



Effect of Preoperative Serum Transthyretin Levels on Postoperative Clinical Results and Morbidity in Patients Undergoing Spinal Surgery

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Abstract

Introduction This study aims to investigate the effects of preoperative serum transthyretin (TTR) levels on surgical success, pain scores, and postoperative morbidity.

Methods Note that, in our clinic, 188 patients who were operated for spinal pathologies between June 2010 and January 2011 were included in this study. Blood samples were drawn from all patients on the morning of surgery and then serum TTR measurements were made. Demographic data of all patients were collected, and then their preoperative and postoperative neurological examinations, Karnofsky scores, visual analog scale (VAS) scores, Oswestry Disability Index (ODI) scores, postoperative infection and wound healing status, hospital stay, and morbidity levels were recorded and TTR levels were compared.

Results When preoperative TTR level of patients were low, their Karnofsky scores decreased, ODI scores increased, the early postoperative VAS and late postoperative VAS values increased, and the length of hospital stay was increased. Moreover, in patients with low TTR levels, postoperative Karnofsky scores were lower, postoperative ODI levels were higher, postoperative early and late VAS scores were higher, hospital stays were longer, peroperative complication rates were higher, wound infection rates were higher, the delay in wound site healing was higher, and the morbidity rate was higher.

Conclusion Consequently, preoperative low TTR levels have been reported to be an effective parameter that can be used to predict surgical results, wound infection and wound site healing status, perioperative complications, and morbidity in spinal surgery.

Keywords

- ▶ spinal surgery
- ▶ surgical results
- ▶ transthyretin

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Introduction

Spinal surgery is extremely important part of neurosurgery practice. Along with technological progress, surgical success in spinal pathologies has been increasing with increased diagnostic possibilities, the development of surgical techniques, and particularly the development of microsurgery. However, despite all these developments, poor results and advanced morbidity can occur in a considerable number of patients after spinal surgery. Transthyretin (TTR) is a homotetrameric protein weighing 54.98 kDa with four identical subunits. This protein was originally named “prealbumin” because it shows more anodal migration in electrophoresis compared with albumin.¹ After nerve damage, in cases where TTR is low, recovery of locomotor activity is delayed and nerve conduction velocity slows down.² Moreover, TTR has an accelerating effect on nerve regeneration.³ The mechanisms underlying this neurogenic effect have not been clearly understood. In this study, we aimed to investigate the effects of preoperative serum TTR levels on surgical success, pain scores, and postoperative morbidity.

Methods

Note that, in this study, 188 patients who underwent spinal surgery in our clinic between 2010 and 2011 were included. Written consent was obtained from the patient (or legal guardian) that his medical data could be published; patients who refused to sign the informed consent form were excluded from the study. A certificate of conformity was obtained for the study from the ethics evaluation commission of Ankara Diskapi Yildirim Beyazit Training and Research Hospital (26.08.2010, Decision No: 07). All spinal surgery cases were included in the study group:

- Patients who underwent cervical discectomy + cage.
- Spinal tumor cases.
- Patients who underwent lumbar discectomy.
- Patients who underwent posterior lumbar stabilization.
- Patients who were operated for lumbar stenosis.

Patients using steroids, those with chronic inflammatory disease, those with chronic renal failure, those with high liver function tests, those patients who had myocardial infarction in the last month, and patients with symptoms of preoperative acute infection were excluded from this study. The demographic data (age, sex, height, weight, weight 6 months ago, and body mass index [BMI]) of the patients included in the study and length of hospital stay were recorded. The activity levels of patients were evaluated between 1 and 4 points: sedentary (1), mild activity (2), moderate activity (3), and heavy activity (4). Comorbidities accompanying the disease, including the presence of pulmonary diseases, diabetes mellitus, hypertension, hypercholesterolemia/hyperlipidemia, gastroesophageal diseases, smoking, coronary artery disease, and hyperthyroidism were recorded. Venous blood samples were obtained from the patients on the morning of the surgery, just before the operation and their complete blood count, protein, albumin, TTR, C-reactive

protein (CRP), and ferritin levels were measured. Preoperative and postoperative neurological examinations of patients were performed, and muscle strength examinations in relation with the patients' primary spinal pathology were recorded: 0, no contraction; 1, slight muscle contraction, no movement; 2, motion without gravity; 3, motion with gravity; 4, some resistance against the examiner, but not fully; and 5, full muscle strength. Preoperative and postoperative Karnofsky scores of patients were evaluated. Preoperative and postoperative Oswestry Disability Index (ODI) and visual analog scale (VAS) and pain levels of patients were evaluated in the preoperative, early postoperative (second day), and late postoperative (first month) periods. It was recorded whether the patients had wound site infection in the postoperative periods. A postoperative wound site infection diagnosis was made in patients with purulent drainage from the wound site and the causative microorganism could be grown in culture in the postoperative period. The wound sites of the patients were evaluated on the 7th postoperative day. During this period, wound site healing problem was evaluated as positive in patients whose wound site did not close and were macerated. Preoperative complications (dural tears, nerve damage, and massive hemorrhage) were recorded. Postoperative morbidity was defined as permanent damage after surgery and/or the requirement for serious additional investigation and treatment. Deep wound infection, prosthetic malposition, myocardial infarction, pulmonary thromboembolism, newly developed neurological deficit, incorrect surgical distance, pseudomeningocele, and vascular injuries were recorded as morbidity. In this study, patients' preoperative variables (particularly blood TTR level, CRP/TTR, albumin/TTR, ferritin/TTR ratios) and postoperative results were compared.

Statistical Analysis

Data analysis was performed using SPSS for Windows 11.5 package program (SPSS Inc., Chicago, Illinois, United States). Whether the distribution of continuous variables was close to normal was investigated using the Shapiro-Wilk test. The homogeneity of variances was examined using the Levene's test. Descriptive statistics were observed as mean \pm standard deviation or median (smallest–largest). The significance of difference between the groups in terms of means was determined using Student's *t*-test. When the number of independent groups was two, the significance of the difference between the groups in terms of median values was determined using the Mann-Whitney *U* test. When the number of independent groups was more than two, the significance of the difference between groups was investigated using the Kruskal-Wallis test. If the Kruskal-Wallis test statistics were reported to be significant, the conditions causing the difference were determined using the Conover's test of multiple comparisons. Whether there was a statistically significant change between preop and postop measurements was examined using the Wilcoxon signed-rank test. Categorical variables were evaluated using the Pearson's chi-square test. The Spearman's correlation test was used to investigate

whether there was a significant relationship between continuous variables. For $p < 0.05$, the results were considered to be statistically significant.

Results

Note that 188 patients were included in this study. The age range of the patients was 18 to 85, and the mean age was 49.3 ± 12.5 years. Of the patients participating in the study, 113 were female (60.1%) and 75 were male (39.9%). The patients were grouped as per the spinal surgery they underwent. Group I included 150 patients (79.8%) who were operated for lumbar discectomy, posterior lumbar stabilization, and lumbar stenosis. Group II included 26 patients (13.8%) who underwent anterior cervical discectomy and cage application. Group III included 12 patients (6.4%) who were operated for spinal tumors. Of the patients, 41.5% ($n = 78$) had at least one comorbid disease. The mean preoperative motor strength of the patients was 4 (0–5). In the postoperative period, the mean motor strength was evaluated as 5 (0–5). This improvement in postoperative examination was considered to be statistically significant ($p < 0.001$). The mean preoperative Karnofsky score of the patients was 80 (50–100), while the postoperative Karnofsky scores were reported to be 100 (40–100). This postoperative improvement in the Karnofsky scores was statistically significant ($p < 0.001$). The preoperative ODI scores of the patients were 43 (0–100), while the postoperative ODI scores were reported as 10 (0–88). This improvement in the ODI scores was statistically significant ($p < 0.001$). The mean preoperative VAS values of the patients were reported to be 8 (0–10). The mean VAS values in the early postoperative period were 4 (0–10) and the mean VAS values in the late postoperative period were found as 1 (0–10). Compared with the preoperative VAS values, the decrease in both early postoperative and late postoperative VAS values was statistically significant ($p < 0.001$). Postoperative wound site infection was observed in 14 patients (7.4%), whereas postoperative morbidity was observed in 25 patients (13.3%). Perioperative complications occurred in 13 patients (6.9%). When the correlation analysis was examined, the following results were reported to be statistically significant:

As the age of patients increases, hospital stay is prolonged ($p = 0.009$, correlation coefficient [kk] = 0.189).

As the BMI of the patients increases, Karnofsky scores decrease ($p = 0.022$, $kk = -0.167$), ODI scores increase ($p < 0.001$, $kk = 0.261$), early postoperative VAS ($p = 0.08$, $kk = 0.193$) and late postoperative VAS ($p = 0.04$, $kk = 0.193$) levels increase, and also length of hospital stay is prolonged ($p = 0.011$, $kk = 0.186$).

As the patient's activity level increases, early postoperative VAS values decrease ($p = 0.017$, $kk = -0.174$), and length of hospital stay is shortened ($p = 0.005$, $kk = -0.206$).

As the patient's preoperative hemoglobin level increases, ODI scores decrease ($p = 0.002$, $kk = -0.222$), early postoperative VAS ($p < 0.001$, $kk = -0.247$) and late postoperative VAS values ($p = 0.022$, $kk = -0.166$) decrease, and also length of hospital stay is shortened ($p < 0.001$, $kk = -0.248$).

As the patient's preoperative total protein level decreases, Karnofsky scores decrease ($p = 0.004$, $kk = 0.207$) and ODI scores increase ($p = 0.024$, $kk = -0.165$).

As the patient's preoperative albumin level decreases, Karnofsky scores decrease ($p < 0.001$, $kk = 0.295$), ODI scores increase ($p < 0.001$, $kk = -0.275$), early postoperative VAS ($p = 0.021$, $kk = -0.169$) and late postoperative VAS values ($p = 0.01$, $kk = -0.189$) increase, and also length of hospital stay is prolonged ($p = 0.017$, $kk = -0.174$).

As the patient's preoperative TTR level decreases, Karnofsky scores decrease ($p < 0.001$, $kk = 0.309$), ODI scores increase ($p < 0.001$, $kk = -0.344$), early postoperative VAS ($p < 0.001$, $kk = -0.259$) and late postoperative VAS values ($p < 0.001$, $kk = -0.323$) increase, and also length of hospital stay is prolonged ($p < 0.001$, $kk = -0.355$).

As the patient's preoperative CRP level increases, Karnofsky scores decrease ($p = 0.016$, $kk = -0.175$), early postoperative VAS ($p = 0.046$, $kk = 0.146$) and late postoperative VAS values ($p = 0.034$, $kk = 0.154$) increase, and also length of hospital stay is prolonged ($p < 0.001$, $kk = 0.236$).

As the patient's preoperative ferritin level decreases, Karnofsky scores decrease ($p = 0.017$, $kk = 0.174$) and ODI scores increase ($p = 0.012$, $kk = -0.183$).

As the patient's preoperative CRP/TTR ratio increases, Karnofsky scores decrease ($p < 0.001$, $kk = -0.344$), ODI scores increase ($p < 0.001$, $kk = 0.291$), early postoperative VAS ($p < 0.001$, $kk = 0.282$) and late postoperative VAS values ($p < 0.001$, $kk = 0.341$) increase, and also length of hospital stay is prolonged ($p < 0.001$, $kk = 0.390$).

As the patient's preoperative albumin/TTR ratio increases, Karnofsky scores decrease ($p < 0.001$, $kk = -0.248$), ODI scores increase ($p < 0.001$, $kk = 0.297$), early postoperative VAS ($p < 0.001$, $kk = 0.230$) and late postoperative VAS values ($p < 0.001$, $kk = 0.288$) increase, and also length of hospital stay is prolonged ($p < 0.001$, $kk = 0.333$).

When the data were compared between genders in term of scores, postoperative early VAS scores decreased less in women compared with preoperative VAS scores ($p = 0.027$). No significant correlation could be established between other variables and genders ($p > 0.05$).

When a comparison was made between diagnostic groups, group II had the highest improvement in motor strength scores while group III had the least improvement. The change in motor strength scores between all groups showed a statistically significant difference. When the change in Karnofsky scores was compared, the difference between group I and group II was not statistically significant; however, the differences between group I and III and group II and III were statistically significant. Similarly, when the change in ODI scores was compared, the difference between group I and group II was not statistically significant; however, the differences between group I and III and group II and III were statistically significant. When the change in early and late postoperative VAS scores was compared, the difference between group I and group II was not statistically significant; however, the differences between group I and III and group II and III were statistically significant. When the length of hospital stay was compared, the patients in group I and

group II showed similar characteristics; however, patients in group III had longer hospital stays.

Low levels of TTR are predictive for postoperative wound site infection. TTR levels were 209.4 ± 81.9 g/dL in the group with wound site infection and 286.6 ± 70.8 g/dL in the group without infection. When statistical analysis was performed, the rate of wound site infection increased in the patient group with low TTR levels ($p < 0.001$). Similarly, increased CRP/TTR ratio and albumin/TTR ratio were reported to be correlated with a high risk of wound site infection ($p = 0.007$ and $p = 0.005$, respectively).

TTR levels of patients with delayed wound site healing (182.4 ± 68.5) were reported to be lower than the group without delay in wound site healing (292.6 ± 65.9) ($p < 0.001$). Similarly, increased CRP/TTR ratio and albumin/TTR ratio were reported to be correlated with delay in wound site healing ($p < 0.001$). Furthermore, lower hemoglobin ($p = 0.016$), albumin ($p = 0.015$), and ferritin ($p = 0.005$) levels were reported in the group with delayed wound site healing compared with the group without delay. TTR levels (202.9 ± 86.4) were lower in the group with postoperative morbidity compared with the group without morbidity (292.8 ± 64.7) ($p < 0.001$). Moreover, high CRP/TTR and albumin/TTR ratios were found to be statistically correlated with increased morbidity ($p < 0.001$). In addition, lower hemoglobin ($p = 0.002$), protein ($p = 0.034$), albumin ($p = 0.041$), and ferritin levels ($p = 0.003$) were determined in the group with morbidity compared with the group without morbidity; CRP levels were observed to be higher ($p = 0.018$).

To summarize the results in terms of TTR, in patients with low TTR: postoperative Karnofsky scores were lower, postoperative ODI levels were higher, postoperative early and late VAS scores were higher, length of hospital stay was prolonged, preoperative complication rates were higher, wound site infection rates were higher, delay in wound site healing increased, and morbidity rates were higher.

Discussion

Spinal interventions form an important part of daily neurosurgery practice. Although we use developed microneurosurgical techniques, advanced radiological examinations, and modern stabilization and fusion materials, spinal surgery still can lead to unsuccessful results, causing more serious morbidity and mortality.⁴ It is extremely important for the surgeon and the patient to predict which patient is at risk before surgery, which patient will develop postoperative complications, which patient will benefit from surgery, and which patient will be exposed to morbidity. However, because there are multiple factors that affect this evaluation, it is not possible to predict postoperative results based on a single factor. Possible complications after spinal surgery have been the subject of many retrospective studies.⁴⁻¹³ In these studies, many variables had an effect on surgical results and contributed to morbidity and mortality; however, the predictive role of a single factor in the occurrence of these adverse events has not been studied. Moreover, there is no

clear definition of the terms “complication,” “adverse event,” and “morbidity” in the literature. Because of this ambiguity, a 7% complication rate was reported in one series¹³; however, this rate was 42% in another series.⁴

In this prospective study, the effects of preoperative TTR levels on postoperative surgical outcomes (Karnofsky score, ODI, VAS) of patients who underwent spinal surgery, length of hospital stay, perioperative complication rates, postoperative morbidity, wound site infection development, and wound site healing were examined. The relationship between malnutrition and diseases has been well known. Changes in nutritional status cause suppression in organ functions and immune system.¹⁴ In a study, up to 50% of hospitalized patients were susceptible to protein energy malnutrition.¹⁵

Wound site healing was delayed in patients with malnutrition, and the rates of infection and morbidity increased.¹⁴ Moreover, surgical morbidity and mortality increased in patients with impaired nutritional status.^{16,17} Because of the importance of malnutrition, it is recommended to perform a nutritional evaluation in all hospitalized patients, especially in patients undergoing major surgery.¹⁸ However, there is no consensus in the literature on which parameters the nutritional assessment should be based on previous studies.¹⁹⁻²¹ To perform nutritional evaluation, clinicians require a fast, easily available, inexpensive, and effective screening test. For this purpose, visceral proteins such as albumin, transferrin, and TTR have been used. In previous studies, TTR was defined as a good indicator of nutritional status in patients with malnutrition.²²⁻²⁵ Moreover, a significant correlation has been identified between protein energy nutrition and TTR levels in large clinical studies.¹⁹⁻²¹ However, in cases where acute phase reactants²⁶ and inflammatory cytokines²⁷ are high, low TTR levels have been shown to be an independent indicator of acute phase reactants in evaluating malnutrition. Bernstein stated that TTR is the best parameter for evaluating malnutrition.²⁸ In conclusion, TTR is accepted as an inexpensive, applicable, and reliable tool for evaluating malnutrition in patients.^{24,29}

Abnormal TTR levels correlate with the increasing number of complications in patients undergoing elective surgery.³⁰ A close relationship was reported between low TTR levels and the risk of infection, infection-related mortality rates, and infection-related complications.³¹ Moreover, low TTR levels were correlated with increased complications and delayed wound site healing in patients operated for ovarian cancer.³² Jewell et al reported that TTR levels are the best indicator of perfect wound healing.³³ Beck and Rosenthal reported that low TTR levels correlated with prolonged hospital stay, delayed wound healing, and prolonged sepsis duration.¹⁴ Furthermore, higher mortality levels were reported in patients with low TTR levels compared with patients with normal TTR levels. Similarly, low serum TTR levels were reported to be correlated with delayed wound healing in other studies.^{32,34-36} High TTR levels are a strong indicator of complete wound site healing in burn patients and that the TTR level correlates with wound healing.^{37,38} Salvetti et al reported that preoperative low TTR levels are a marker of

increased surgical site infections for elective spinal surgery cases.³⁹

Furthermore, young stroke patients with high serum TTR levels have a better prognosis; low TTR levels were reported to be seriously compatible with a poor prognosis.⁴⁰ Under physiological conditions, TTR passes to the peripheral nerve either by crossing the blood–nerve barrier or through cerebrospinal fluid (CSF). Similarly, it passes to the central nervous system through both CSF and blood. TTR circulating in CSF has neuroprotective properties.⁴¹ It has been shown in a similar study that TTR accumulates in damaged neural tissues and increases neural growth.⁴⁰ In a study conducted with mice that were genetically unable to produce TTR, TTR had an enhancing effect on regeneration in the damaged nerve.³ Moreover, TTR has a neuroprotective effect through polyphenols.⁴² In another study, low TTR levels detected in CSF were compatible with increased dementia in Alzheimer's patients.⁴³

In conclusion, TTR is an indicator of nutritional status in studies previously published in the literature, and low TTR levels have been shown to be an indicator of impaired nutrition. Impaired nutrition is known to cause increased morbidity, mortality, delayed wound site healing, increased susceptibility to infection, and prolonged hospital stay in surgical patients. Low TTR levels have been shown to delay wound site healing, increase mortality and morbidity, prolong hospital stay, and cause susceptibility to infection.

Moreover, TTR's neuroprotective effects have been shown to accelerate nerve regeneration. Furthermore, TTR, found in human serum and CSF, is an easy to measure and inexpensive protein with multiple functions.⁴⁴ For these reasons, in this study, the effects of preoperatively measured serum TTR levels on surgical outcomes, complication rates, wound site healing, postoperative infection, and hospital stay were studied in patients operated for spinal pathologies.

In our study, the preoperatively measured low TTR levels were reported to be consistent with low Karnofsky score, increased ODI scores, and high early and late postoperative VAS values. Therefore, low TTR levels were reported to correlate with poor clinical outcomes after spinal surgery. The length of hospital stay increased in patients with low TTR levels. Moreover, patients with low TTR levels have more wound site infection and delayed wound site healing. Similarly, patients with low TTR levels were exposed to increased perioperative complications and postoperative morbidity. However, a high CRP/TTR ratio was reported to be compatible with low Karnofsky score, increased ODI scores, and high early and late postoperative VAS values.

Based on these results, similar to TTR, CRP/TTR ratio was evaluated as a data that can be used to predict postoperative clinical outcomes in spinal surgery. Furthermore, high CRP/TTR ratio was reported to be correlated with increased wound site infection and delayed wound site healing. It was found to be correlated with perioperative complications and increased morbidity in patients with a high CRP/TTR ratio. Based on these results, serum TTR levels preoperatively measured in patients undergoing spinal surgery emerge as a parameter that can be used to predict postoperative

surgical results, wound site healing status and wound site infection, perioperative complications, and morbidity risks.

Conclusion

In patients with low preoperative serum TTR level measured before spinal surgery, the following were found

- Postoperative Karnofsky scores were lower.
- Postoperative ODI levels were higher.
- Postoperative early and late VAS scores were higher.
- Length of hospital stay was prolonged.
- Perioperative complication rates were higher.
- Wound site infection rates were higher.
- Delay in wound site healing increased.
- Morbidity rates were higher.

In conclusion, preoperative low TTR levels were reported to be an effective parameter that can be used to predict surgical outcomes, wound site infection and wound site healing status, perioperative complications, and morbidity in spinal surgery.

Conflict of Interest

None declared.

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