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# Correlation between carcinoembryonic antigen and systemic immune-inflammation index with the outcomes of colorectal cancer patients who underwent radical surgery at Dr. Soetomo Surabaya during 2022-2024

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**Abstract:** Colorectal cancer is the third most common malignancy. It occurs due to the accumulation of genetic and epigenetic changes in the cell genome that transform normal epithelial cells into adenocarcinoma. CEA (Carcinoembryonic Antigen) is a marker that is often used and is associated with carcinogenesis. The SII (Systemic Immune Inflammatory Index) is an integrated indicator based on peripheral lymphocytes, neutrophils, and platelets; it is a strong prognostic marker for hepatocellular carcinoma but has not been widely reported in cases of colorectal cancer. This research is an observational analytical study with a cohort retrospective method to link CEA and SII with the outcomes of colorectal cancer patients at RSUD Dr. Soetomo from 2022 to 2024. Data collection was obtained from medical records that met the inclusion criteria. Data analysis was carried out using SPSS software. According to the ROC curve, the optimal cutoff values for CEA and SII are 0.564 and 0.641, respectively. Based on these data, 44 samples were divided into high CEA, low CEA, high SII, and low SII groups. Statistically, there was a significant relationship between CEA and length of stay and stage; SII and length of stay also had a significant relationship ($p < 0.05$). However, the relationship between CEA and SII with mortality was not significant ($p > 0.05$). There was a significant relationship between CEA and SII values with length of stay and tumor stage. However, there was no significant relationship between CEA and SII values and mortality in colorectal cancer patients.

***Keywords:*** *Colorectal cancer, Carcinoembryonic Antigen, Systemic Immune-inflammation index.*

## 1. Introduction

Colorectal cancer (CRC) is the third most common cancer globally, responsible for a significant number of new diagnoses (approximately 1.9 million, or 10% of all cancers) and the second highest number of cancer-related deaths (over 937,000 annually) [1, 2]. In Indonesia, CRC ranks fourth in prevalence, with nearly 400,000 new cases and over 230,000 deaths [3].

Colorectal cancer staging, which helps predict patient outcomes, relies on the American Joint Committee on Cancer (AJCC) system. This system integrates information gathered before, during, and after surgery, including pathological examination of tissue samples. Generally, higher AJCC stages are associated with worse prognoses [4, 5].

The development of CRC is driven by accumulated genetic and epigenetic changes that transform healthy colon cells into cancerous ones (adenocarcinoma). These cancerous cells can further evolve, acquiring the ability to spread (metastasize) to distant organs, most often the liver and lungs, primarily through the lymphatic system [6].


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Inflammation and immune responses play a complex role in cancer development. The inflammatory environment surrounding a tumor involves various factors like cytokines, immune cells, and inflammatory proteins. These factors can be measured in the blood, including levels of white blood cells, neutrophils, lymphocytes, platelets, and C-reactive protein [7].

Carcinoembryonic antigen (CEA) is a common blood test used to help detect and monitor gastrointestinal cancers. Elevated CEA levels (above 5 µg/ml) can suggest the presence of cancer, and in some patients, CEA levels can also be useful for detecting cancer recurrence after surgery [8].

Another potential prognostic marker is the Systemic Immune-inflammation Index (SII), which is calculated from routine blood counts of lymphocytes, neutrophils, and platelets. While SII has shown promise in other cancers like hepatocellular carcinoma, its value in CRC is not yet well established. A key advantage of SII is that it's easily calculated from readily available blood test results [9].

While doctors often use the pathological stage of the cancer to predict outcomes, patients with the same stage can have very different prognoses. CEA is already used as a prognostic marker in CRC, and SII is being explored for the same purpose. However, research on SII in CRC is still limited. This study aims to explore the relationship between CEA and SII as predictors of outcomes in CRC patients undergoing surgery at Dr. Soetomo Hospital.

## 2. Method

This study was an observational analytic with a cohort retrospective study design. Data was collected from the medical records of patients treated at Dr. Soetomo General Hospital during the 2022–2024 period. The study sample consists of patients diagnosed with colorectal cancer who underwent radical surgery at Dr. Soetomo General Hospital during the same period. The inclusion criteria for this study were medical records of colorectal cancer patients who underwent radical surgery. Data on CEA and SII values were obtained from laboratory results documented in the patients's medical records, and patient outcome data were assessed based on data in the patients's medical records. From this study, 44 samples were obtained that met the inclusion and exclusion criteria. The data obtained in this study were analyzed univariately to determine the characteristics of the research subjects. Data analysis was conducted using SPSS 23.0 software. Biomarker cut-off values in this study was determined using Receiver Operating Characteristic (ROC) curve analysis. Data from independent and dependent variables, which were ordinal, was analyzed using the Chi-Square Test. The strength of the correlation between Carcinoembryonic Antigen (CEA) and the Systemic Immune-inflammation Index (SII) with patient outcomes was assessed using Spearman's rank correlation test. A P-value of less than 0.05 was indicated statistically significant results. Multinomial logistic regression was performed to identify the superior biomarker for evaluating outcomes in colorectal cancer patients.

## 3. Result

The following describes the profile of the study samples that were analyzed. In this study, patients of various ages were included. Based on age groups, it was found that the age range of 60-69 years was the largest group with a percentage of 36.4%. The average age of patients was 58.3 (± 11.317) years with the youngest age being 29 years and the oldest age being 80 years. The most common gender was male at 59.1% (26 samples) compared to female at 40.9% (18 samples).

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**Table 1.**
Sociodemographic characteristics.

| | Frequency (N=44) | Percentage (%) |
|---|---|---|
| Sex | | |
| Male | 26 | 59,1% |
| Female | 18 | 40,9% |
| Age | | |
| <40 | 3 | 6,8% |
| 40-49 | 4 | 9,1% |
| 50-59 | 14 | 31,8% |
| 60-69 | 16 | 36,4% |
| >69 | 7 | 15,9% |
| | Mean (SD) | Median (Min.-Max.) |
| Age (years) | ±11,317 | 58,30 (29-80) |

**Table 2.**
Outcome characteristics.

| | Frequency (N=44) | Percentage (%) |
|---|---|---|
| Stage | | |
| 1 | 7 | 15,9% |
| 2 | 19 | 43,2% |
| 3 | 14 | 31,8% |
| 4 | 4 | 9,1% |
| Length of stay | | |
| <7 days | 7 | 15,6% |
| 7-14 days | 28 | 62,2% |
| >14 days | 9 | 20% |
| Mortality | | |
| Death | 5 | 11,1% |
| Alive | 39 | 86,9% |

Based on table 2 above, it was found that the most common stage was stage 2 at 43.2% and the least common stage was stage 4 at 9.1%. The most frequent length of hospital stay was 7-14 days at 62.2% and the least frequent was <7 days at 15.6%. In the case of mortality, it was found that 86.9% of patients (39 cases) survived, which was higher than the 5 deaths (11.1%).

The results of the Carcinoembryonic Antigen (CEA) and Systemic Immune-inflammation Index (SII) blood tests were divided into two categories:

1. High = above the cut-off point in this study
2. Low = below the cut-off point in this study.

The cut-off point for this study was obtained from creating a receiver operating characteristic curve (ROC) for CEA and SII in this study.

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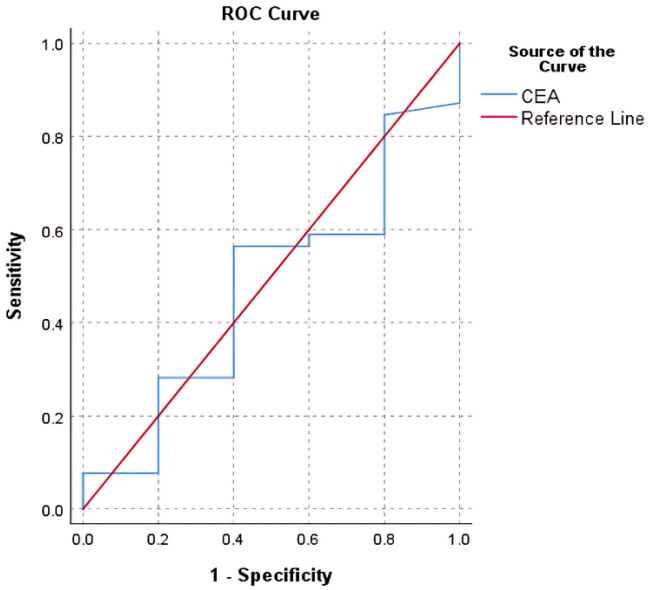


**Figure 1.**
ROC curve of CEA and mortality.

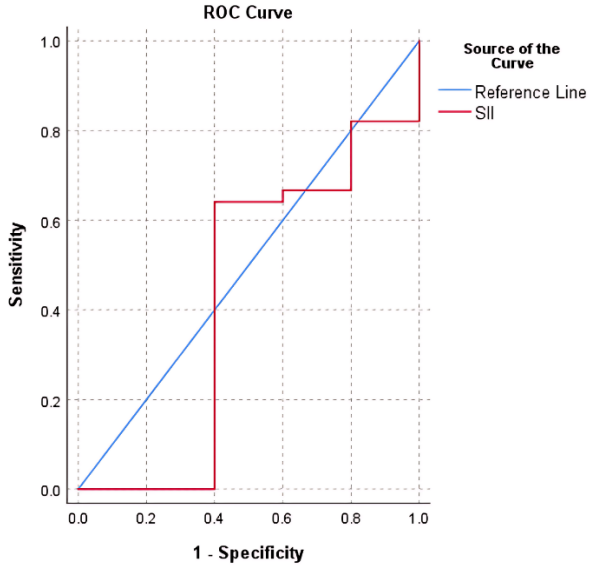


**Figure 2.**
ROC curve of SII and mortality.

The ROC curve of serum markers (SII) has area under the curve (0.426) which is strong correlation between disease and markers as prognosis value, the sensitivity of marker (64.1%) and the specificity (60%) with cut off (836.688 ng/ml), and for (CEA) marker the cut off (8.515 U/ml) and the sensitivity (56.4%), the specificity (60%) and the area under the curve was (0.474) which is strong correlation with the disease as prognosis value.

**Table 3.**
The area under the curve of CEA.

| Area | Std. Error | Sig. | IK (95%) |
|---|---|---|---|
| 0.474 | 0.132 | 0.846 | 0,734-0,215 |

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**Table 4.**
The Area Under the Curve of SII.

| Area | Std. Error | Sig. | IK (95%) |
|---|---|---|---|
| 0.426 | 0.164 | 0.649 | 0,746-0,105 |

**Table 5.**
Correlations between CEA and *length of stay* (LOS).

| | | LOS | | | Total | P-value | Correlation coefficient |
|---|---|---|---|---|---|---|---|
| | | <7 | 14-Jul | >14 | | | |
| CEA level | Low (<=8.5150) | 3 | 15 | 2 | 20 | 0,019 | 0.352 |
| | % of LOS | 42.86% | 53.57% | 22.22% | 45.45% | | |
| | High (>8.5150) | 4 | 13 | 7 | 24 | | |
| | % of LOS | 57.14% | 46.42% | 77.78% | 54.55% | | |

From the data presented in table 5, it was found that patients with a short length of stay (<7 days) 57.14% (4 samples) had high CEA values, but it was not much different from 42.86% (3 samples) who had low CEA values. Patients with care between 7-14 days as much as 53.57% had high CEA values. Patients with care >14 days 77.78% had high CEA. The correlation coefficient value of 0.352 indicates a fairly strong positive relationship between CEA and length of stay. That is, the higher the CEA value, the longer the patient's length of stay. The p-value result of 0.019 is less than 0.05, indicating that this positive relationship is statistically significant.

From the data presented in table 6, it was found that 71.43% of patients with low CEA category had tumors at stage 1, while only 28.57% with high CEA had stage 1. Meanwhile, patients with high CEA category 75% experienced tumors at stage 4, and patients with low CEA category 25% experienced tumors at stage 4. The correlation coefficient value of 0.737 indicates a fairly strong positive relationship between CEA and stage. That is, the higher the CEA value, the higher the stage. The p-value result of 0.000 is less than 0.05, indicating that this positive relationship is statistically significant.

**Table 6.**
Relationship between CEA and Tumor staging.

| | Stage | | | | | P-Value | Correlation coefficient |
|---|---|---|---|---|---|---|---|
| CEA category | 1 | 2 | 3 | 4 | Total | | |
| Low (<=8.5150) | 5 | 10 | 4 | 1 | 20 | | |
| % of stage | 71.43% | 52.63% | 28.57% | 25% | 45.45% | **0.000** | |
| High (>8.5150) | 2 | 9 | 10 | 3 | 24 | | |
| % of stage | 28.57% | 47.37% | 71.43% | 75% | 54.55% | | 0.737 |

**Table 7.**
Relationship between CEA and Mortality.

| | Outcome | | | P-Value | Correlation coefficient |
|---|---|---|---|---|---|
| **CEA category** | **Hidup** | **Meninggal Dunia** | **Total** | | |
| Low (<=8.5150) | 17 | 3 | 20 | | |
| % of CEA | 85% | 15% | 100% | | |
| % of Outcome | 43.59% | 60% | 45.45% | 0.856 | |
| High (>8.5150) | 22 | 2 | 24 | | -0.028 |
| % of CEA | 91.67% | 8,33% | 100% | | |
| % of Outcome | 56.41% | 40% | 54.55% | | |

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**Table 8.**
Relationship between SII and *Length of Stay* (LOS).

| | | LOS | | | Total | P-value | Correlation coefficient |
|---|---|---|---|---|---|---|---|
| | | <7 | 14-Jul | >14 | | | |
| SII category | Low (<=836.68) | 3 | 21 | 2 | 26 | 0.046 | 0.302 |
| | % of LOS | 42.86% | 75% | 22.22% | 59.09% | | |
| | High (>836.68) | 4 | 7 | 7 | 18 | | |
| | % of LOS | 57.14% | 25% | 77.78% | 40.91% | | |

From the data presented in Table 7, it was found that patients with low CEA values had a survival outcome of 43.59%, while patients with high CEA died in a proportion of 40%. From the table, the positive predictive value (PPV) and negative predictive value (NPV) were also obtained, which were 43.59% and 40%, respectively, for the low CEA score against the outcome of patient survival. A correlation coefficient value of -0.28 was obtained, indicating a fairly negative relationship between CEA and mortality. That is, the higher the CEA value, the lower the patient's chance of survival. However, the p-value result of 0.856 is greater than 0.05, indicating that this negative relationship is not statistically significant. Therefore, there was no strong evidence that CEA affects mortality. Based on the results, it can be concluded that there was non-significant negative relationship between CEA values and mortality.

From the data presented in table 8, it was found that patients with a short length of stay (<7 days) 57.14% (4 samples) had high SII values, but it was not much different from 42.86% (3 samples) who had low SII values. Patients with care between 7-14 days had 53.37% with high SII values. Patients with care >14 days 88.88% had high SII. The correlation coefficient value of 0.35 indicates a fairly strong positive relationship between SII and length of stay. That is, the higher the SII value, the longer the patient's length of stay. The p-value result of 0.019 is less than 0.05, indicating that this positive relationship is statistically significant.

From the data presented in table 9, the correlation coefficient value of 0.286 indicates a fairly strong positive relationship between SII and stage. That is, the higher the SII value, the higher the stage. The p-value result of 0.04 is less than 0.05, indicating that this positive relationship is statistically significant. Patients with a low SII category 85.71% had tumors at stage 1. Meanwhile, patients with a high SII category 78.57% experienced tumors at stage 3 and 75% experienced stage 4 tumors.

**Table 9.**
Relationship between SII and Tumor stage.

| | Tumor Stage | | | | | P-Value | Correlation Coefficient |
|---|---|---|---|---|---|---|---|
| **SII category** | **1** | **2** | **3** | **4** | **Total** | | |
| Low (<=836.68) | 6 | 8 | 3 | 1 | 26 | 0.040 | 0.286 |
| % of stage | 85.71% | 42.11% | 21.43% | 25% | 59.09% | | |
| High (>836.68) | 1 | 11 | 11 | 3 | 18 | | |
| % of stage | 14.29% | 57.89% | 78.57% | 75% | 40.91% | | |

**Table 10.**
Relationship between SII and mortality.

| | Outcome | | | P-Value | Correlation Coefficient |
|---|---|---|---|---|---|
| SII category | **Alive** | **Death** | **Total** | | |
| Low (<=836.68) | 16 | 2 | 18 | 0.598 | -0.082 |
| % of SII | 88.89% | 11.11% | 100% | | |
| % of Outcome | 41.03% | 40% | 38.64% | | |
| High (>836.68) | 23 | 3 | 26 | | |
| % of SII | 88.46% | 11.54% | 100% | | |
| % of Outcome | 58.97% | 60% | 61.36% | | |

From the data presented in table 10, a correlation coefficient value of -0.082 was obtained, indicating a fairly weak negative relationship between SII and mortality. This means that the higher the

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SII value, the lower the patient's chance of survival. However, the p-value result of 0.598 is greater than 0.05, indicating that this negative relationship is not statistically significant.

Therefore, there is no strong evidence that SII affects mortality. Based on the results, it can be concluded that there is a non-significant negative relationship between SII values and mortality. Patients with low SII values had a survival outcome of 41.03%, while patients with high SII died in a proportion of 60%. From the table, the positive predictive value (PPV) and negative predictive value (NPV) were also obtained, which were 41.03% and 60%, respectively, for the low SII score against the outcome of patient survival.

## 4. Discussion

In this study, a total of 44 colorectal cancer patients who received surgical treatment at Dr. Soetomo Hospital Surabaya were obtained. According to the American Cancer Society in 2023, it is predicted that there will be 153,020 cases of colorectal cancer, with the majority diagnosed at the age of 65 and over as much as 56%, 13% occurring at the age of less than 50 years and one third will occur at the age of 50-64 years [2]. This is in line with the results of this study that the percentage of events in the age group of 50-59 years with a percentage of 31.8% and the age group of 60-69 years with the highest percentage of 36.4%.

The incidence of colorectal cancer from 2015-2019 showed that the prevalence in men (41.5 per 100,000) was 33% higher than in women (31.2 per 100,000). Colorectal cancer is more common in men than women and is 3-4 times more common in developing countries than in developed countries. The global incidence per 100,000 of colorectal cancer for both sexes is 23.6 in men, and in women it is 16.3 [3]. This is in line with this study that the average age is 58.3 years and the most common gender is male at 59.1% (26 samples) compared to female at 40.9% (18 samples). This may be related to high meat consumption, alcohol consumption habits, and smoking habits in men. Siegel, et al. [2] also noted that the mortality rate in colorectal cancer patients from 2012-2020 was 2% of the total cases. The proportion of this mortality rate is also consistent with the results of this study, which found that 11.1% of patients died. This means that the survival rate reaches 86.9% of the total sample.

Colorectal cancer stage is grouped using the tumor, node, metastasis (TNM) system, which assesses the depth of tumor growth into the layers of the intestinal wall (T stage), spread to regional lymph nodes (N stage), and the presence or absence of distant metastasis (M stage). This TNM system was developed by the American Joint Committee on Cancer (AJCC) and approved by the International Union Against Cancer. This classification combines clinical information obtained before surgery with data obtained during surgery and after histological examination of the specimen. This TNM classification is then grouped into stages 1, 2, 3, and 4 of the AJCC Cancer Staging eighth edition [5]. In this study, seven samples (15.9%) were found to be in stage 1, 19 samples (43.2%) were in stage 2, 14 samples (31.8%) were in stage 3, and 4 samples (9.1%) were in stage 4.

In the study conducted by Li Destri, et al. [10] the average preoperative CEA value was 7.51 µg/L, where in 27.34% of patients whose CEA value exceeded the normal value (≤5 µg/L) the average value reached 21.53 µg/L. In this study, the patient's CEA value had an average of 21.02 µg/L. Furthermore, the lowest CEA value in colorectal cancer patients in this study was 0.21 µg/L and the highest CEA value was 430.30 µg/L.

In this study, it was found that patients with a short length of stay (<7 days) as many as 57.14% (4 samples) had high CEA values, but it was not much different from 42.86% (3 samples) who had low CEA values. Patients with care between 7-14 days as many as 53.57% had high CEA values. Patients with care >14 days 77.78% had high CEA. The p-value result of 0.019 is less than 0.05, indicating that this positive relationship is statistically significant. In a study conducted by Iacuzzo, et al. [11] this may occur because patients with low CEA values have a low cancer stage and underwent surgery laparoscopically and was related to the acceleration of postoperative recovery.

For the Relationship between CEA and stage as the data presented by table 5.8, it was found that 71.43% of patients with low CEA category had tumors at stage 1, while only 28.57% with high CEA had

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stage 1. Meanwhile, patients with high CEA category 75% experienced tumors at stage 4, and patients with low CEA category 25% experienced tumors at stage 4. The p-value result of 0.000 is less than 0.05, indicating that this positive relationship is statistically significant. This is in accordance with a study by Huh et al in 2010, where serum CEA levels were associated with tumor size, increased T (depth of tumor invasion in the intestinal wall), increased N (regional lymph node metastasis), and the number of lymph nodes taken during surgery.

The relationship between CEA and mortality according to table 5.9 shows that patients with low CEA values had a survival outcome of 43.59%, while patients with high CEA died in a proportion of 40%. From the table, the positive predictive value (PPV) and negative predictive value (NPV) were also obtained, which were 43.59% and 40%, respectively, for the low CEA score against the outcome of patient survival. A correlation coefficient value of -0.28 was obtained, indicating a fairly negative relationship between CEA and mortality. That is, the higher the CEA value, the lower the patient's chance of survival. However, the p-value result of 0.856 is greater than 0.05, indicating that this negative relationship is not statistically significant. So, there is no strong evidence that CEA affects mortality. A study conducted by Firut, et al. [12] also found that there was no statistically significant relationship between serum CEA levels and early postoperative mortality in patients.

At the Systemic Immune-inflammation Index (SII) value, the average value is 2056.56 cells/L with the lowest and highest SII being 115.67 cells/L and 11,735.36 cells/L, respectively. The relationship between SII and stage as the data presented by table 5.10 shows that the correlation coefficient value of 0.286 indicates a fairly strong positive relationship between SII and stage. That is, the higher the SII value, the higher the stage. The p-value result of 0.04 is less than 0.05, indicating that this positive relationship is statistically significant. Patients with a low SII category 85.71% had tumors at stage 1. Meanwhile, patients with a high SII category 78.57% experienced tumors at stage 3 and 75% experienced stage 4 tumors. This is in line with a study conducted by Tao, et al. [13] which found a relationship between SII levels and patient tumor category. High SII values indicate high inflammation in the tumor microenvironment that infiltrates into immune cells. The presence of neutrophils in the peripheral blood is generally associated with poor prognosis in patients with cancer. Neutrophils can activate endothelial cells and parenchymal cells and thus facilitate metastasis of circulating tumor cells. Neutrophils also mediate the proliferation and metastasis of cancer cells by releasing inflammatory mediators. In addition, platelets can also protect circulating tumor cells from antitumor immunity and promote angiogenesis and metastasis of cancer cells. Platelets also release various growth factors that increase cancer cell proliferation in vitro. Lymphocytes, especially tumor-infiltrating lymphocytes, play a role in the immune response to malignancy [7]. The correlations between SII and length of stay as the data presented by table 5.11 shows that patients with a short length of stay (<7 days) 57.14% (4 samples) had high SII values, but it was not much different from 42.86% (3 samples) who had low SII values. Patients with length of stay between 7-14 days had 53.37% with high SII values. Patients with length of stay >14 days 88.88% had high SII. The p-value result of 0.019 is less than 0.05, indicating that this positive relationship is statistically significant. This is in line with a study by Tao, et al. [13] which showed that preoperative SII levels had a positive correlation with length of stay. The higher the SII, the higher the inflammatory process that occurs. Inflammation is a significant risk factor in the length of stay of patients undergoing surgery, as it will cause complications such as infection, sepsis, and organ failure which can potentially lead to prolonged length of stay.

From the data presented in table 5.12, a correlation coefficient value of -0.082 was obtained, indicating a fairly weak negative relationship between SII and mortality. This means that the higher the SII value, the lower the patient's chance of survival. However, the p-value result of 0.598 is greater than 0.05, indicating that this negative relationship is not statistically significant. Therefore, there is no strong evidence that SII affects mortality.

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## 5. Conclusion

There was significant relationship between serum concentration of Carcinoembryonic Antigen (CEA) (with the cut-off of 8.515 U/ml) and length of stay and staging of colorectal cancer, but there was no relationship with mortality of the patient. There was significant relationship between serum concentration of Systemic Immune-inflammation Index (SII) (with the cut-off of 836.688 ng/ml) and length of stay and staging of colorectal cancer, but there was no relationship with mortality of the patient.

## Transparency:

The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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