



EFFECT OF PREOPERATIVE GABAPENTIN ON SERUM NGAL RESPONSES AFTER LAPAROSCOPIC SLEEVE GASTRECTOMY: A SECONDARY ANALYSIS OF A RANDOMIZED TRIAL

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DOI: <https://doi.org/10.5281/zenodo.22253584>

How to cite this Article: Kholoud Salah Ibrahim Amin^{*1,2}, Sahar Kamal Tawfeek Hegazy², Hosam Mohamed Mostafa Elghadban³, Ahmed Mohammed Hassan Shata⁴ (2026). Effect Of Preoperative Gabapentin On Serum Ngal Responses After Laparoscopic Sleeve Gastrectomy: A Secondary Analysis Of A Randomized Trial. *European Journal of Biomedical and Pharmaceutical Sciences*, 13(9), 260–271.

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Article Received on 05/08/2026

Article Revised on 25/08/2026

Article Published on 03/09/2026

ABSTRACT

Background: Early postoperative renal stress remains a concern after laparoscopic sleeve gastrectomy (LSG), particularly in patients with severe obesity. Serum neutrophil gelatinase-associated lipocalin (NGAL) is an early biomarker of renal tubular stress, but the effect of perioperative gabapentin on its postoperative response remains unclear. **Methods:** This prespecified secondary biomarker analysis included 90 adults with morbid obesity. Thirty non-operative participants formed an external reference cohort (Group I), while 60 undergoing LSG were randomized to surgery without gabapentin (Group II) or after a single preoperative 1200-mg oral dose (Group III). Serum NGAL was measured at baseline, 24 hours, and 6 months in the randomized groups. The primary analysis compared 24-hour NGAL between randomized groups after baseline adjustment. **Results:** At 24 hours, serum NGAL was significantly lower in Group III than Group II (adjusted ratio, 0.542; 95% CI, 0.500–0.588; $P < 0.0001$), corresponding to an approximately 45.8% lower adjusted level. Exploratory comparison showed higher NGAL in Group II than in Group I, whereas Group III did not differ significantly from Group I. Postoperative acute kidney injury (PO-AKI) occurred in 2/30 participants in Group III versus 9/30 in Group II ($P = 0.0419$). Serum NGAL showed good concurrent discrimination for PO-AKI (AUC, 0.874; 95% CI, 0.763–0.945). No significant between-group NGAL difference was observed at 6 months. **Conclusion:** A single preoperative gabapentin dose (1200 mg) was associated with an attenuated 24-hour serum NGAL response and lower PO-AKI incidence after LSG. Larger randomized studies are needed to confirm these findings.

KEYWORDS: Gabapentin; Neutrophil gelatinase-associated lipocalin (NGAL); Acute kidney injury; Laparoscopic sleeve gastrectomy.

INTRODUCTION

Obesity is associated with an increased risk of kidney dysfunction and may predispose patients to acute kidney injury (AKI) during the perioperative period.^[1] Although laparoscopic sleeve gastrectomy (LSG) may improve renal and metabolic outcomes over the longer term,^[2] early postoperative kidney stress remains a clinical concern.^[3] Conventional renal measures, particularly serum creatinine (Scr), may not detect tubular injury at

an early stage, supporting the need for more sensitive biomarkers of postoperative renal stress.^[4]

Neutrophil gelatinase-associated lipocalin (NGAL) is a tubular injury biomarker that may rise rapidly after renal tubular damage and before clinically apparent changes in Scr.^[5] Previous studies have evaluated serum, plasma, or urinary NGAL for the early identification and risk stratification of AKI in different clinical and surgical

settings, including cardiac surgery, critical illness,^[6] and bariatric surgery.^[7] However, its perioperative kinetics following LSG and the potential influence of pharmacological interventions on the NGAL response remain less well characterized.^[8]

Gabapentin is widely used as an adjuvant in multimodal perioperative analgesia and has also demonstrated anti-inflammatory and antioxidant effects in experimental models of AKI.^[9] These properties raise the possibility that preoperative gabapentin may influence the early renal stress response following surgery. However, its effect on perioperative NGAL changes after laparoscopic sleeve gastrectomy has not been well defined.

This prespecified secondary biomarker analysis of a randomized trial aimed to evaluate the effect of a single preoperative dose of gabapentin on the early postoperative serum NGAL response following LSG. The main outcome of the present analysis was the baseline-adjusted between-group difference in serum NGAL at 24 hours postoperatively, with secondary analysis assessing longitudinal NGAL changes and its exploratory discriminative performance for postoperative acute kidney injury (PO-AKI).

MATERIALS AND METHODS

Study design and participants

This study was a prespecified secondary biomarker analysis of data from the registered prospective, randomized, single-blind controlled parent trial registered at ClinicalTrials.gov (NCT06254183) and focused specifically on the serum NGAL outcome. The parent study included 90 adults with morbid obesity. Thirty participants who did not undergo surgery during the study period constituted a non-randomized external reference cohort (Group I, $n = 30$) and underwent a single blood sampling assessment at enrollment. The remaining 60 participants underwent elective LSG and were randomized in a 1: 1 ratio to LSG without preoperative gabapentin (Group II, $n = 30$) or LSG following a single oral dose of gabapentin 1200 mg administered approximately 1 hour before surgery (Group III, $n = 30$).

Participants were recruited from Tanta and Mansoura University Hospitals, Egypt, between December 2024 and May 2025. Eligible participants were 18–65 years old with a BMI ≥ 40 kg/m² without comorbidities or ≥ 35 kg/m² in the presence of obesity-related comorbidities and had preserved baseline kidney function.

Group I was included as an external reference cohort for exploratory cross-sectional comparison of serum NGAL levels. The primary treatment-effect analysis was restricted to the two randomized surgical groups (Groups II and III).

The study protocol was approved by the National Research Ethics Committee, Tanta University (approval

code: TP/RE/12/22M-0073). Written informed consent was obtained from all participants before enrollment.

Clinical and laboratory assessment

Clinical and anthropometric data, including age, sex, body weight, and body mass index (BMI), were recorded at baseline. Renal function was assessed by measuring serum creatinine (SCr) and blood urea nitrogen (BUN) and calculating estimated glomerular filtration rate (eGFR) using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation.^[10] Serum NGAL was measured at the prespecified study time points as described below.

Randomization and intervention

For the 60 surgical participants, the random allocation sequence was generated by an independent researcher using an online randomization program (www.randomizer.org). Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes. Participants were randomized 1: 1 to undergo LSG without preoperative gabapentin (Group II, $n = 30$) or to receive a single oral dose of gabapentin 1200 mg approximately 1 hour before surgery (Group III, $n = 30$). The outcome assessor remained blinded to treatment allocation, whereas participants and treating surgeons were not blinded. Both surgical groups received standard perioperative care according to institutional protocols.

Sample collection and NGAL assessment

For Groups II and III, blood samples were collected at baseline before surgery, 24 hours postoperatively, and at the 6-month follow-up. Participants in Group I underwent a single blood sampling assessment at enrollment. This non-operative external reference cohort was included to provide contextual serum NGAL values in morbidly obese participants who were not exposed to the perioperative surgical stress of LSG, allowing exploratory comparison with the postoperative NGAL levels observed in the two surgical groups.

All blood samples were processed according to standardized laboratory procedures, and serum was used for NGAL measurement. Serum neutrophil gelatinase-associated lipocalin (NGAL) concentrations were measured using a commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kit (BT LAB, Bioassay Technology Laboratory; Cat. No. E1719Hu) according to the manufacturer's instructions. The assay had a standard curve range of 5–600 ng/mL and a sensitivity of 2.01 ng/mL. Absorbance was measured at 450 nm, and results were expressed in ng/mL.

Outcome Assessment

The main outcome of the present analysis was the baseline-adjusted between-group difference in serum NGAL concentration at 24 hours postoperatively between Groups II and III. Secondary analysis evaluated longitudinal changes in serum NGAL across baseline, 24

hours postoperatively, and 6 months in the randomized surgical groups. Exploratory analysis included a cross-sectional comparison of serum NGAL between the external reference cohort (Group I) at enrollment and Groups II and III at 24 hours postoperatively. Exploratory analysis also assessed baseline-adjusted between-group differences in 24-hour SCr, BUN, and eGFR among the randomized surgical participants. Correlations between 24-hour serum NGAL and concurrent conventional renal function measures, including blood urea nitrogen (BUN), serum creatinine (SCr), and estimated glomerular filtration rate (eGFR), were also assessed. The incidence of PO-AKI was compared between the two randomized surgical groups. In addition, the discriminative performance of 24-hour serum NGAL for PO-AKI was evaluated.

Postoperative acute kidney injury (PO-AKI) was identified using the Kidney Disease: Improving Global Outcomes (KDIGO) serum creatinine criterion, defined as an increase in serum creatinine of ≥ 0.3 mg/dL from baseline within 48 hours.^[11] In the present study, PO-AKI classification was based on baseline and 24-hour postoperative serum creatinine measurements; urine-output criteria were not used.

Sample size calculation

The sample size for the parent trial was determined a priori using G*Power version 3.1.9.2 (Heinrich Heine University Düsseldorf, Germany). Based on pilot data from five participants per group, a one-way ANOVA across three groups, with a two-sided significance level of 0.05 and 95% power, indicated a required sample of 26 participants per group. To account for potential attrition, the target sample was increased to 30 participants per group, yielding a total sample of 90 participants. The present study represents a prespecified secondary biomarker analysis of the same trial; therefore, no separate sample-size calculation was performed specifically for serum NGAL. Treatment-effect analysis was restricted to the 60 randomized surgical participants, while Group I served as a non-randomized external reference cohort.

Statistical analysis

Statistical analysis was performed using GraphPad Prism version 10.4.1 and MedCalc version 23.4.9. Continuous variables were summarized as mean $\pm$ SD and categorical variables as n (%). Baseline serum NGAL was compared among the three groups using ordinary one-way ANOVA, whereas exploratory cross-sectional NGAL comparisons were performed using Welch's ANOVA followed by Dunnett's T3 test. For the main analysis, serum NGAL values were log₁₀-transformed, and 24-hour NGAL was compared between Groups II and III using ANCOVA adjusted for centered log₁₀ baseline NGAL; treatment effects were back-transformed and reported as adjusted ratios with 95% CIs. Longitudinal NGAL changes were analyzed using two-way repeated-measures ANOVA with Geisser–

Greenhouse correction and Šidák-adjusted comparisons. Exploratory baseline-adjusted analyses of 24-hour SCr, BUN, and eGFR were performed using ANCOVA-equivalent multiple linear regression models; treatment group-by-baseline interactions were retained when significant, with baseline covariates mean-centered for interpretation. PO-AKI incidence was compared using the two-sided Fisher's exact test. Associations between 24-hour NGAL and concurrent renal markers were assessed using Pearson and treatment-group-adjusted partial correlations. ROC analysis evaluated the discrimination of 24-hour NGAL for PO-AKI, with the optimal cutoff determined by the maximum Youden index. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Results

Participant flow and analysis population

A total of 103 participants were evaluated for eligibility. Seven of them did not match the inclusion criteria, and six refused to participate. The remaining 90 participants were enrolled in the parent study. Thirty participants constituted the non-randomized external reference cohort (Group I), while 60 surgical participants were randomized equally in a 1: 1 ratio to Group II (30 morbidly obese participants who underwent LSG without gabapentin) and Group III (30 morbidly obese participants who underwent LSG after administration of a single oral 1200 mg dose of gabapentin approximately 1 hour before surgery). All randomized participants completed the planned follow-up, with no losses to follow-up or exclusions from analysis. Accordingly, all 60 randomized surgical participants were included in the main and longitudinal analysis, whereas Group I was included only in the exploratory external-reference comparisons. Participant flow is shown in **Fig.1.**^[12]

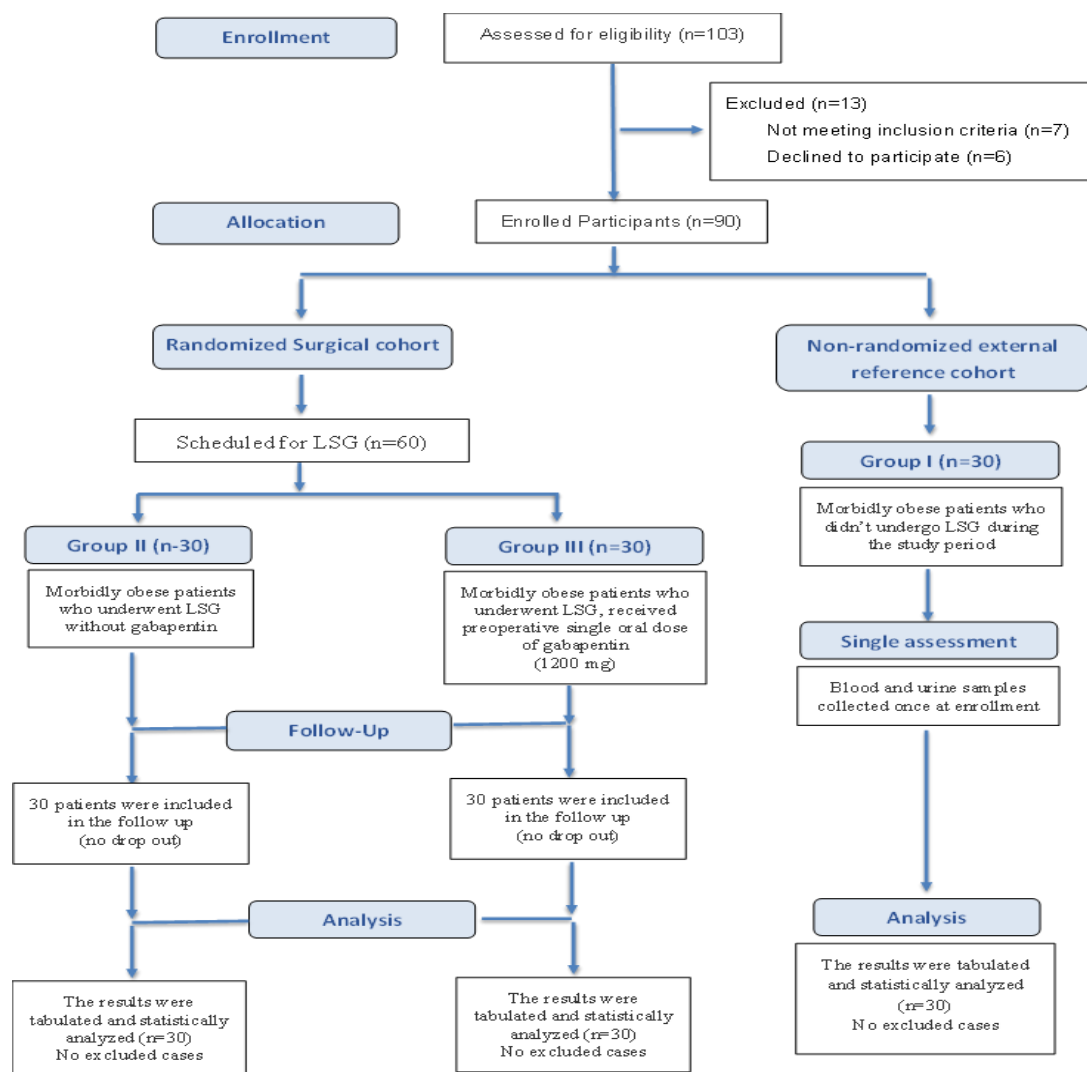


Fig. 1. CONSORT-style participant flow diagram and analysis population.

Group I was a non-randomized external reference cohort and was included only in exploratory external-reference analysis. Groups II and III constituted the randomized surgical population and were included in the primary and longitudinal analysis. Abbreviations; LSG, laparoscopic sleeve gastrectomy.

Baseline characteristics

Baseline demographic, clinical, and renal characteristics of the study participants are summarized in **Table 1**. Age, BMI, sex distribution, diabetes mellitus, and hypertension showed no marked descriptive differences

across the three groups. Baseline BUN and serum NGAL values were also similar in magnitude, whereas serum creatinine was descriptively lower and eGFR higher in Group III compared with Groups I and II.

Table 1: Baseline demographic, clinical, and renal characteristics of the study participants.

		Group I (n=30)	Group II (n=30)	Group III (n=30)
Age (years)		41.57 ± 10.79	42.37 ± 7.15	40.37 ± 8.21
Sex	Male	14 (46.67%)	20 (66.67%)	16 (53.33%)
	Female	16 (53.33%)	10 (33.33%)	14 (46.67%)
Body mass index (BMI), Kg/m²		44.4 ± 5.56	42.9 ± 5.68	44.5 ± 6.92
Comorbidities	Diabetes mellitus	10 (33.33%)	8 (26.67%)	11 (36.67%)
	Hypertension	16 (53.33%)	14 (46.67%)	13 (43.33%)
Baseline parameters	Serum Creatinine (mg/dL)	0.89 ± 0.09	0.81 ± 0.10	0.70 ± 0.07
	Blood urea nitrogen (BUN) (mg/dL)	26.46 ± 4.15	25.67 ± 3.73	25.96 ± 3.87
	eGFR (mL/min/1.73m ²)	95.72 ± 17.84	106.6 ± 14.91	114.4 ± 8.77
	Serum NGAL (ng/mL)	25.04 ± 7.49	24.47 ± 7.54	24.60 ± 7.37

Data are presented as mean $\pm$ SD or n (%), as appropriate. For Group I, baseline measurements were obtained at enrollment; for Groups II and III, measurements were obtained preoperatively before the study intervention. **Group I:** 30 participants with morbid obesity who did not undergo LSG and served as a non-randomized external reference cohort. **Group II:** 30 participants with morbid obesity who underwent LSG without gabapentin administration. **Group III:** 30 participants with morbid obesity who underwent LSG and received a single preoperative dose of gabapentin (1200 mg) approximately 1 hour before surgery.

Abbreviations; NGAL, neutrophil gelatinase-associated lipocalin.

Primary analysis of 24-hour serum NGAL

At 24 hours postoperatively, mean serum NGAL was 39.46 ± 14.46 ng/mL in Group II and 21.16 ± 5.79 ng/mL in Group III. After adjustment for baseline serum NGAL, the 24-hour NGAL level was significantly lower

in Group III than in Group II (adjusted ratio, 0.542; 95% CI, 0.500–0.588; $P < 0.0001$), corresponding to an approximately 45.8% lower adjusted NGAL level in Group III **Table 2**.

Table 2: Baseline-adjusted comparison of 24-hour serum NGAL between the randomized surgical groups.

Outcome	Group II (n=30)	Group III (n=30)	Adjusted ratio (95% CI)	P value
Serum NGAL at 24 hours postoperatively (ng/mL)	39.46 ± 14.46	21.16 ± 5.79	0.542 (0.500–0.588)	< 0.0001*

Data are presented as mean $\pm$ SD. The between-group treatment effect was estimated using ANCOVA on log10-transformed serum NGAL, with treatment group as the fixed factor and centered log10 baseline serum NGAL as the covariate. The treatment effect was back-transformed and reported as an adjusted ratio with 95% CI. **Group II:** 30 participants with morbid obesity who underwent LSG without gabapentin administration. **Group III:** 30 participants with morbid obesity who underwent LSG and received a single preoperative dose of gabapentin (1200 mg) approximately 1 hour before surgery.

Abbreviations; CI, confidence interval; NGAL, neutrophil gelatinase-associated lipocalin; SD, standard deviation; LSG, laparoscopic sleeve gastrectomy.

Longitudinal changes in serum NGAL

Longitudinal serum NGAL trajectories in the randomized surgical groups are shown in **Fig. 2**. Analysis of log10-transformed serum NGAL demonstrated a significant treatment group-by-time interaction ($F(2,116) = 15.25$, $P < 0.0001$), together with significant effects of time ($F(1.100,63.80) = 22.19$, $P < 0.0001$) and treatment group

($F(1,58) = 7.041$, $P = 0.0103$). Šidák-adjusted between-group comparisons showed no significant difference at baseline ($P = 0.9995$), significantly higher serum NGAL in Group II than Group III at 24 hours postoperatively ($P < 0.0001$), and no significant difference at 6 months ($P = 0.8304$) **Table 3, Fig. 2**.

Table 3: Longitudinal changes in serum NGAL in the randomized surgical groups.

Time point	Group II (n=30)	Group III (n=30)	Adjusted P value
Baseline	24.47 ± 7.54	24.60 ± 7.37	0.9995
24-hour PO	39.46 ± 14.46	21.16 ± 5.79	<0.0001*
6 months	18.64 ± 8.77	19.15 ± 6.30	0.8304

Data are presented as mean $\pm$ SD. Longitudinal changes in serum NGAL were analyzed using two-way repeated-measures ANOVA on log10-transformed values, with treatment group as the between-subject factor and time as the within-subject factor. The Geisser–Greenhouse correction was applied, and between-group comparisons at each time point were adjusted using Šidák's multiple-comparisons test. **Group II:** 30 participants with morbid obesity who underwent LSG without gabapentin administration. **Group III:** 30 participants with morbid obesity who underwent LSG and received a single preoperative dose of gabapentin (1200 mg) approximately 1 hour before surgery.

Abbreviations; PO; Postoperative; NGAL, neutrophil gelatinase-associated lipocalin; SD, standard deviation; LSG, laparoscopic sleeve gastrectomy.

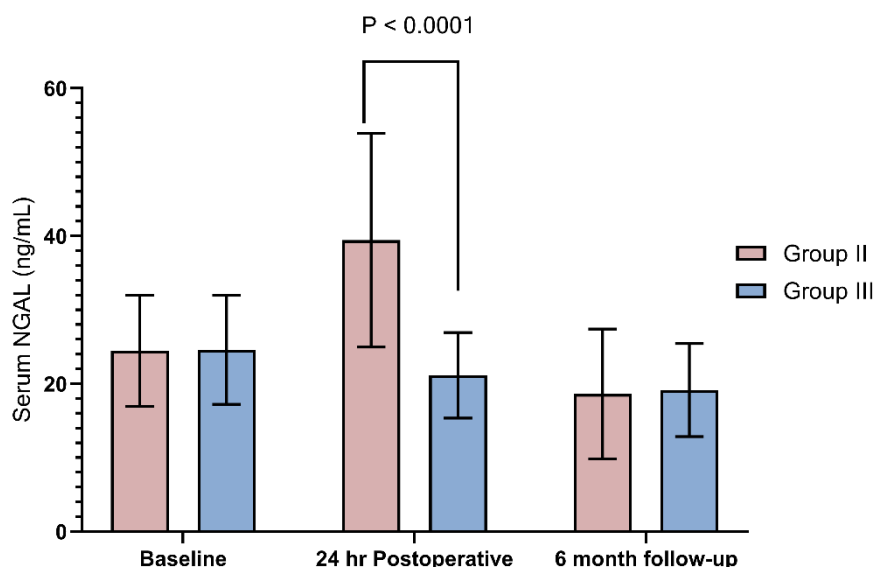


Fig. 2. Longitudinal changes in serum NGAL in the randomized surgical groups.

Data are presented as mean $\pm$ SD. The graph displays raw serum NGAL values (ng/mL), whereas statistical comparisons were performed on log10-transformed values using two-way repeated-measures ANOVA with the Geisser–Greenhouse correction and Šidák-adjusted between-group comparisons. A significant between-group difference was observed at 24 hours postoperatively ($P < 0.0001^*$). **Group II:** 30 participants with morbid obesity who underwent LSG without gabapentin administration. **Group III:** 30 participants with morbid obesity who underwent LSG and received a single preoperative dose of gabapentin (1200 mg) approximately 1 hour before surgery.

Exploratory cross-sectional comparison of serum NGAL

Exploratory cross-sectional comparison of serum NGAL among the three study groups is presented in Fig. 3. Overall differences among groups were statistically significant (Welch's ANOVA, $P < 0.0001^*$). Dunnett's

T3-adjusted comparisons showed significantly higher serum NGAL concentrations in Group II at 24 hours postoperatively compared with both Group I at enrollment and Group III at 24 hours postoperatively (both $P < 0.0001^*$). No significant difference was observed between Group I and Group III ($P = 0.0835$).

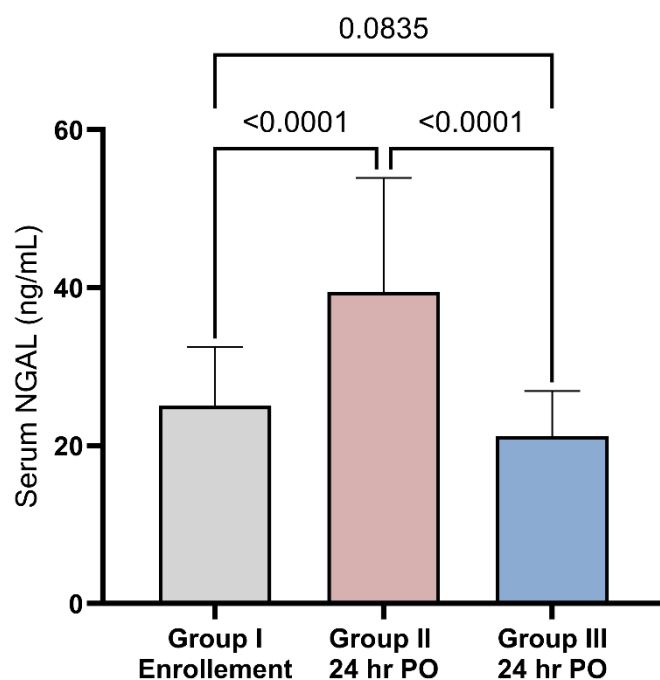


Fig. 3: Exploratory cross-sectional comparison of serum NGAL among the study groups.

Data are presented as mean $\pm$ SD. Group I values represent serum NGAL measured at enrollment, whereas Group II and Group III values represent 24-hour postoperative serum NGAL concentrations. Overall comparisons were performed using Welch's ANOVA followed by Dunnett's T3 multiple-comparisons test. **Group II:** 30 participants with morbid obesity who underwent LSG without gabapentin administration. **Group III:** 30 participants with morbid obesity who underwent LSG and received a single preoperative dose of gabapentin (1200 mg) approximately 1 hour before surgery.

Abbreviations; NGAL, neutrophil gelatinase-associated lipocalin; SD, standard deviation; LSG, laparoscopic sleeve gastrectomy; PO, Postoperative.

Exploratory baseline-adjusted analysis of conventional renal function measures

Exploratory baseline-adjusted analysis showed a more favorable 24-hour renal profile in Group III. After adjustment for baseline SCr, 24-hour SCr was significantly lower in Group III than in Group II (adjusted mean difference, -0.1692 mg/dL; 95% CI, -0.2214 to -0.1169 ; $P < 0.0001$). Significant treatment group-by-baseline interactions were observed for BUN ($P = 0.0003$) and eGFR ($P = 0.0321$). At the mean baseline value, Group III had lower 24-hour BUN (estimated difference, -13.14 mg/dL; 95% CI, -13.73 to -12.56 ; $P < 0.0001$) and higher 24-hour eGFR (estimated difference, 11.26 mL/min/1.73 m²; 95% CI, 6.31 – 16.21 ; $P < 0.0001$) than Group II.

Postoperative acute kidney injury incidence

Postoperative acute kidney injury (PO-AKI) incidence was compared between the randomized surgical groups. PO-AKI occurred in 9 patients (30.0%) in Group II and 2 patients (6.7%) in Group III. The observed incidence of

PO-AKI was significantly lower in the gabapentin-treated group (two-sided Fisher's exact test, $P = 0.0419$; odds ratio for Group II versus Group III, 6.0; 95% CI, 1.250–29.18).

Correlation of 24-hour serum NGAL with renal function markers

Associations between 24-hour serum NGAL concentrations and concurrent renal function markers were assessed in the randomized surgical groups. In pooled Pearson analysis, serum NGAL showed significant positive correlations with SCr ($r = 0.5385$, $P < 0.0001$) and BUN ($r = 0.5956$, $P < 0.0001$), and a significant inverse correlation with eGFR ($r = -0.3606$, $P = 0.0046$). After adjustment for treatment group, however, these associations were markedly attenuated and were no longer statistically significant (partial $r = 0.0791$, $P = 0.5517$ for SCr; partial $r = 0.1274$, $P = 0.3363$ for BUN; and partial $r = 0.0062$, $P = 0.9626$ for eGFR) **Table 4**.

Table 4: Pearson and treatment-group-adjusted partial correlations between 24-hour serum NGAL and concurrent renal function markers.

Renal marker	Pearson r (95% CI)	P value	Treatment-adjusted partial r	Partial P value
SCr	0.5385 (0.3296–0.6971)	<0.0001*	0.0791	0.5517
BUN	0.5956 (0.4025–0.7379)	<0.0001*	0.1274	0.3363
eGFR	-0.3606 (-0.5630 to -0.1175)	0.0046	0.0062	0.9626

Pearson correlations were calculated between 24-hour postoperative serum NGAL concentrations and concurrent renal function parameters in the randomized surgical groups ($n = 60$). Partial correlations were additionally calculated after adjustment for treatment group.

Abbreviations; BUN, blood urea nitrogen; CI, confidence interval; eGFR, estimated glomerular filtration rate; NGAL, neutrophil gelatinase-associated lipocalin; SCr, serum creatinine.

ROC analysis of 24-hour serum NGAL for PO-AKI discrimination

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of 24-hour postoperative serum NGAL to discriminate patients who developed PO-AKI from those who did not among the

randomized surgical groups ($n = 60$). Serum NGAL demonstrated good diagnostic performance, with an area under the ROC curve (AUC) of 0.874 (95% CI, 0.763–0.945; $P < 0.0001$). The optimal cutoff value was >27.256 ng/mL, providing 100% sensitivity and 73.47% specificity (Youden index = 0.7347) **Fig. 4**.

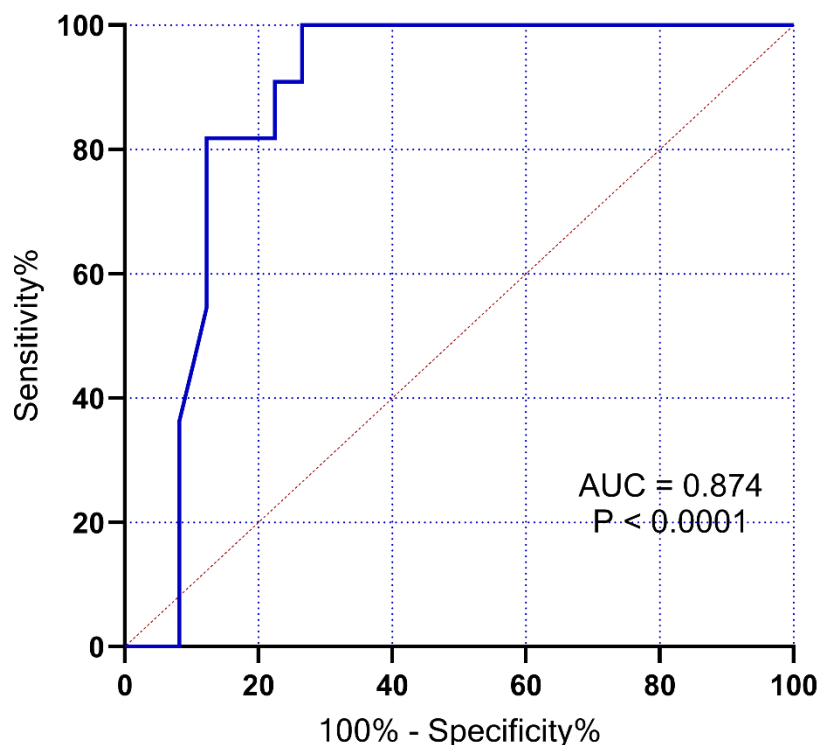


Fig. 4. Receiver operating characteristic (ROC) curve analysis of 24-hour postoperative serum NGAL for discrimination of PO-AKI.

ROC curve analysis was performed using 24-hour postoperative serum NGAL concentrations from the randomized surgical groups (Group II and Group III; $n = 60$). PO-AKI was defined according to KDIGO criteria.

Abbreviations; AUC, area under the curve; CI, confidence interval; NGAL, neutrophil gelatinase-associated lipocalin; PO-AKI, postoperative acute kidney injury.

DISCUSSION

The principal finding of this study was that a single preoperative dose of gabapentin was associated with a markedly attenuated early postoperative serum NGAL response after laparoscopic sleeve gastrectomy. Despite comparable baseline NGAL concentrations between the randomized groups, serum NGAL increased substantially at 24 hours in patients who did not receive gabapentin, whereas this rise was largely absent in those who received gabapentin, resulting in a significant baseline-adjusted between-group difference. This early separation was accompanied by more favorable changes in conventional renal-function indices, but it was no longer evident at six months. Collectively, these findings suggest that preoperative gabapentin may modulate the acute perioperative renal-stress biomarker response; however, they should not be interpreted as definitive evidence of established nephroprotection or confirmed prevention of clinical acute kidney injury.

NGAL has emerged as one of the most extensively investigated early biomarkers of acute kidney stress and injury because its concentration may increase within hours of a renal insult, before a detectable rise in serum creatinine.^[5] A systematic review and meta-analysis by Xu et al. demonstrated that plasma and urinary NGAL

have clinically relevant diagnostic and prognostic value for AKI, although considerable heterogeneity was observed across clinical settings.^[13] Importantly, circulating NGAL is not exclusively kidney derived but is also released by activated neutrophils and may be increased in systemic inflammatory conditions, infection, and other forms of tissue stress.^[14] This limitation is particularly relevant in the perioperative setting, in which surgical trauma, inflammatory activation, and hemodynamic alterations may independently influence serum NGAL concentrations. Therefore, the postoperative NGAL difference observed in the present study should be interpreted as an early perioperative biomarker response that may reflect renal tubular stress while acknowledging that extra-renal inflammatory mechanisms may also contribute.

Recent data suggest that serum NGAL is clinically relevant as an early marker of renal stress in the perioperative period; however, its diagnostic performance appears to depend on the timing of measurement and the clinical setting. Erhan Ozyurt et al. reported that early postoperative serum NGAL was significantly associated with the subsequent development of postoperative AKI and improved discrimination when considered alongside conventional clinical

assessment.^[15] Consistent with the early responsiveness of circulating NGAL, a 2022 systematic review and meta-analysis including 3,131 adults undergoing cardiac surgery found that plasma NGAL had its greatest diagnostic performance when measured 4–8 hours postoperatively, whereas later measurements, including those obtained at 24 hours, showed lower discriminatory performance.^[16] Similarly, a broader meta-analysis of 110 studies involving 38,725 patients determined that serum NGAL is among the biomarkers with the highest overall diagnostic accuracy for AKI, although their performance varied depending on the clinical context and biomarker panel.^[17]

Particularly relevant to the present study, Yang *et al.* prospectively evaluated serum NGAL in patients with obesity undergoing bariatric surgery and demonstrated significant postoperative changes in subclinical renal injury biomarkers despite differing trajectories in filtration-based renal indices.^[18] Collectively, these results suggest that serum NGAL may reflect early renal stress or structural alterations that are not fully captured by conventional functional markers. Accordingly, the observed 24-hour increase in serum NGAL levels in the untreated surgical group in our study is biologically plausible and consistent with an acute postoperative stress response. However, since NGAL levels may reach their peak before 24 hours have elapsed, the sampling schedule we followed cannot determine whether the value recorded over the 24-hour period represents the peak of the response or a later phase of its postoperative course.

Published clinical evidence directly examining the effect of perioperative gabapentin on serum NGAL or other early kidney-injury biomarkers remains limited, as most contemporary studies have focused primarily on analgesic efficacy and opioid consumption rather than renal biomarker responses. In a 2020 systematic review and meta-analysis of 281 randomized trials involving 24,682 surgical patients, Verret *et al.* found that perioperative gabapentinoids produced statistically significant reductions in postoperative pain and opioid consumption; however, the reductions in pain intensity did not reach thresholds considered clinically meaningful.^[19] More recently, the multicenter GAP randomized controlled trial, which included 1,196 patients undergoing major cardiac, thoracic, or abdominal surgery, showed that perioperative gabapentin reduced in-hospital opioid consumption by approximately one-quarter to one-third and produced only a small reduction in pain during the first 24 hours without shortening hospital stay or improving health-related quality of life.^[20] These findings indicate that the attenuated serum NGAL response observed in our study cannot be attributed simply to superior analgesic efficacy or opioid sparing. Rather, other perioperative mechanisms may have contributed to the biomarker difference, although these pathways were not directly evaluated in the present study.

One possible explanation for the reduced postoperative serum NGAL response observed with gabapentin is a modulation of the inflammatory response to surgical stress. NGAL is not only a marker for tubular injury, but also an acute-phase protein produced by activated neutrophils and other immune cells and circulating NGAL concentrations may increase in response to systemic inflammation.^[14] This biological relationship is relevant because perioperative gabapentin has been reported to influence postoperative cytokine responses. In a randomized placebo-controlled study of patients undergoing total knee arthroplasty, Erkılıç *et al.* found that a single preoperative dose of gabapentin significantly attenuated the postoperative increase in IL-6 at both 4 and 24 hours, despite no significant reduction in analgesic requirements.^[21] More recent preclinical evidence also suggests that gabapentin may modulate inflammatory signaling, including IL-6, TNF- α , and IL-1 β pathways, although these findings have not yet been adequately confirmed in perioperative clinical populations.^{[9],[22]}

Accordingly, attenuation of surgery-induced inflammatory activation represents a biologically plausible explanation for the lower 24-hour serum NGAL observed in our gabapentin group. However, because inflammatory mediators were not measured in the present study, this mechanism remains hypothetical and should not be interpreted as evidence that the observed NGAL difference was mediated by an anti-inflammatory effect of gabapentin.

At 24 hours, pooled Pearson analysis showed that serum NGAL was positively correlated with SCr and BUN and inversely correlated with eGFR, suggesting that higher NGAL concentrations were associated with a less favorable early postoperative renal profile. However, after adjustment for treatment group, these associations were markedly attenuated and were no longer statistically significant, indicating that the pooled correlations were largely influenced by between-group differences related to treatment allocation rather than reflecting independent associations between NGAL and conventional renal-function measures. Nevertheless, NGAL and conventional renal indices should not be considered interchangeable measures. Contemporary biomarker frameworks distinguish damage- or stress-related biomarkers, such as NGAL, from functional markers such as serum creatinine, because they reflect different components and potentially different time courses of AKI.^[23] Serum creatinine may respond relatively slowly to acute changes in kidney function and is influenced by several nonrenal factors, while creatinine-based estimates of GFR become particularly difficult to interpret when serum creatinine is changing and has not reached steady state.^{[23],[24]}

Therefore, the present findings support the complementary biological roles of structural or stress-related and functional renal markers while emphasizing

that the observed pooled correlations should not be interpreted independently of treatment allocation.

The favorable early biomarker profile observed with gabapentin was associated with a considerably lower incidence of PO-AKI: 2 of 30 participants in group III versus 9 of 30 participants in group II. This is clinically important, as AKI, although relatively rare after bariatric surgery, is associated with substantial postoperative morbidity. Wang *et al.* performed a systematic review and meta-analysis of 11 studies that included 242,159 obese adults undergoing bariatric surgery. A pooled postoperative AKI prevalence of 2.5% of surgery patients was reported. However, the results were diverse throughout the research probably because of differences in patient populations, study methods, and definitions of AKI between the investigations.^[25] Similarly, in a large registry analysis of 747,926 patients following sleeve gastrectomy or Roux-en-Y gastric bypass, Valera *et al.* also observed that PO-AKI was associated with higher rates of complications, readmission, reoperation, and mortality.^[3]

The absolute incidence observed in our untreated surgical group (group II) was higher than that reported in these larger populations, which may partly reflect differences in AKI ascertainment, patient selection, and the relatively small sample size. Nevertheless, the direction of the PO-AKI finding is consistent with the differences observed in serum NGAL and conventional renal indices. Although the between-group difference in PO-AKI reached statistical significance, only 11 AKI events occurred overall, and the study was not powered specifically to evaluate clinical AKI. Therefore, this finding should be viewed as supportive and hypothesis-generating rather than as conclusive evidence that a single preoperative dose of gabapentin may prevent PO-AKI.

The discriminative performance of 24-hour serum NGAL adds an important clinical dimension to the biomarker findings reported in this study. In the randomized surgical groups (Group II and Group III), serum NGAL discriminated participants with PO-AKI from those without PO-AKI with an AUC of 0.874, indicating good overall discrimination. This finding is consistent with previous studies supporting the role of NGAL as a useful biomarker for AKI detection. In a systematic review and meta-analysis of 110 studies, Pan *et al.* identified Serum NGAL levels among the biomarkers with the highest diagnostic accuracy of acute renal damage. However, the use of this biomarker was highly dependent on the clinical setting and methodological considerations.^[17] In our cohort, the sensitivity and specificity were 100% and 73.47% with a serum NGAL cut-off value of >27.256 ng/mL. However, the cutoff obtained in this investigation should be considered with caution because NGAL concentrations and cutoff values for diagnosis depend on sampling time, patient characteristics, biological matrix and test technology.^{[16],[17]} Moreover, the cutoff was

derived and evaluated within the same relatively small cohort, with only 11 PO-AKI events and no external validation. Because serum NGAL and the SCr measurements used to classify PO-AKI were obtained at the same 24-hour time point, the present ROC analysis reflects concurrent discrimination rather than true prospective prediction. Larger studies incorporating earlier serial measurements and independent validation are therefore needed before a clinically applicable serum NGAL cutoff can be established.

The convergence of serum NGAL concentrations in the two randomized groups at six months further supports the temporary nature of the early treatment-related response following surgery. Serum NGAL concentrations were similar at six months despite a significant difference between the two groups 24 hours postoperatively. Thus, the effect associated with a single preoperative dose of gabapentin was largely limited to the perioperative period and did not induce a sustained change in NGAL levels. This interpretation is biologically plausible given the single-dose exposure and the substantial physiological and metabolic changes occurring during the months after LSG.

This concept is supported by Yang *et al.*^[18] who showed that structural kidney injury biomarkers, including serum NGAL, may follow trajectories that differ from filtration-based renal indices following sleeve gastrectomy. Thus, these biomarkers might reflect distinct aspects of the kidney's postoperative adaptation. Therefore, the lack of a sustained difference between the two groups at 6 months does not weaken the 24-hour finding but instead supports the interpretation that the observed gabapentin-related effect was predominantly an acute response in biomarkers in the perioperative period.

Several features support the interpretation of the present findings. The treatment-effect analysis was based exclusively on the randomized surgical groups, with allocation concealment, blinded outcome assessment, complete follow-up, and no post-randomization exclusions. Serum NGAL was measured longitudinally, and the principal 24-hour comparison incorporated adjustment for baseline NGAL, reducing the influence of baseline variability. The evaluation of serum NGAL alongside conventional renal indices, PO-AKI occurrence, and ROC analysis also provided complementary perspectives on the early postoperative renal response.

First, this was a prespecified secondary biomarker analysis of the parent trial, and no separate sample-size calculation was performed specifically for serum NGAL; consequently, the relatively small, randomized sample and the limited number of PO-AKI events reduce the precision of estimates for clinical kidney outcomes. Second, postoperative NGAL was assessed at 24 hours without earlier serial measurements, precluding characterization of the initial rise or peak biomarker

response. Third, PO-AKI classification relied on the serum creatinine component of the KDIGO definition because urine-output criteria were not available. Fourth, circulating NGAL may be influenced by extra-renal inflammatory processes, and inflammatory mediators were not measured, preventing direct evaluation of the proposed mechanistic pathway. In addition, although the external reference cohort was non-randomized and assessed at a single time point, it served an important descriptive purpose by characterizing renal function and baseline serum NGAL in adults with morbid obesity in the absence of perioperative stress. Accordingly, this cohort should be interpreted as a physiologic reference for the study population rather than as a comparator for causal treatment effects.

Finally, the findings were obtained in adults with severe obesity and preserved baseline kidney function undergoing LSG after a single 1200-mg preoperative dose of gabapentin; therefore, their generalizability to patients with pre-existing renal impairment, other surgical procedures, or different gabapentin dosing regimens remains uncertain.

CONCLUSION

A single preoperative dose of gabapentin (1200 mg) was associated with a markedly attenuated 24-hour serum NGAL response after LSG, accompanied by more favorable conventional renal-function measures and a lower incidence of PO-AKI. This effect was not sustained at six months, suggesting a predominantly early perioperative association. Larger randomized studies are needed to confirm the clinical significance of these findings.

ACKNOWLEDGEMENTS

The authors would like to thank Hadeer Abou-Hany and Heba Ali Abdelaziz for their valuable discussions and academic support during the preparation of the manuscript.

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