ORIGINAL ARTICLE

DOI: 10.4274/hamidiyemedj.galenos.2026.66376

Hamidiye Med J 2026;7(3):184-191

Cardiopulmonary Bypass Induces Differential Neuroregenerative, Inflammatory, and Oxidative Stress Responses

Kardiyopulmoner Baypasın Nörorejeneratif, Enflamatuvar ve Oksidatif Stres Yanıtları Üzerindeki Farklılaştırıcı Etkileri

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ABSTRACT

Background: Cardiopulmonary bypass (CPB) is a fundamental technique in cardiac surgery; however, it is associated with systemic inflammation, oxidative stress, and adverse postoperative outcomes, including cognitive dysfunction. The pathophysiological mechanisms underlying these complications are not fully understood. Although both traditional and newly identified inflammatory markers have been studied, data on perioperative changes in neuronal plasticity and regeneration markers, such as growth-associated protein 43 (GAP43) and neuregulin-1 (NRG1), remain limited. This study aimed to evaluate preoperative and postoperative levels of GAP43 and NRG1 in patients undergoing CPB and to compare them with markers of oxidative stress, systemic inflammation, and neurological inflammation.

Materials and Methods: A total of 41 patients (32 males, 9 females) undergoing elective cardiac surgery with CPB were enrolled. Peripheral blood samples were collected pre- and postoperatively. Serum levels of GAP43, NRG1, brain-derived neurotrophic factor, and osteoprotegerin (OPG) were measured by enzyme-linked immunosorbent assay. Oxidative stress was assessed using total oxidant status (TOS) and total antioxidant status (TAS). Protein expression of sirtuin 2 (SIRT2) and C-X3-chemokine ligand 1 (CX3CL1) was analyzed by Western blotting. Data normality was evaluated with the Shapiro-Wilk test, and appropriate parametric or non-parametric tests were used for paired comparisons.

Results: Postoperative GAP43 levels decreased ($p < 0.05$), and the decrease was more pronounced in males. NRG1 showed no overall change but exhibited sex-specific trends, decreasing in females and increasing in males. OPG increased only in males, while TOS increased and TAS remained unchanged in both groups. Western blot analysis showed a loss of SIRT2 expression and an induction of CX3CL1.

Conclusion: CPB induces oxidative stress, neuroinflammation, and disruption of neuroregenerative processes. GAP43, a marker of neuronal plasticity, decreases postoperatively, particularly in males, whereas NRG1 shows a sex-dependent response. Combined assessment of GAP43, NRG1, and inflammatory and oxidative-stress markers may help predict postoperative neurological dysfunction and guide future protective strategies.

Keywords: Cardiopulmonary bypass, GAP43, NRG1, oxidative stress, neuroregeneration, biomarkers

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Received: 04.04.2026 **Accepted:** 11.06.2026 **Epub:** 25.08.2026 **Publication Date:** 08.09.2026

Cite this article as: Sarı Ak D, Helvacı Kurt N, Kural A, Güzel Y, Omarova N, Bakır RN, et al. Cardiopulmonary bypass induces differential neuroregenerative, inflammatory, and oxidative stress responses. Hamidiye Med J. 2026;7(3):184-191

ÖZ

Amaç: Kardiyopulmoner baypas (KPB), kalp cerrahisinde yaygın olarak kullanılmakla birlikte, oksidatif stres, enflamasyon ve nörolojik komplikasyonlarla ilişkilidir. Bu çalışmada, nöronal plastisite ile ilişkili büyüme ile ilişkili protein 43 (GAP43) ve neuregulin-1 (NRG1) düzeylerindeki perioperatif değişimlerin, oksidatif stres ve enflamatuvar belirteçlerle birlikte değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: KPB uygulanan 41 hasta (32 erkek, 9 kadın) çalışmaya dahil edildi. Ameliyat öncesi ve sonrası alınan kan örneklerinde GAP43, NRG1, beyin kaynaklı nörotrofik faktör (BDNF) ve osteoprotegerin (OPG) düzeyleri enzime bağlı immünosorbent analiz ile ölçüldü. Toplam oksidan durum (TOS) ve toplam antioksidan durum (TAS) değerleri spektrofotometrik yöntemlerle değerlendirildi. Sirtuin 2 (SIRT2) ve C-X3-C motifli kemokin ligand 1 (CX3CL1) ekspresyonları Western blot ile analiz edildi. İstatistiksel değerlendirmede uygun parametrik ve non-parametrik testler kullanıldı.

Bulgular: GAP43 düzeylerinde ameliyat sonrası anlamlı azalma saptandı ($p < 0,05$) ve bu değişimin erkek hastalarda daha belirgin olduğu görüldü. NRG1 düzeylerinde genel olarak anlamlı fark izlenmezken, kadınlarda azalma, erkeklerde artış eğilimi dikkat çekti. Erkek hastalarda OPG düzeyleri artış gösterdi. TOS düzeyleri her iki cinsiyette artarken, TAS düzeylerinde değişiklik gözlenmedi. Western blot analizinde SIRT2 ekspresyonunun kaybolduğu, CX3CL1'in ise ameliyat sonrası belirgin olarak arttığı saptandı. Bu bulgular, KPB'nin oksidatif stres ve enflamasyonla birlikte nöronal yanıtları da etkilediğini göstermektedir.

Sonuç: Bu bulgular, kardiyopulmoner baypasın nörorejeneratif ve enflamatuvar süreçler arasındaki dengeyi bozabileceğini ve bunun postoperatif nörokognitif disfonksiyona katkıda bulunabileceğini düşündürmektedir. Gözlenen biyobelirteç değişimleri, erken risk değerlendirmesi ve hedefe yönelik nöroprotektif stratejilerin geliştirilmesi için potansiyel bir temel sunmaktadır.

Anahtar Kelimeler: Kardiyopulmoner baypas, GAP43, NRG1, oksidatif stres, nörorejenerasyon, biyobelirteçler

Introduction

Cardiopulmonary bypass (CPB) is a critical component of most heart surgery procedures, allowing surgeons to work on a "still heart." While essential for the surgical treatment of heart disease, postoperative complications such as systemic inflammation, oxidative stress, and neurocognitive dysfunction can occur in patients undergoing CPB (1-3). The clinical manifestations of neurocognitive disturbance after cardiac surgery include persistent decline in cognitive function, stroke, as well as more subtle neuropsychological changes that can affect a patient's quality of life after discharge from the hospital and impact postoperative outcome (4,5).

The biological response to CPB includes an inflammatory response, endothelial damage and increased production of reactive oxygen species (1-3). Levels of several inflammatory markers have been studied, but changes in neurobiological parameters are not completely understood, especially early changes (6,7). This is especially true for markers of neuronal plasticity or regeneration (8).

Growth-associated protein 43 (GAP43) is known to be associated with neuronal growth and plasticity, thus may serve as a marker of neuronal plasticity (9,10). Neuregulin-1 (NRG1) has been demonstrated to modulate neuronal survival, calcium signaling, neurovascular and autonomic nervous system interactions, and modulate cardiovascular functions (11,12). An understanding of the neurovascular modifications occurring during CPB and of the perioperative variations in these proteins in adult CPB patients has not been well elucidated.

In addition to affecting neuroregenerative factors, CPB alters oxidative-antioxidative balance and the inflammatory response (2,13,14). We therefore determined the following biomarkers as indicators of vascular inflammation, neurovascular regulation, immune cell recruitment, and oxidative stress defense: osteoprotegerin (OPG), brain-derived neurotrophic factor (BDNF), C-X3-chemokine Ligand 1 (CX3CL1)/fractalkine, and the sirtuins, particularly sirtuin 2 (SIRT2), which are part of cellular defense against oxidative stress (15-18).

Beyond experimental measurements, integrating biomarker data with *in silico* approaches may help contextualize molecular interactions and functional pathways associated with CPB-related neurovascular alterations (19,20).

The aim of this study was to determine GAP43 and NRG1 levels in patients undergoing CPB and to compare them with markers of oxidative stress and inflammation. An *in silico* analysis of the obtained results was performed to predict potential interactions among the studied biomarkers and to identify relevant biological pathways. The goal of this work was to combine experimental data with *in silico* analysis to provide a systems-level view of neurovascular changes caused by CPB at the molecular level.

Materials and Methods

Study Population and Sample Collection

A total of 41 patients (32 males and 9 females) undergoing elective cardiac surgery with CPB were included in this study. Peripheral blood samples were collected preoperatively and postoperatively. Serum samples were obtained by centrifugation and stored at -80 °C until further analysis.

The study was approved by the University of Health Sciences Türkiye, Hamidiye Faculty of Medicine Ethics Committee (approval number: 24/727; decision number: 14/16, date: 28.11.2024). All procedures were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment in the study.

Biochemical Analysis

Serum levels of GAP43, BDNF, OPG, and NRG1 were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturers' instructions. GAP43 levels were measured using an ELISA kit (Catalog No: YLA2806HU, YL Biont, Shanghai, China). NRG1 levels were determined using a human Neuregulin-1 ELISA kit (Catalog No: YLA1122HU, YL Biont, Shanghai, China). BDNF levels were measured using a commercial ELISA kit (Catalog No: E1302Hu, BT Lab, China). OPG levels were measured using a commercially available ELISA kit (Catalog No. E1558Hu; BT Lab, China).

Serum total antioxidant status (TAS) and total oxidant status (TOS) levels were quantified using fully automated colorimetric assays as described in previously published method (21,22). The TAS method relies on the capacity of antioxidants in the sample to neutralize the $ABTS^{+}$ radical cation, resulting in reduced color intensity. In contrast, TOS measurement is based on the oxidation of the ferrous ion-o-dianisidine complex by oxidant molecules in the sample. TAS results were expressed as mmol Trolox equivalents per liter, whereas TOS results were expressed as μmol H_2O_2 equivalents per liter. All measurements were performed in duplicate to ensure accuracy.

Western Blot Analysis

Serum samples stored at -80 °C were processed prior to analysis. High-abundance proteins were depleted using a Top14 depletion resin (Thermo Scientific, USA) according to the manufacturer's instructions. Total protein concentrations were determined using the Bradford assay.

Equal amounts of protein (50 μg) were denatured, separated by SDS-PAGE, and transferred to PVDF membranes. Membranes were blocked with 3% bovine serum albumin and incubated overnight at 4 °C with primary antibodies against SIRT2 (1:1000, ABclonal, A-0273, USA) and fractalkine (CX3CL1) (1:1000, Abcam, ab25088, UK). After washing, membranes were incubated with HRP-conjugated anti-rabbit secondary antibody (1:5000, Cell Signaling Technology, 7074, USA).

Protein bands were visualized using chemiluminescence and imaged with a ChemiDoc imaging system (Bio-Rad, USA). Band intensities were assessed using ImageJ software (NIH, USA). No housekeeping-protein normalization was performed; equal protein loading was ensured by Bradford-based protein quantification and loading 50 μg of total protein per lane. Uniform contrast adjustments were applied to entire blots without altering individual bands.

In Silico Network and Functional Enrichment Analysis

To explore potential functional relationships among the studied biomarkers, an *in silico* analysis was conducted using GAP43, NRG1, BDNF, TNFRSF11B (OPG), CX3CL1, and SIRT2 as input genes. Protein-protein interaction networks were constructed using the STRING database (version 12.0), incorporating both experimentally validated and predicted interactions.

Functional enrichment analysis was performed using g:Profiler to identify significantly overrepresented Gene Ontology terms and Kyoto Encyclopedia of Genes and Genomes pathways. Multiple testing correction was applied using the false discovery rate, and pathways with an adjusted p-value < 0.05 were considered statistically significant.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). Data normality was assessed using the Shapiro-Wilk test. Because most variables did not meet the criteria for a normal distribution, analyses were primarily conducted using non-parametric approaches.

Paired comparisons between preoperative and postoperative values were conducted using the Wilcoxon signed-rank test. For normally distributed variables, paired t-tests were applied when appropriate. Differences between independent groups were assessed using the Mann-Whitney U test or the independent samples t-test, as appropriate. Data were presented as median with interquartile range or mean ± standard error/standard deviation, depending on distribution characteristics. A p-value < 0.05 was considered statistically significant.

Results

Study Population

A total of 41 patients undergoing CPB were included in the study, comprising 32 males and 9 females. Biochemical analyses were performed on the entire cohort, whereas Western blot analyses were performed on a subgroup of two patients (one female and one male). Preoperative and postoperative measurements were obtained for all evaluated parameters. Detailed descriptive data for all biomarkers are presented in Table 1.

Table 1. Perioperative changes in the evaluated serum biomarkers.

	OPG (pg/mL)	GAP43 (pg/mL)	TOS (μmol H_2O_2 equiv./L)	TAS (mmol Trolox equiv./L)	NRG1 (pg/mL)	BDNF (ng/mL)
Female preop (n = 9)	109.44 (182.18)	10065.0 (41.25)	0.67 (0.13)	3.22 (0.45)	19.86 (34.35)	0.31 (0.45)
Female postop (n = 9)	117.58 (235.71)	8100.0 (4068.53)	0.9350 (0.31)*	3.17 (0.15)	19.0 (20.67)	0.55 (0.84)
Male preop (n = 32)	101.68 (289.76)	6639.56 (5302.0)	0.62 (0.11)	3.17 (0.38)	3.57 (11.02)	0.68 (1.54)
Male postop (n = 32)	126.25 (344.47)*	6723.9 (4564.03)*	1.14 (0.61)*	3.15 (0.48)	5.00 (4.61)	1.14 (1.77)

Perioperative changes in serum levels of OPG (pg/mL), GAP43 (pg/mL), TOS (μmol H_2O_2 equiv./L), TAS (mmol Trolox equiv./L), NRG1 (pg/mL), and BDNF (ng/mL) in female and male patients undergoing CPB. Data are presented as median (IQR). Preoperative and postoperative values are shown separately for each sex. *p < 0.05 compared with preoperative values. IQR, interquartile range; GAP43, growth-associated protein 43; OPG, osteoprotegerin; TOS, total oxidant status; TAS, total antioxidant status; NRG1, neuregulin-1; BDNF, brain-derived neurotrophic factor; CPB, cardiopulmonary bypass.

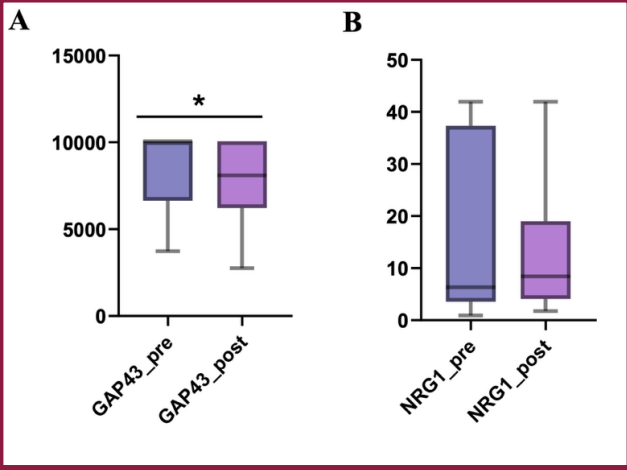

Figure 1. Perioperative alterations in serum GAP43 and NRG1 levels following CPB. (A) GAP43 levels were significantly reduced postoperatively compared to preoperative values. (B) NRG1 levels did not exhibit a statistically significant overall change, although distribution patterns differed between pre- and postoperative measurements. Data are presented as median (IQR) for the overall cohort (n = 41). *p < 0.05. Paired statistical analyses were performed to assess perioperative differences. IQR, interquartile range; GAP43, growth-associated protein 43; CPB, cardiopulmonary bypass; NRG1, neuregulin-1.

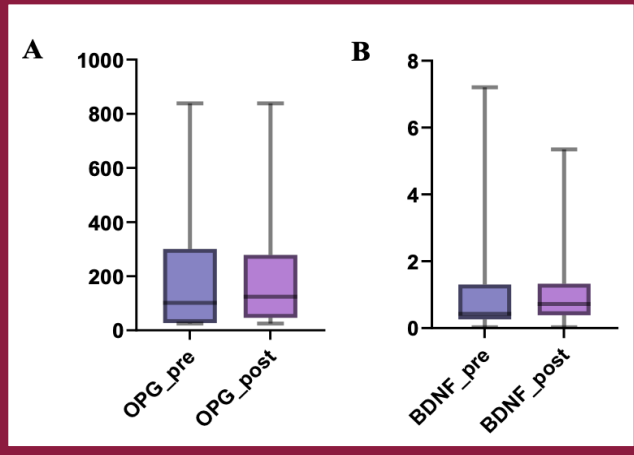

Figure 2. Perioperative alterations in inflammatory and neurotrophic biomarkers following CPB. (A) OPG levels did not differ significantly between preoperative and postoperative measurements in the overall cohort, although a significant postoperative increase was observed in male patients in the sex-stratified analysis. (B) BDNF levels did not differ significantly between pre- and postoperative measurements; however, opposite directional trends were observed between the sexes. Data are presented as median (IQR) for the overall cohort (n = 41). Paired statistical analyses were used for comparisons. CPB, cardiopulmonary bypass; OPG, osteoprotegerin; BDNF, brain-derived neurotrophic factor; IQR, interquartile range.

Serum GAP43 levels decreased significantly following CPB in the overall cohort (p = 0.046). Sex-stratified analysis demonstrated that this reduction was more pronounced in male patients, whereas no significant change was observed in females (Table 1, Figure 1).

In the overall cohort, NRG1 levels did not differ significantly between preoperative and postoperative measurements (p = 0.438). However, after surgery, distinct sex-specific patterns were observed: NRG1 levels decreased in female patients and increased in male patients (Table 1).

Inflammatory and Neurotrophic Markers

Serum OPG levels increased postoperatively in male patients (p = 0.04), whereas no significant change was observed in female patients (Figure 2A). BDNF levels did not show statistically significant differences between pre- and postoperative measurements in either sex; however, opposite trends were observed, with an increase in females and a decrease in males (Figure 2B).

Oxidative Stress Parameters

TOS levels increased significantly after CPB in both female and male patients ($p = 0.0088$ and $p = 0.0009$, respectively), indicating elevated oxidative stress. In contrast, TAS levels remained unchanged in both groups (female: $p = 0.36$; male: $p = 0.35$) (Figure 3, Table 1).

Western Blot Findings

Western blot analysis demonstrated that SIRT2 expression was present in preoperative samples but undetectable postoperatively. In contrast, CX3CL1 expression was absent before surgery and became clearly detectable following CPB (Figure 4).

In Silico Network and Functional Enrichment Analysis

Protein-protein interaction analysis using the STRING database (version 12.0) demonstrated that GAP43, NRG1, BDNF, TNFRSF11B (OPG), CX3CL1, and SIRT2 were functionally connected in a common interaction network (Figure 5A).

Subsequent functional enrichment analysis showed that these proteins were significantly associated with pathways related to neuronal signaling, inflammatory response, and oxidative stress, including neurotrophin, TNF, chemokine, and cyclic adenosine monophosphate (cAMP) signaling pathways (Figure 5B).

Discussion

Changes in molecular markers of neuroregeneration, as well as in some inflammatory and oxidative stress molecules, occur before, during, and after clinical CPB. We investigated these changes in 41 adult patients undergoing cardiac surgery with CPB. Blood samples obtained before and after CPB were analyzed. A decrease in GAP43 levels was found in all samples, and NRG1 levels showed a sex-dependent pattern in blood samples. Our results provide new insights into the neurobiological changes associated with CPB.

GAP43 is a protein critical for axonal growth, synaptic plasticity, and neuronal repair, and is therefore a marker of neuronal plasticity. GAP43 remains a key molecule associated with axonal growth, regeneration, and injury-induced neuronal plasticity, supporting its relevance as a marker of altered neuroplastic responses after CPB (23). A postoperative reduction in GAP43 suggests an impairment of neuronal plasticity following CPB. Most studies investigating CPB-induced inflammation have not considered markers of neuronal regeneration. Notably, the decrease in GAP43 was greater in men, suggesting that the neurobiological response to CPB may be modulated by sex-related differences in hormonal regulation, vascular response, and cellular resilience.

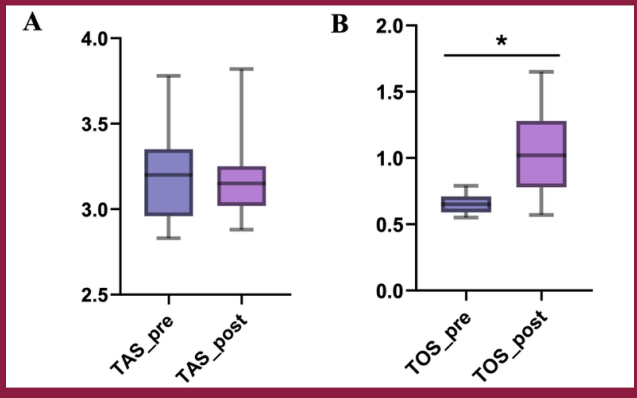

Figure 3. Perioperative changes in oxidative stress parameters following CPB. (A) TAS levels did not differ significantly between preoperative and postoperative measurements. (B) TOS levels increased significantly in the postoperative period compared with preoperative values. Data are presented as median (IQR) for the overall cohort (n = 41). *p < 0.05. Paired statistical analyses were used to evaluate perioperative differences. CPB, cardiopulmonary bypass; TOS, total oxidant status; TAS, total antioxidant status; IQR, interquartile range.

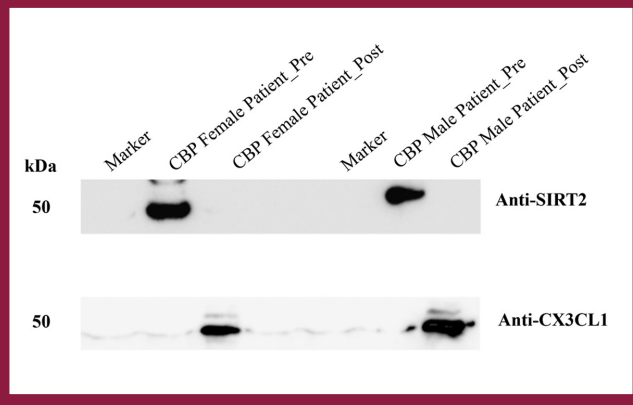

Figure 4. Representative Western blots showing SIRT2 and CX3CL1 protein expression in paired preoperative and postoperative serum samples from a subgroup of two patients (one female and one male). Molecular-weight marker lanes were included to indicate the approximate sizes of the detected proteins. SIRT2 was detectable in the preoperative samples but not in the corresponding postoperative samples, whereas CX3CL1 became detectable postoperatively. SIRT2, sirtuin 2; CX3CL1, C-X3-C motif chemokine ligand 1; CPB, cardiopulmonary bypass.

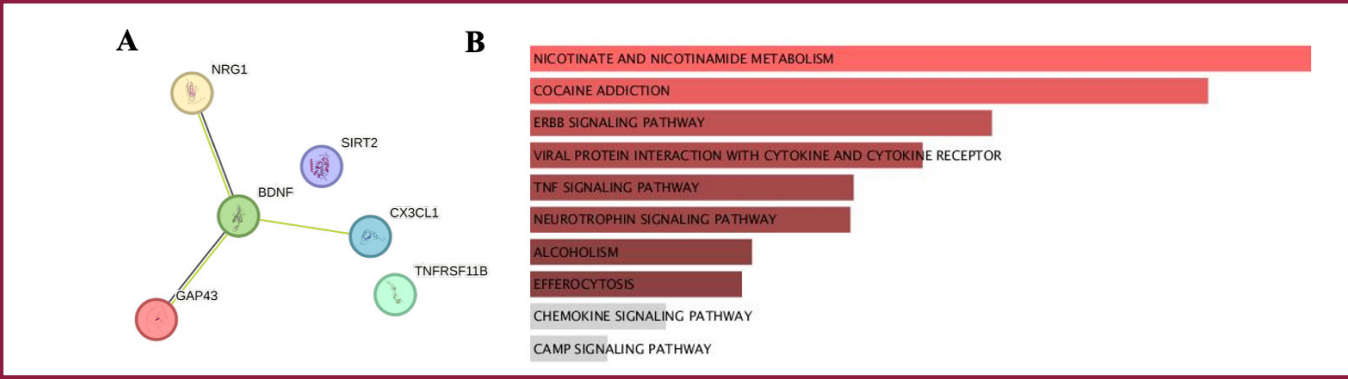

Figure 5. Integrated in silico analysis of the studied biomarkers. (A) A protein-protein interaction network was constructed using the STRING database (version 12.0), demonstrating functional connectivity among GAP43, NRG1, BDNF, TNFRSF11B (OPG), CX3CL1, and SIRT2. (B) KEGG pathway enrichment analysis identifying pathways associated with neuronal signaling, inflammatory response, and cellular stress regulation, including neurotrophin, TNF, chemokine, and cAMP signaling pathways. The analysis highlights coordinated interactions linking neuroregeneration, inflammation, and oxidative stress-related processes. GAP43, growth associated protein 43; NRG1, neuregulin-1; BDNF, brain-derived neurotrophic factor; TNFRSF11B, tumor necrosis factor receptor superfamily member 11B; OPG, osteoprotegerin; CX3CL1, C-X3-chemokine Ligand 1; SIRT2, sirtuin 2; STRING, Search Tool for the Retrieval of Interacting Genes/Proteins; KEGG, Kyoto Encyclopedia of Genes and Genomes; TNF, tumor necrosis factor; cAMP, cyclic adenosine monophosphate.

NRG1 did not show an overall significant change, but exhibited different trends in males and females, both of which are biologically significant. An increase in NRG1 in males may reflect up-regulation of a protein that helps cells survive under stress, compensating for the effects of surgery, whereas a decrease in females may indicate a different mechanism. NRG1 signals through the ErbB family of receptor tyrosine kinases and is involved in calcium homeostasis; thus, these findings support the hypothesis that sex-specific modulation of neuroprotective signaling pathways that can impact recovery from surgery.

Elevated OPG levels in the male patients studied suggest increased vascular inflammation following CPB. OPG has been shown to be involved in endothelial dysfunction and vascular remodelling; thus, its elevation could be an early marker of inflammation related to extracorporeal circulation. Interestingly, the trends in BDNF levels are opposite to those of OPG and suggest that neurotrophic support is complex and highly regulated in this context. Although the sex differences were not significantly increased, they may still be important.

In addition to neuroinflammation, CPB-induced brain injury likely involves oxidative stress. Recent experimental studies have further demonstrated that CPB-induced neuroinflammation contributes to persistent deficits in neurogenesis and cognitive function (24). The TOS increased severalfold, whereas the TAS remained unchanged. This increase in TOS relative to TAS is expected to promote cellular injury and impair neuroregenerative processes, consistent with the postoperative decrease observed in GAP43, a protein involved in neuronal sprouting and synaptic plasticity.

The brain exhibited signs of a disrupted cellular response following recovery from CPB. SIRT2 was downregulated post-CPB, which may suggest a loss of neuroprotective pathways involved in metabolic and stress responses that enable cells to resist oxidative stress and maintain cellular homeostasis. SIRT2 has emerged as an important regulator of oxidative stress, mitochondrial homeostasis, and neuroinflammatory signaling, although its functional effects appear to depend on the specific cellular and pathological context (25). Conversely, increased expression of CX3CL1 suggests activation of inflammatory signaling, alteration of neuron-immune communication, and chemotaxis of immune cells to the brain, all of which may contribute to neuroinflammation. CX3CL1 signaling is increasingly recognized as a central regulator of neuron–microglia communication and a critical mediator of neuroinflammatory responses (26,27).

The identified molecular changes were incorporated into an *in silico* analysis of alterations occurring during recovery from hypothermic CPB. A protein-protein interaction network was built using the subset of markers GAP43, NRG1, BDNF, OPG, CX3CL1, and SIRT2 identified as altered during recovery from hypothermic CPB (Figure 5). The network revealed numerous interactions among the identified markers, including several that potentially play a central role in recovery from hypothermic CPB, notably GAP43, which is implicated in neuronal plasticity, inflammation, and oxidative stress. An *in silico* pathway enrichment analysis revealed that major pathways that changed during

recovery from hypothermic CPB included those related to neurotrophin signaling, TNF signaling, chemokine signaling, and cAMP signaling. In parallel with the hypothesis, the results also claim that CPB induces a series of changes that link neuroregenerative, inflammatory, and stress responses. However, these results must be confirmed by experimental analysis.

In addition to inducing oxidative stress and a whole-body inflammatory response, the surgical stress associated with CPB could modulate positive neuroregenerative signals. The loss of GAP43, a marker of enhanced neuronal plasticity, might signal a postoperative shift toward decreased plasticity.

Overall, our results suggest that CPB is accompanied by integrated alterations in neuroregenerative, inflammatory, and oxidative stress-related processes. The integration of GAP43 and NRG1 with conventional biomarkers provides a more comprehensive framework for understanding CPB-related neurobiological changes and may contribute to the identification of novel targets for early intervention and risk stratification.

Study Limitations

This study has certain limitations. Notably, the relatively limited sample size—especially within sex-based subgroups—may have reduced the statistical power and reliability of subgroup analyses. The lack of long-term neurological follow-up prevents establishing a direct correlation between biomarker alterations and clinical neurocognitive outcomes. Additionally, Western blot analyses were performed in an exploratory subgroup of two patients and were interpreted qualitatively without densitometric or statistical comparison. Therefore, these representative findings should be considered preliminary and require confirmation in a larger cohort. Although *in silico* analyses provided insights into potential molecular interactions, these findings require further experimental validation.

Conclusion

CPB induces a complex biological response characterized by oxidative stress, inflammation, and altered neuroregenerative signaling. The postoperative decrease in GAP43 suggests impaired neuronal plasticity, whereas the sex-dependent behavior of NRG1 indicates differential neurobiological adaptation.

The combined evaluation of neuroregenerative, inflammatory, and oxidative stress markers provides a more integrated view of CPB-related changes. Additionally, *in silico* analyses support the notion that these biomarkers are functionally interconnected, linking neuronal, immune, and stress-response pathways.

Overall, GAP43 and NRG1 may serve as promising candidates for early detection of CPB-associated neurobiological alterations, although larger and longitudinal studies are needed to confirm their clinical utility. These results underscore the potential value of combined neuroregenerative and inflammatory biomarkers as early indicators of CPB-associated neurovascular alterations and may contribute to improved perioperative monitoring strategies.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Hamidiye Faculty of Medicine Ethics Committee (approval number: 24/727; decision number: 14/16, date: 28.11.2024).

Informed Consent: Written informed consent was obtained from all participants prior to enrollment in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.A., Concept: D.S.A., A.K., Design: D.S.A., Data Collection or Processing: N.H.K., Y.G., N.O., R.N.B., D.E., Analysis or Interpretation: D.S.A., N.H.K., A.K., F.C., Ü.Ç., Literature Search: D.S.A., N.O., Writing: D.S.A., N.H.K., A.K., Y.G., N.O., R.N.B., D.E., F.C., S.A., Ü.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This study was supported in part by the Scientific and Technological Research Council of Türkiye (TÜBİTAK) under the 2209-A University Students Research Projects Support Programme (application/project number: 1919B012417406).

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