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Accuracy of Serum Neuron-specific Enolase (NSE) as a Predictor of Diagnosis in Colorectal Cancer Patients

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ABSTRACT

Aim: The aim of this study was to see in focus of the accuracy of serum NSE as a predictor of diagnosis in patient with colorectal cancer.
Methods: The cross-sectional study evaluated the accuracy of serum NSE as colorectal cancer diagnostic predictor. Data were collected through for 9 months and consisted of two groups (control and CRC patient). Serum NSE was determined by enzyme lined immunosorbent assay (ELISA).
Results: A total of 29 subjects were included in this study from each group (control and CRC patient). The mean age of each group were 53 years and 54 years old and predominantly male population in both groups. The predilection was found dominantly at the left colon (55.17%). The median of serum NSE of the CRC group (14,82 ng/ml) was significantly higher than that of the control (5,80 ng/ml). The area under the receiver operating characteristic curve (AUC) for NSE in CRC was 0,7759.
Conclusion: Serum NSE has a good specificity and sensitivity that may represent as a tumor biomarker for diagnosing CRC in less invasive method.

Keywords: colorectal cancer (CRC), neuron-specific enolase (NSE), tumor biomarker

INTRODUCTION

Colorectal cancer (CRC) is a malignancy that originates from the colon tissue, consisting of the colon (the longest part of the large intestine) and or the rectum (the last small part of the large intestine). According to the Global Cancer Observatory (GLOBOCAN) report in 2018, CRC accounted about 15,9% of new cancer cases and 17,4% of the total number of deaths, which is higher than the other cancers (1,2). Based on the World Health Organization (WHO) in 2020, in Indonesia, new cases of CRC were recorded in up to 34,189 patients or around 8,6% of all malignancies. This incidence rate ranks fourth in malignancies in both men and women. As in men, CRC cases are higher which are 21,764 new cases than in women with 12,425 new case (2-5).
During this time, the gold standard examination for CRC are colonoscopy and histopathology biopsy. However, these procedures are categorised as invasive method and higher cost, therefore patient might feel less compliance to do the procedures. Another non-invasive with lower cost like faecal occult blood test (FOBT) is one of the screening method for CRC, but this test has low specificity, sensitivity and less patient's compliance (5,6). These past few years, tumor markers have been used for early screening, diagnosis, guidance of treatment, as well as monitoring the

recurrence and metastasis even could act as a prognosis and survival. Particularly, carcinoembryonic antigen (CEA) has been showing a certain value for differential diagnosis, disease monitoring and evaluation of the treatment efficacy towards the malignant tumor (7-10).

Human neuron-specific enolase (NSE) is a major brain protein that constitutes between 0,4% to 2,2% of total soluble brain protein, depending on the region. In several neurons, NSE accounts for 3-4% of total soluble protein, which is why NSE is commonly used as a clinical marker for neuronal, neuroendocrine and amine precursor uptake and decarboxylation (APUD) cells. APUD cells themselves are a group of endocrine cells that originate from the gastrointestinal tracts. Elevated serum NSE could be associated with poor tumor differentiation (11,12). However, there are few studies regarding the value of NSE in CRC. The aim of this study was to see in focus of the accuracy of serum NSE as a predictor of diagnosis in patient with colorectal cancer.

MATERIALS & METHODS

This study was conducted at the Haji Adam Malik General Hospital, Medan, Indonesia, during the period June 2023 and March 2024. All patients provided written informed consent and the experiments were performed in accordance with the relevant guideline.

Patients and samples

Tumor were staged based on the Tumor-Node-Metastasis (TNM) classification of the American Joint Committee on Cancer Staging 2010(13).

The patient CRC group comprised 29 patients who were hospitalized as an in-patient and out-patient between June 2023 and March 2024 at the Haji Adam Malik General Hospital, Medan, Indonesia and the other group consisted of 29 patients as control.

Both of the CRC group and control group comprised 18 men (62,1%) and 11 women (37,9%). As for the CRC group, aged 53,21±11,04 and for the control group was 54,72±8,36. As for the predilection, most widely found at the left colon as many as 16 patients (55,17%), followed by rectum 10 patients (34,48%), and lastly right colon 3 patients (10,34%). For the histopathology differentiation, well differentiated group was found the most, 15 patients (51,7%), followed by poorly differentiated 8 patients (27,6%) and moderated differentiated 6 patients (20,7%). Based on the staging of the CRC patients in this study, it was found mostly at stage 3A (31,03%) (Table 1).

Table 1. Baseline characteristics

Characteristics	**CRC groups (n=29)**
Sex	
Male	18 (62,1%)
Female	11 (37,9%)
Age	53,21±11,04
Location	
Right colon	3 (10,34%)
Left colon	16 (55,17%)
Rectum	10 (34,48%)
Histopathology	
Well Differentiated	15 (51,7%)
Moderated Differentiated	6 (20,7%)
Poorly Differentiated	8 (27,6%)
Stage	
Stage 2A	6 (20,69%)
Stage 2B	3 (10,34%)
Stage 3A	9 (31,03%)
Stage 3B	1 (3,45%)
Stage 3C	2 (6,90%)
Stage 4A	5 (17,24%)
Stage 4B	3 (10,34%)

Methods

Detection of serum tumor markers

Venous blood samples (2ml) were collected from the elbow of all patients. Blood samples were centrifuged at room temperature at 2000-3000 RPM for 20 minutes, and the supernatant collected without sediment.

All laboratory test were performed in accordance with the standard operating procedures. The experiments were performed on the day of sample collection, and the reports were used to guide the clinical decisions of the physicians.

Histopathological analysis

All of the samples were fully diagnosed as CRC patients through radiologic examination such as thorax x-ray then abdominal scanning, colonoscopy and histopathology biopsy of the colorectal tissue.

STATISTICAL ANALYSIS

The data was analyzed descriptively to determine the sample frequency distribution based on characteristics. Furthermore, Kruskal-Wallis test was conducted to evaluate the serum of NSE and CRC in patients stratified by histopathology results. For each tumor biomarker, a receiver operating characteristic (ROC) curve, area under the ROC (AUC), 95% confidence interval (CI), and Youden index (sensitivity + specificity -1) were calculated. All of the tests statistical analyses were performed using SPSS. P <0.05 was considered statistically significant.

RESULT

CEA and NSE levels

This study showed the comparison of serum NSE and CEA between CRC patients group and control group. With the same subjects in both groups (n=29), it was found that the median CEA level in CRC patients 6,14 ng/ml (1,17-228,0) were significantly higher compared with the control group was 2,3 ng/ml (1,14-14,3) with p-value=0,005. As for the serum NSE in CRC patients was 14,82 ng/ml (3,4-56,0) were also significantly higher compared to the control group which was 5,8 ng/ml (1.2-46) with p-value=0,000, showed a statistically significant difference (Table 2).

Table 2. CEA and NSE levels

Variable	CRC groups (n=29)	Control groups (n=29)	p-value
CEA	6,14 (1,17-228,0)	2,30 (1,14-14,3)	0,005
NSE	14,82 (3,40-56,0)	5,80 (1,20-46,0)	0,000

Analyzed by Mann-Whitney test

Differences between CEA and NSE level based on histopathological grade

Furthermore, this study also analyzed the difference of serum CEA and NSE through the histopathology differentiation results (well differentiated, moderately differentiated and poorly differentiated). The CEA level for the well differentiated category was 6,14 ng/ml (1,17-228,0) then the moderately differentiated category is 7,0 ng/ml (1,64-57,8) and the poorly differentiated category was 7,87 ng/ml (1,41-55,5), with p-value=0,935 which showed that the difference was not significant. Meanwhile, the NSE level for the well differentiated category was 12,3 ng/ml (3,4-33,12), then moderate differentiated category was 15,15 ng/ml (5,34-36,4) and the poorly differentiated category was 22,77 ng/ml (10,4-56,0), with a p-value of 0,14 which was also not significant. Then a post hoc follow-up test was carried out using Mann-Whitney method as a analysis. The results showed that there was a significant difference between the NSE level in the well differentiated and poorly differentiated groups with p-value=0,018 (Table 3).

Table 3. Differences between CEA and NSE levels based on histopathological grade

Variable	Well differentiated	Moderately differentiated	Poorly differentiated	p-value
CEA	6,14(1,17-228,0)	7,0 (1,64-57,8)	7,87 (1,41-55,5)	0,935[a]
NSE	12,3[b] (3,4-33,12)	15,15 (5,34-36,4)	22,77[b] (10,4-56,0)	0,104[a]

a. Analyzed by Kruskal Wallis; b. Post hoc test p<0,05 for well differentiated and poorly differentiated groups

CEA diagnostic analysis of CRC

In this study, the cut off value for CEA level was set at 3,275 mg/dl to detect CRC. Diagnostic test results for CEA level are in table 4. The sensitivity for detecting CRC at this level was 96,55%, while the specificity was 10,34%. The positive predictive value was 51,85% and the negative predictive value was 75,00% (Table 4). The area under the receiver operating characteristic curve (ROC) for CEA in CRC was 0,5345 (Figure 1).

Table 4. CEA and NSE diagnostic analysis of CRC

Biomarker	CRC Groups	Control Groups	Sensitivity	Specificity	Positive Predictive	Negative Predictive	Accuracy
CEA							
≥ 3,275	28	26	96,55%	10,34%	51,85%	75,00%	53,45%
< 3,275	1	3					
NSE							
≥10,285	23	7	79,31%	75,86%	76,67%	78,57%	77,59%
<10,285	6	22					

NSE diagnostic analysis of CRC

Based on the ROC graph and point coordinates, the highest Youden index value was obtained if the cut off value for NSE level was ≥ 10,825 mg/dl. Then, the analysis of the sensitivity and specificity for NSE as diagnostic marker for CRC was carried out as in table 4. The sensitivity for detecting CRC at this level was 79,31%, while the specificity was 75,86%. The positive predictive value was 76,67% and the negative predictive value was 78,57% (Table 4). The area under the receiver operating characteristic curve (ROC) for NSE in CRC was 0,7759 (Figure 1).

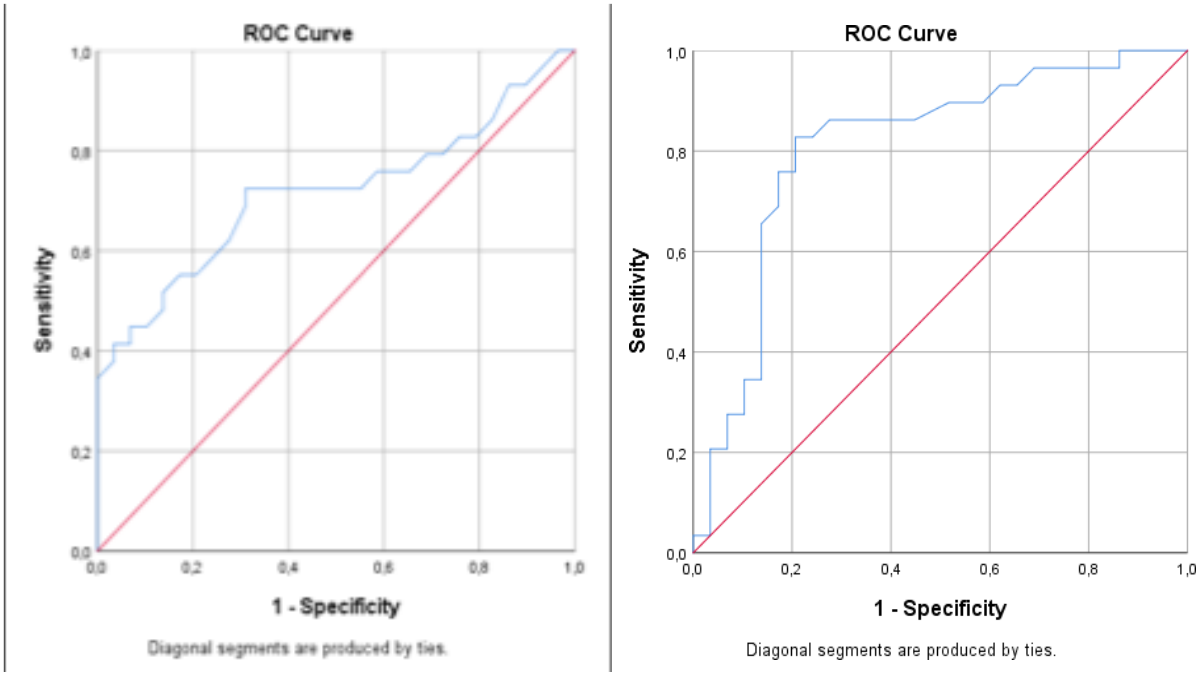

Figure 1. ROC curve of CEA (Figure A) and NSE (Figure B) in colorectal cancer diagnosis

DISCUSSION

In this study, NSE level could be seen between patients with CRC and healthy controls. Serum NSE in CRC patients were also significantly higher compared to the control group. This is in line with the previous study conducted in China by Luo et al (5) in 2022 which showed that serum NSE were found to be increased in CRC patients compared to the control group. As for the NSE, it is an enolase isoenzyme involved in glycolysis, a metabolic pathway that undergoes upregulation in cancer cells to meet their increased energy requirements, a phenomenon known as the Warburg effect. By promoting glycolysis, NSE may aid the rapid growth and survival of cancer cells. Increasing serum NSE can increase the proliferation and survival of cancer cells. This is due in part to its role in metabolic pathways especially in glycolysis process, that provide the energy and biosynthetic precursors necessary for rapid cell division (5,14-16).

This study shows that there is no significant relationship between histopathological differentiation and NSE level but after analysis with further tests, there is a significant difference in the poorly differentiated and well differentiated groups with p-value = 0.018. Meanwhile, in previous research by Luo et al (5), there was no significant difference between histopathological differentiation and NSE level. This is thought to be because histopathological data may have large variations within each category, which can obscure the overall correlation. However, when comparing two specific groups, the analysis becomes more focused and specific to those two groups, whereas NSE level on the poorly differentiated group was significantly higher than the other groups.

Then, it was found in this study, that the sensitivity and specificity of CEA in diagnosing CRC were 96,55% and 10,34% respectively after using a threshold of 3,275 ng/ml with accuracy 53,45%. While the sensitivity and specitivity for NSE were 79,31% and 75,86% with accuracy 77,59%. From the result of this study, it was found that the accuracy of NSE in diagnosing CRC was better than CEA. With these results, it is hoped that NSE can become a biomarker that can help in diagnosing CRC. However, this study was also limited because all patients came from one health centre and the population size was small. Thus, the results of previous studie and this study indicate that the relationship between NSE and CRC may be very useful to assist clinicians in carrying out early detection of the disease.

CONCLUSION

This study demonstrates that serum neuron-specific enolase (NSE) levels are significantly higher in patients with colorectal cancer (CRC) compared to healthy controls. Although NSE levels were not significantly different across all histopathological differentiation groups, further analysis showed that poorly differentiated tumors had significantly higher NSE levels compared to well-differentiated ones. Compared to carcinoembryonic antigen (CEA), NSE showed better diagnostic accuracy for CRC, with higher specificity and overall diagnostic performance. These findings suggest that NSE may serve as a valuable complementary biomarker for the early diagnosis and monitoring of CRC. However, larger multicenter studies are needed to further validate these results.

Declaration by Authors

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REFERENCES

1. M Gopal, Recio-Boiles A, Lotfollahzadeh S, Cagir B. Colon Cancer.StatPearls Publishing 2024
2. Alteri A, Anderson J, Barnes C, Brooks D, Butterly L, DelFavero M, DeSantis C, Gansler T, Jacobs E, Kalidas M, McCullough M, O'Brien M, Patel A, Simpson S, Smith R, Toree L, Wagner D, Zauber A. American

Cancer Society. Colorectal Cancer Facts & Figures 2020-2022. Atlanta: Georgia 2022
3. Gholamreza R, Ghasemi-Kebria, Malekzadeh R. Colorectal cancer: epidemiology, risk factors, and prevention. Cancers 2024; 16:1530
4. World Health Organization. Cancer Country Profile. 2020
5. Luo H, Shen K, Li B, Li R, Wang Z, Xie Z.Clinical significance and diagnostic value of serum NSE, CEA, CA19-9, CA125 and CA242 levels in colorectal cancer. Oncology Letters 2020;20(1):742-750
6. Barbulescu LN, Mogoanta SS, Barbulescu LF, Kamal C, Popa DL, Popa RT. A pilot colorectal cancer study using fecal occult blood tests and colonoscopy to identify the weaknesses of the Romanian public healthcare system before implementing national screening. Int. J. environ. Res. Public Heath 2023; 20:2531
7. Luo H, Shen K, Sun H, Li R, Wang Z, Xie Z. Correlation study between serum neuro-specific enolase and gastric and colorectal cancer. Medicine 2020; 99:16
8. Jelski W, Mroczko B. Biochemical markers of colorectal cancer – present and future. Cancer management and research 2020; 12:4789-4797
9. Kabel AM, Kabel SM. Tumor markers of colorectal carcinoma: new perspectives. Journal of cancer research and treatment 2024; 12:1-7
10. Ren G, Li R, Zheng G, Du K, Dan H, Wu H, Duo X, Duan L, Xie Z, Niu L, Tian Y, Zheng J, Feng F. Prognostic value of normal levels of preoperative tumor markers in colorectal cancer. Nature portofolio 2023; 13:22930
11. Isgro MA, Bottoni P, Scatena R. In: Neuron-specific enolase as a biomarker: biochemical and clinical aspects, 1st ed. United State: Springer, 2015:125-139
12. Gunawardene AR, Corfe BM, Staton CA. Classification and functions of enteroendocrine cells of the lower gastrointestinal tract. Int. J. Exp. Path 2011; 92:219-231
13. Keputusan Menteri Kesehatan Republik Indonesia Nomor HK.01.07/MENKES/4-6/2-18 tentang Pedoman Nasional Pelayanan Kedokteran Tatalaksana Kanker Kolorektal. Indonesia 2018
14. Babkina AS, Lyubomudrov M, Golubev MA, Pisarev MV, Golubev AM. Neuron-specific enolase-what are we measuring? Int. J. Mol. Sci 2024; 25:5040
15. Ni J, Huang Y, Li C, Yin Q, Ying J. Beyond ENO1, emerging roles and targeting strategies of others enolases in cancers. Molecular therapy: oncolytics 2023; 31:1-13
16. Qiao G, Wu A, Chen X, Tian Y, Lin X. Enolase 1, a moonlighting protein, as a potential target for cancer treatment. Int. J. Biol. Sci 2021:17:3981-3992

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