis. *Angiology.* 2024:33197241263399.
6. Hosseninia S, Ghobadi H, Garjani K, Hosseini SAH, Aslani MR. Aggregate index of systemic inflammation (AIS) in admission as a reliable predictor of mortality in COPD patients with COVID-19. *BMC Pulm Med.* 2023;23(1):107.
7. Wobbrock JO, Findlater L, Gergle D, Higgins JJ, editors. The aligned rank transform for nonparametric factorial analyses using only anova procedures. *Proceedings of the SIGCHI conference on human factors in computing systems*; 2011.