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# A composite score of neutrophil gelatinase-associated lipocalin and fibroblast growth factor-23 is associated with survival in multiple myeloma: A retrospective study

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**Abstract.** *Multiple myeloma (MM) is frequently complicated by renal impairment, but traditional markers like the estimated glomerular filtration rate (eGFR) are inherently late indicators that fail to capture early structural damage. We aimed to evaluate the combined prognostic value of neutrophil gelatinase-associated lipocalin (NGAL), a marker of tubular injury, and fibroblast growth factor-23 (FGF-23), a reflection of bone-mineral dysregulation and tumor burden, independently of eGFR and disease stage.*

*Methods. This retrospective cohort study included 95 adult patients with a confirmed diagnosis of MM. Baseline serum NGAL and FGF-23 concentrations were quantified using an enzyme-linked immunosorbent assay (ELISA). Optimal prognostic cutoffs were determined using maximally selected rank statistics. A composite risk score was constructed to compare patients with concurrent biomarker elevations (score 2) against those with zero or one elevated marker (score 0–1). Overall survival was assessed using Kaplan-Meier analysis and multivariable Cox proportional hazards regression models adjusted for eGFR and International Staging System (ISS) stage.*

*Results. The optimal prognostic cutoffs were identified as 153.8 ng/mL for NGAL and 36.4 pg/mL for FGF-23. Patients with a composite score of 2 experienced significantly lower overall survival probabilities (log-rank $p = 0.0071$). In multivariable analysis, the composite risk score remained a potential independent prognostic marker for mortality after adjustment for baseline eGFR (adjusted HR = 6.32, 95% CI: 1.25–31.88, $p = 0.025$) and ISS stage ($p = 0.0057$).*

*Conclusions. The combined assessment of serum NGAL and FGF-23 provides additional prognostic insight over standard eGFR evaluations. Due to the critically low number of events, these findings are strictly hypothesis-generating. This exploratory composite score may aid in identifying a highly vulnerable patient subgroup, independent of baseline filtration status and global tumor burden, but requires validation in larger cohorts.*

**Keywords:** *multiple myeloma, neutrophil gelatinase-associated lipocalin, fibroblast growth factor-23, overall survival, composite risk score.*

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# Комбінований показник ліпокаліну, асоційованого з желатиназою нейтрофілів, та фактора росту фібробластів-23 асоціюється з виживаністю пацієнтів з множинною мієломою: ретроспективне дослідження

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**Резюме.** *Множинна мієлома (ММ) часто ускладнюється ураженням нирок, однак традиційні маркери, такі як розрахункова швидкість клубочкової фільтрації (ШКФ), є за своєю суттю пізніми індикаторами, які не здатні зафіксувати ранні структурні пошкодження. Ми мали на меті оцінити комбіноване прогностичне значення ліпокаліну, асоційованого з желатиназою нейтрофілів (NGAL), який є маркером тубулярного пошкодження, та фактора росту фібробластів-23 (FGF-23), що відображає кістково-мінеральну дисрегуляцію та пухлинне навантаження, незалежно від ШКФ та стадії захворювання.*

*Методи. У це ретроспективне когортне дослідження було включено 95 дорослих пацієнтів із підтвердженим діагнозом ММ. Вихідні концентрації NGAL та FGF-23 у сироватці крові кількісно визначали за допомогою імуноферментного аналізу (ELISA). Оптимальні прогностичні точки відсічення визначали за допомогою максимально відібраних рангових статистик. Було створено комбіновану шкалу ризику для порівняння пацієнтів із одночасним підвищенням обох біомаркерів (2 бали) з пацієнтами, які мали нуль або один підвищений маркер (0–1 бал). Загальну виживаність оцінювали за допомогою аналізу Каплана-Маєра та багатофакторних моделей пропорційних ризиків Кокса з поправкою на ШКФ та стадію за Міжнародною системою стадіювання (ISS).*

*Результати. Оптимальні прогностичні точки відсічення були визначені на рівні 153,8 нг/мл для NGAL та 36,4 пг/мл для FGF-23. Пацієнти з комбінованим показником у 2 бали мали достовірно нижчі показники загальної виживаності (log-rank p = 0,0071). У багатофакторному аналізі комбінована шкала ризику залишалася потенційним незалежним прогностичним маркером смертності після поправки на вихідну ШКФ (скоригований ВР = 6,32, 95% ДІ: 1,25–31,88, p = 0,025) та стадію ISS (p = 0,0057).*

*Висновки. Комбінована оцінка сироваткових NGAL та FGF-23 надає додаткову прогностичну інформацію порівняно зі стандартним визначенням ШКФ. З огляду на обмежену кількість подій, ці результати мають виключно гіпотезогенеруючий характер. Ця дослідницька комбінована шкала може сприяти виявленню групи пацієнтів із високою вразливістю, незалежно від вихідного стану фільтрації та глобального пухлинного навантаження.*

**Ключові слова:** *множинна мієлома, ліпокалін асоційований з желатиназою нейтрофілів, фактор росту фібробластів-23, загальна виживаність, комбінована шкала ризику.*

**Introduction.** Multiple myeloma (MM) is frequently complicated by renal impairment, a clinical manifestation that significantly diminishes overall patient survival [1, 2]. In routine practice, the assessment of renal function relies predominantly on serum creatinine levels and the estimated glomerular filtration rate (eGFR) [3]. However, these traditional metrics are inherently late indicators that reflect global glomerular filtration, often failing to capture early and specific structural nephron damage [4]. In the context of MM, renal injury is primarily driven by the toxic aggregation of free light chains within the tubular apparatus, classically known as cast nephropathy [5]. Because this acute tubular injury frequently precedes a measurable decline in eGFR, relying solely on standard filtration markers can result in delayed recognition of high-risk patients and suboptimal prognostic stratification [6].

To overcome the limitations of traditional filtration metrics, novel biomarkers reflecting specific pathways of myeloma-induced damage have emerged [7]. Neutrophil gelatinase-associated lipocalin (NGAL) has been identified as an early and sensitive indicator of active tubular injury and cast nephropathy, rising significantly before a measurable decline in eGFR [8]. Concurrently, fibroblast growth factor-23 (FGF-23) has garnered attention not only as a marker of secondary mineral-bone dysregulation in chronic kidney disease but also as a direct reflection of myeloma-induced skeletal destruction and tumor burden [9, 10]. While previous studies have independently validated the prognostic relevance of NGAL and FGF-23, they represent two distinct pathophysiological targets of the disease:

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the renal tubular apparatus and the skeletal system. Despite their individual clinical utility, the combined assessment of these biomarkers to capture the dual nature of myeloma-associated organ damage remains largely unexplored.

We hypothesized that integrating these two distinct biomarkers into a single exploratory score could provide a more comprehensive assessment of myeloma-associated organ damage and potentially complement standard filtration metrics. Therefore, the primary objective of this study was to evaluate the independent prognostic value of baseline serum NGAL and FGF-23 in patients with MM. Furthermore, we aimed to develop a composite risk score based on optimal biomarker cutoffs and to assess its capacity to predict overall survival independently of baseline eGFR.

**Materials and methods.** *Study design and ethical considerations*. This was a dual-center, retrospective observational cohort study utilizing biobanked serum samples. Clinical data and survival outcomes were retrospectively collected for patients diagnosed and treated at the State Institution «Institute of Blood Pathology and Transfusion Medicine of the National Academy of Medical Sciences of Ukraine» and St. Panteleimon Hospital of the First Territorial Medical Association (Lviv, Ukraine) between 2010 and 2023. The laboratory quantification of novel biomarkers using the stored serum samples was performed between 2023 and 2025. The study protocol and the informed consent form were reviewed and approved by the Ethics Committee of the Danylo Halytsky Lviv National Medical University (Protocol No. 11, dated November 17, 2025). All patients provided written informed consent prior to inclusion, in strict adherence to the ethical principles of the Declaration of Helsinki. The study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

*Patient population and diagnostic criteria*. A total of 95 adult patients with a confirmed diagnosis of MM were included in this study. The diagnosis of MM was established according to updated national and international guidelines (International Myeloma Working Group, IMWG) [**11**]. Renal impairment was defined and stratified based on the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines [**12**].

The inclusion criteria were: (1) documented MM; (2) age between 18 and 85 years; (3) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; (4) patient consent and ability to adequately cooperate during the study; (5) availability of properly stored baseline serum samples collected at the time of initial diagnosis, strictly prior to the initiation of any specific anti-myeloma therapy; and (6) availability of complete clinical, biomarker, and follow-up data required for survival analysis.

The exclusion criteria included: (1) refusal to participate; (2) signs of acute infectious processes of any etiology; (3) pregnancy and lactation; (4) decompensated heart failure; (5) decompensated type 2 diabetes mellitus; (6) psychiatric disorders or any conditions limiting the ability to comprehend informed consent; and (7) requirement for acute renal replacement therapy at inclusion.

Based on their baseline eGFR, calculated via the CKD-EPI equation, the 95 patients were stratified into two groups: a preserved or mildly decreased eGFR group (≥ 60 mL/min/1.73m$^2$, n = 68) and a moderately to severely decreased eGFR group (< 60 mL/min/1.73m$^2$, n = 27).

*Routine clinical and laboratory measurements*. Baseline demographic characteristics (patient age) were recorded at inclusion. A targeted hematological and biochemical assessment was performed. Hemoglobin levels were determined using the YUMIZEN H500 5-Diff automated hematology analyzer (Horiba ABX, France). Serum biochemical parameters, specifically creatinine, urea, total protein, albumin, total calcium, and β2-microglobulin, were measured on the Pentra 400 automated clinical chemistry analyzer using ABX Pentra reagents (Horiba ABX, France). Serum C-reactive protein (CRP) was quantified via an enzyme-linked immunosorbent assay (ELISA) on an APE ELITE microplate analyzer (Das S.R.L., Italy). Serum monoclonal protein (M-protein) was evaluated using the Hellabio electrophoretic system (Greece). The urinary albumin-to-creatinine ratio (ACR) was assessed using MICROLABBU-PLAN test strips (Erba Lachema, Czech Republic), with microalbuminuria visually corresponding to an albumin concentration of 20–300 mg/L.

*Quantification of FGF-23 and NGAL*. Peripheral blood samples were collected from all patients at the time of initial diagnosis. The samples were promptly centrifuged, processed to serum, aliquoted, and continuously stored at -80°C in the institutional biobank until batched analysis to prevent protein degradation.

Serum concentrations of FGF-23 and NGAL were quantified utilizing sandwich ELISA techniques. FGF-23 levels were measured using the Human FGF-23 ELISA Kit (Catalog No. EH3058, FineTest, China). The assay detection range was 15.625–1000 pg/mL, with a sensitivity of 9.375 pg/mL. NGAL concentrations were determined using the Human Lipocalin-2 ELISA Kit (Catalog No. EH20020, FineTest, China), which has a detection range of 31.25–2000 pg/mL and a sensitivity of 18.75 pg/mL.

For both assays, thawed serum samples were appropriately diluted with the respective sample dilution buffers prior to analysis (minimum dilution 1:2). Standards were prepared via serial dilution. Briefly, 100 µL of standards or diluted samples were added to the microplate wells and incubated for 90 minutes at 37°C. Following two wash cycles, 100 µL of biotin-labeled antibodies were added and incubated for 60 minutes at 37°C. After three washes, 100 µL of streptavidin-HRP conjugate (SABC) was added, followed by a 30-minute incubation at 37°C. The plates were washed five

times, and 90–100 μL of TMB substrate was added for a 10–20 minute incubation in the dark. The reaction was terminated using 50 μL of stop solution, and optical density was immediately measured at 450 nm. Final concentrations were calculated using a four-parameter logistic regression curve fit, strictly accounting for the sample dilution factors. Reference values provided for healthy individuals were 0–25 pg/mL for FGF-23 and 29–184 ng/mL for NGAL.

*Study endpoints and statistical analysis*. The primary endpoint was overall survival (OS), defined as the time from the baseline blood sampling (which coincided with the time of initial MM diagnosis) to death from any cause or the date of last follow-up (maximum follow-up ~160 months). Statistical analyses were performed using R software (version 4.5.1). Continuous variables were assessed for normality (Shapiro-Wilk test) and compared using the Mann-Whitney U test or Welch's t-test, as appropriate.

Optimal prognostic cutoffs for NGAL and FGF-23 were determined using maximally selected rank statistics (survminer package). A composite risk score was subsequently constructed (Score 0–1 vs. Score 2). Survival probabilities were estimated via the Kaplan-Meier method (log-rank test). Hazard ratios (HR) were calculated using univariate and multivariable Cox proportional hazards regression models, adjusting for baseline eGFR and ISS stage in separate models. To prevent mathematical overfitting and adhere to epidemiological guidelines given the limited number of events (n=12), the multivariable adjustments for baseline eGFR and ISS stage were performed in separate, conservatively parameterized models rather than a single combined model. A two-tailed p-value $< 0.05$ was considered statistically significant.

**Results.** *Patient characteristics*. A total of 95 patients were included in the study and stratified into two groups based on their baseline renal function: preserved or mildly decreased eGFR (eGFR $\geq$ 60 mL/min/1.73m$^2$, n = 68) and moderately to severely decreased eGFR (eGFR $<$ 60 mL/min/1.73m$^2$, n = 27). The baseline clinical and laboratory characteristics of the study cohort are summarized in Table 1.

*Table 1*

**Baseline clinical and laboratory characteristics of the study cohort stratified by eGFR**

| Variable | eGFR ≥ 60 mL/min/1.73m² (n = 68) | eGFR < 60 mL/min/1.73m² (n = 27) | p-value |
|---|---|---|---|
| **Demographics** | | | |
| Age (years) | 58.0 (49.8–63.0) | 60.0 (54.5–66.0) | 0.181 |
| Laboratory parameters | | | |
| Hemoglobin (g/L) | 127.0 (117.0–134.0) | 110.0 (85.5–119.5) | <0.001 |
| Serum creatinine (μmol/L) | 69.1 (56.3–82.9) | 125.5 (115.0–147.2) | <0.001 |
| Blood urea (mmol/L) | 4.8 (3.8–6.3) | 7.8 (6.2–9.9) | <0.001 |
| Total protein (g/L) | 78.5 (73.5–83.5) | 80.0 (75.0–85.5) | 0.394 |
| Serum albumin (g/L) | 42.5 (41.6–43.8) | 42.3 (41.2–43.5) | 0.265 |
| Serum calcium (mmol/L) | 2.3 (2.2–2.5) | 2.4 (2.2–2.5) | 0.626 |
| C-reactive protein (mg/L) | 6.0 (6.0–6.0) | 6.0 (6.0–12.0) | 0.043 |
| **Specific biomarkers & Myeloma parameters** | | | |
| Monoclonal protein (g/L) | 0.0 (0.0–7.7) | 4.4 (0.0–19.1) | 0.046 |
| β2-microglobulin (mg/L) | 2.4 (2.1–3.1) | 4.2 (2.7–5.8) | <0.001 |
| ACR (mg/mmol) | 11.4 (5.6–34.1) | 136.2 (45.4–136.2) | <0.001 |
| NGAL (ng/mL) | 177.8 (157.2–199.2) | 202.2 (188.2–210.3) | 0.003 |
| FGF-23 (pg/mL) | 59.0 (40.5–294.2) | 57.1 (45.5–96.6) | 0.824 |

*Note:* *data are presented as median (Q1–Q3). Continuous variables were compared between groups using the non-parametric Mann-Whitney U test, except for hemoglobin, which met the assumption of normality and was analyzed using Welch's two-sample t-test. P-values with statistical significance ($p < 0.05$) are highlighted in bold. ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; FGF-23, fibroblast growth factor-23; NGAL, neutrophil gelatinase-associated lipocalin.*

The median age of the patients was comparable between the preserved and impaired renal function groups (58.0 vs. 60.0 years, p = 0.181). Furthermore, there were no statistically significant differences in serum total protein, albumin, and calcium levels (all $p > 0.05$), indicating a similar baseline nutritional and metabolic status across the cohort. As anticipated, patients with eGFR $<$ 60 mL/min/1.73m$^2$ exhibited significantly worse standard renal and hematological parameters. This included elevated serum creatinine (125.5 vs. 69.1

μmol/L, p < 0.001) and blood urea (7.8 vs. 4.8 mmol/L, p < 0.001), alongside a pronounced decline in hemoglobin levels (110.0 vs. 127.0 g/L, p < 0.001). Disease-specific myeloma parameters and inflammatory markers were also significantly elevated in the context of reduced renal function (Figure 1). The eGFR < 60 group demonstrated higher levels of monoclonal protein (4.4 vs. 0.0 g/L, p = 0.046) and β2-microglobulin (4.2 vs. 2.4 mg/L, p < 0.001). Systemic inflammation, indicated by C-reactive protein (CRP), was also significantly higher in the impaired eGFR cohort (p = 0.043).

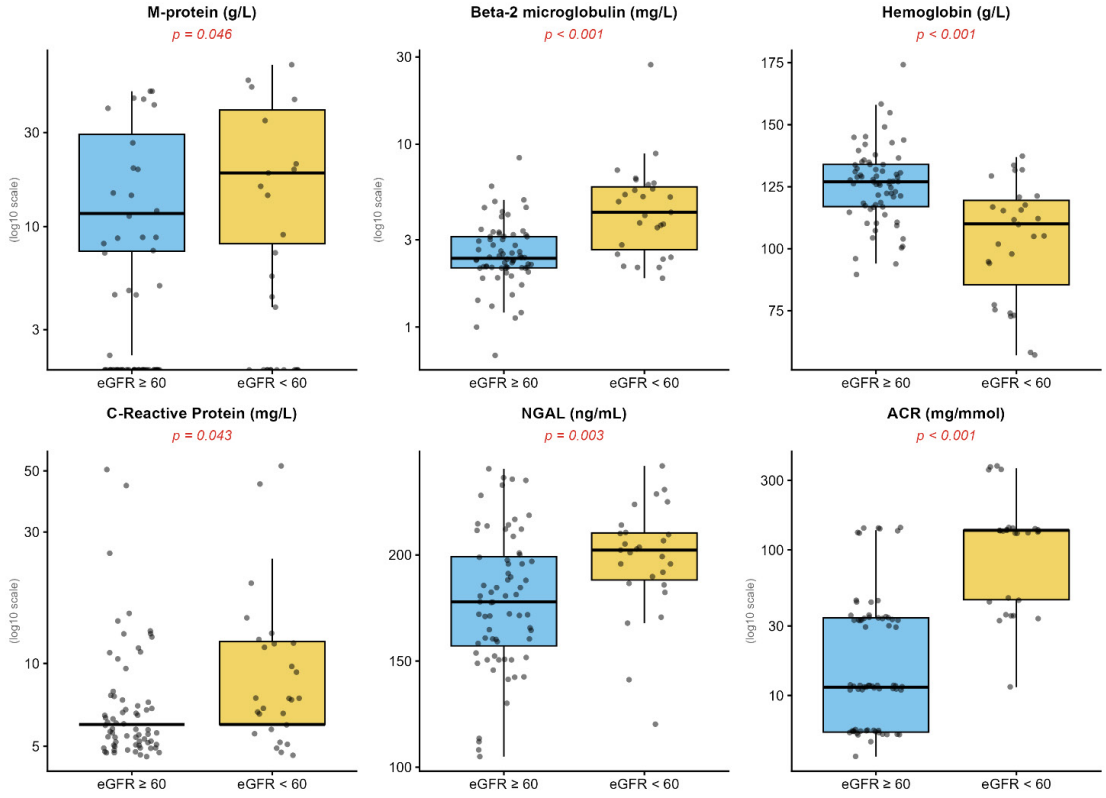


Fig. 1. Distribution of significant clinical and laboratory biomarkers stratified by eGFR.

*Note:* *boxplots illustrate the median and interquartile ranges, with individual patient data points overlaid as jitter to show distribution. Variables exhibiting high positive skewness (e.g., ACR, CRP, β2-microglobulin, and M-protein) are plotted on a logarithmic (log10) scale for visual clarity. P-values were determined using the non-parametric Mann-Whitney U test, except for hemoglobin (Welch's t-test).*

*Overall patients' survival.* The clinical outcomes of the 95 patients were evaluated over a maximum follow-up period of approximately 160 months. During this period, a total of 12 events (deaths) were recorded. The overall survival (OS) of the entire study cohort was estimated using the Kaplan-Meier method (Fig. 2).

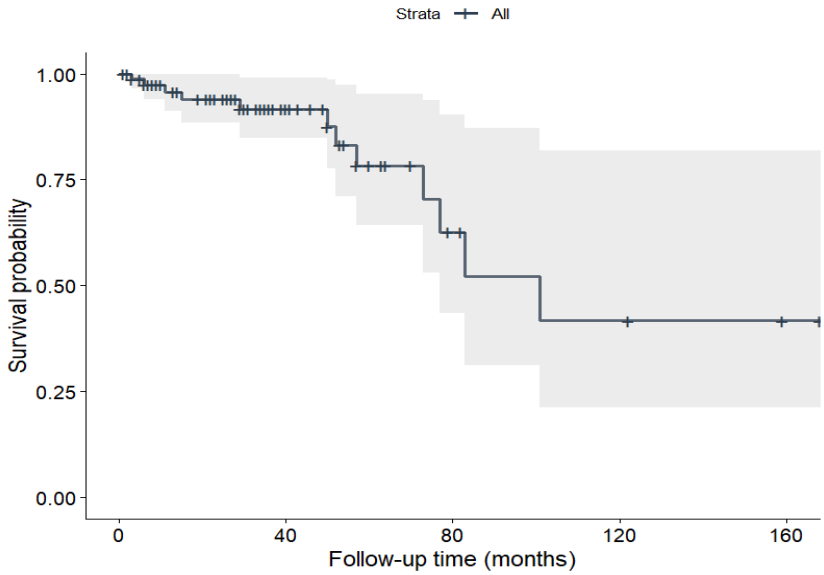


Fig. 2. Kaplan-Meier estimates of overall survival for the entire study cohort.

The Kaplan-Meier survival curve demonstrated a relatively stable clinical course during the initial phase of observation, with a high survival probability maintained throughout the first three years. A more pronounced decline in survival probability was observed between 50 and 100 months of follow-up. The estimated median overall survival for the entire cohort was 101 months (95% CI: 77—not reached). The overall 3-year survival rate was excellent at 91.7% (95% CI: 84.9–99.2%), which subsequently decreased to 78.3% (95% CI: 64.3–95.3%) at the 5-year follow-up mark.

Initial evaluation of NGAL and FGF-23 as continuous variables in univariate Cox models did not yield statistical significance (p = 0.283 and p = 0.363, respectively). This indicates a non-linear, threshold-based biological effect on mortality risk rather than a linear continuous correlation, justifying the categorization of these variables.

To further evaluate the impact of specific biomarkers on patient survival and translate continuous laboratory values into clinically actionable risk categories, we determined the optimal prognostic thresholds. Maximally selected rank statistics were employed to identify the exact cutpoints that provided the most significant split in overall survival. The results of this threshold optimization are summarized in Table 2.

*Table 2*

**Maximally selected rank statistics for NGAL and FGF-23**

| Biomarker | Optimal Cutoff | Log-rank Statistic | Hazard Ratio | 95% CI | Adjusted p-value* | Patients, n (Low / High risk) |
|---|---|---|---|---|---|---|
| NGAL (ng/mL) | 153.8 | 2.379 | 6.78 | 0.83–55.00 | 0.024 | 19 / 76 |
| FGF-23 (pg/mL) | 36.4 | 2.594 | 5.89 | 0.73–47.37 | 0.039 | 12 / 83 |

*Note:* ** Adjusted p-values for the optimal cutpoints were calculated using maximally selected rank statistics.*

The optimal prognostic cutpoint for NGAL was identified at 153.8 ng/mL (Log-rank statistic = 2.379). Based on this threshold, the cohort was stratified into a low-risk group (≤153.8 ng/mL, n = 19) and a high-risk group (>153.8 ng/mL, n = 76).

Similarly, the optimal threshold for FGF-23 was established at 36.4 pg/mL (Log-rank statistic = 2.594). This cutpoint divided the patients into a low-risk category (≤36.4 pg/mL, n = 12) and a high-risk category (>36.4 pg/mL, n = 83).

Establishing these statistically validated cutoffs provided a robust foundation for the subsequent Kaplan-Meier survival analysis and allowed us to construct a powerful composite risk score.

To assess the predictive power of the established biomarker cutoffs, we performed Kaplan-Meier survival analysis followed by Cox proportional hazards regression. The survival trajectories of patients stratified by individual markers and the composite risk score are visualized in Figures 3–5, and the regression outcomes are detailed in Table 3.

*Table 3*

**Cox proportional hazards regression analysis of individual biomarkers and the composite risk score**

| Model | Variable | Hazard Ratio (HR) | 95% CI | p-value |
|---|---|---|---|---|
| NGAL Only | NGAL (High vs. Low) | 6.78 | 0.83–55.00 | 0.073 |
| FGF-23 Only | FGF-23 (High vs. Low) | 5.89 | 0.73–47.37 | 0.096 |
| Composite Score | Score 2 vs. Score 0–1 | 7.02 | 1.44–34.30 | 0.016 |

*Note:* *hazard ratios were calculated using univariate Cox proportional hazards regression. «High» groups represent patients exceeding the optimal cutoffs (NGAL > 153.8 ng/mL; FGF-23 > 36.4 pg/mL). For the composite score, patients with Score 2 (both markers elevated) were compared against the combined reference group (Score 0–1). P-values with statistical significance (p < 0.05) are highlighted in bold. CI, confidence interval; FGF-23, fibroblast growth factor-23; NGAL, neutrophil gelatinase-associated lipocalin.*

Kaplan-Meier analysis revealed that patients with high NGAL levels (>153.8 ng/mL) experienced a significantly worse overall survival compared to the low-risk group (Log-rank p = 0.043; Fig. 3). Similarly, elevated FGF-23 (>36.4 pg/mL) demonstrated a distinct trend towards poorer survival outcomes (Log-rank p = 0.062; Fig. 4). Univariate Cox regression analysis further supported the clinical relevance of these individual markers. High NGAL and high FGF-23 were associated with pronounced hazard ratios of 6.78 (95% CI: 0.83—55.00, p = 0.073) and 5.89 (95% CI: 0.73—47.37, p = 0.096), respectively. While these individual hazard ratios indicated a strong trend toward elevated mortality risk, their wide confidence intervals reflected the limited number of events in the low-risk subgroups.

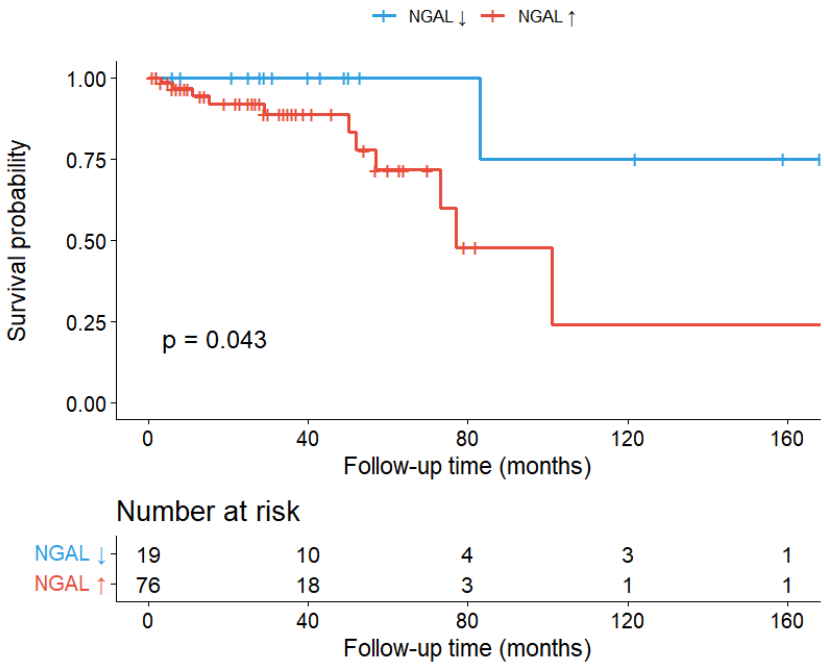


Fig. 3. Kaplan-Meier survival analysis stratified by NGAL levels.

Patients in the high-risk group (NGAL > 153.8 ng/mL, red line) demonstrated significantly poorer outcomes compared to those with lower levels (blue line; Log-rank p = 0.043). Tick marks along the curves indicate censored events. The number of patients at risk is provided below the plot.

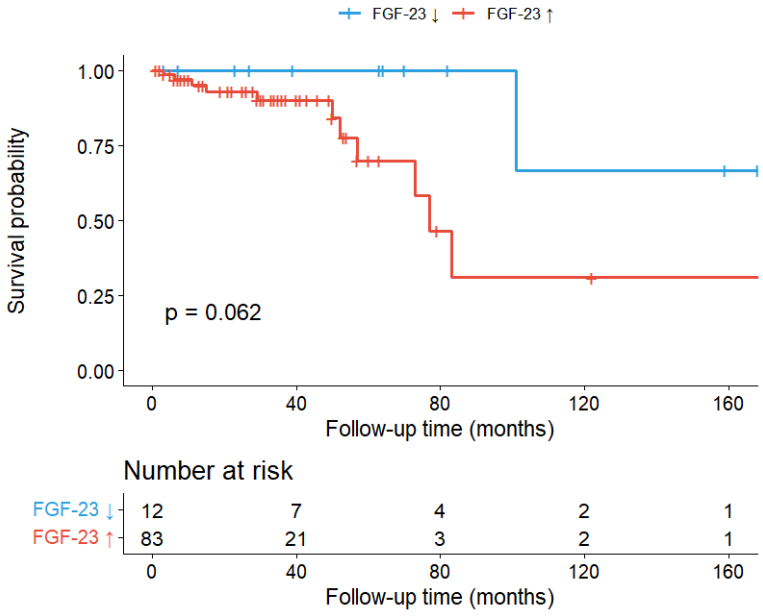


Fig. 4. Kaplan-Meier survival analysis stratified by FGF-23 levels.

Survival trajectories based on baseline FGF-23 concentrations. A trend toward decreased survival was observed in patients with elevated levels (FGF-23 > 36.4 pg/mL, red line) compared to the low-risk group (blue line; Log-rank p = 0.062). Tick marks indicate censored events, and the number at risk is detailed below the plot.

To optimize prognostic accuracy, we evaluated the novel composite risk score. Patients were categorized into a low-to-intermediate risk group (Score 0–1; having zero or one elevated biomarker) and a high-risk group (Score 2; having both NGAL and FGF-23 elevated). The composite score demonstrated excellent discriminatory power. Kaplan-Meier curves for the two risk groups diverged early and significantly (Log-rank p = 0.0071; Fig. 5). Furthermore, Cox regression confirmed that the composite risk score demonstrated a statistically significant association with mortality. Patients with a Score of 2 faced a 7-fold increased risk of death compared to those with a Score of 0–1 (HR = 7.02, 95% CI: 1.44–34.30, p = 0.016).

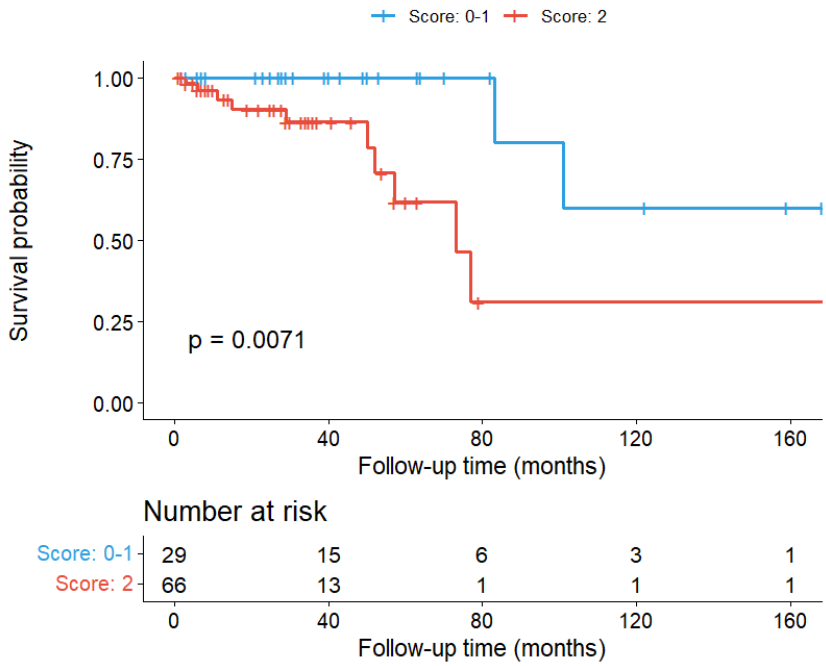


Fig. 5. Kaplan-Meier survival analysis using the composite risk score.

Superior risk stratification achieved by combining NGAL and FGF-23 cutoffs. Patients with a Score of 2 (both biomarkers elevated, red line) had a significantly lower survival probability compared to the combined low/intermediate risk group (Score 0–1, blue line; Log-rank p = 0.0071). Tick marks indicate censored events. Number at risk is provided below the corresponding plot.

These findings indicate that while individual elevation of NGAL or FGF-23 suggests a high risk of adverse outcomes, their combined use in a composite score provides an exploratory method for potential risk assessment in these patients.

To further validate the independent prognostic value of the composite risk score, a multivariate Cox proportional hazards regression model was constructed, adjusting for baseline eGFR. Strikingly, after adjustment, the composite risk score (Score 2) remained a statistically significant potential prognostic marker of mortality (Adjusted HR = 6.32, 95% CI: 1.25–31.88, p = 0.025). Conversely, baseline eGFR did not demonstrate a statistically significant association with overall survival in this multivariable model (p = 0.403). These findings highlight that the combined assessment of NGAL and FGF-23 may provide complementary prognostic information alongside standard glomerular filtration rate evaluation. Internal validation of the composite risk score model was performed using 1,000 bootstrap resamples. The original Harrell's C-index of 0.707 demonstrated high stability after optimism correction, with a final optimism-corrected C-index of 0.705. This minimal degree of optimism (0.002) confirms the reliability and robustness of the established prognostic model. Furthermore, in an additional separate multivariable analysis adjusting for the ISS stage, the composite risk score retained its robust independent prognostic significance (p = 0.0057). Finally, when adjusting for both eGFR and ISS stage simultaneously in a highly constrained combined model, the composite score still remained a significant potential prognostic marker (Adjusted HR = 30.85, 95% CI: 2.59–368.0, p = 0.0067). However, including three covariates in a cohort with only 12 events violates standard event-per-variable guidelines, leading to mathematical overfitting and clinically unintuitive, extremely wide confidence intervals. For this methodological reason, the separate, stable adjustment models (adjusting for eGFR and ISS independently) were chosen as the primary and most reliable method for clinical reporting (see Table 3).

**Discussion.** In this study, we demonstrated that the combined assessment of serum NGAL and FGF-23 serves as a potential prognostic marker for overall survival in patients with MM. This potential prognostic utility is pathophysiologically justified by the disease's simultaneous impact on the skeletal system (FGF-23) [**10, 13**] and the renal tubular apparatus (NGAL) [6, 14]. While global filtration markers like eGFR often miss localized tissue damage [**3, 15**], our composite score integrates NGAL — a sensitive marker of cast nephropathy and acute tubular injury [**5, 8, 18**] — with FGF-23, which reflects myeloma-induced bone-mineral disruptions and tumor burden [9, 10, 16, 19]. By capturing both main targets of MM, this dual-biomarker approach may facilitate the exploratory identification of patients at significantly elevated mortality risk who might otherwise be misclassified by standard filtration metrics alone [**7**].

While isolated elevations of NGAL and FGF-23 have been previously linked to adverse outcomes [**8, 9, 17**], our study integrates them into a unified score that offers additional prognostic insight [**20**]. In our multivariable analysis, patients with simultaneous elevation

of both markers (Score 2) exhibited a more than six-fold higher risk of mortality. We utilized an unweighted 0-2 scoring system rather than assigning fractional weights to each biomarker. This intentional approach prevents statistical overfitting to our specific pilot cohort and maximizes bedside utility for clinicians, prioritizing practical simplicity over complex mathematical stratification. Crucially, this exploratory prognostic signal remained statistically significant even after rigorous adjustment for baseline eGFR and ISS stage [21]. This suggests that the exploratory composite score provides clinicians with a potential tool to assess high-risk patients, regardless of their baseline disease stage or filtration status.

The absence of significant differences in FGF-23 levels between kidney function groups likely reflects a complex counter-balancing relationship between renal clearance and tumor-driven production. In patients with preserved eGFR, efficient renal excretion is coupled with lower tumor burden and minimal bone involvement [22]. In contrast, patients with advanced renal impairment typically exhibit higher tumor-induced osteolysis and bone-derived FGF-23 production, which occurs alongside reduced renal clearance [23]. This dual-pathway mechanism results in a stabilized systemic level across GFR strata while maintaining the marker's independent prognostic value. This highlights that FGF-23 in multiple myeloma serves as a surrogate for bone microenvironment activation and tumor activity rather than a mere indicator of renal filtration capacity [24].

Our study has several limitations that should be acknowledged. The primary limitation of this study is the relatively small cohort size (n=95) and the low event rate (n=12), which led to wide confidence intervals in the multivariable analysis [25]. This identifies our work as a hypothesis-generating pilot study, rather than a precise calculator for individual risk prediction according to current prediction model guidelines [26]. However, the robustness of the observed pro-survival signal was confirmed by internal bootstrap validation, which yielded a stable optimism-corrected C-index of 0.705. This suggests that despite the sample size, the composite risk score provides reliable independent prognostic information. Furthermore, the long enrollment period (2010–2023) introduces unavoidable treatment heterogeneity. Patients received varying anti-myeloma regimens reflecting the significant evolution of clinical protocols over the past decade, and our models could not be adjusted for specific therapeutic agents. Finally, as our cohort was derived from two centers within a single country, the observational design limits the generalizability of the established cutoffs to other ethnic populations or different healthcare settings. Future large-scale, multicenter prospective studies are required to externally validate this composite risk score, assess its performance across diverse treatment regimens, and establish definitive clinical thresholds. Nevertheless, our findings provide a pathophysiological rationale for evaluating combined NGAL and FGF-23 testing in the prognostic assessment of patients with MM.

**Conclusions.** In conclusion, the combined assessment of serum NGAL and FGF-23 serves as a potential prognostic marker for overall survival in patients with MM. By capturing aspects of both tubular injury and bone-mineral dysregulation, this exploratory composite score provides additional prognostic insight beyond standard eGFR evaluations. However, due to the small cohort size and critically low number of events (n=12), our results are strictly hypothesis-generating and should not be interpreted as a confirmed predictive model. These exploratory findings provide a strong pathophysiological rationale, but future large-scale, multicenter prospective studies are strictly required before any routine clinical application or formal risk stratification can be recommended.

**Ethics statement.** The study protocol and the informed consent form were reviewed and approved by the Ethics Committee of the Danylo Halytsky Lviv National Medical University (Protocol No. 11, dated November 17, 2025). Written informed consent was obtained from all participants prior to their inclusion in the study.

**Conflict of interest statement.** The authors have no conflicts of interest to declare.

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**Author contributions.**

***Halyna Savuliak:*** conceptualization, investigation, writing – original draft;

***Vladyslav Bardash:*** conceptualization, methodology, software, formal analysis, data curation, writing – original draft, visualization;

***Tetiana Maksymets:*** methodology, investigation, writing – review & editing;

***Halyna Kovalchuk:*** validation, investigation, writing – review & editing;

***Nataliia Karpyshyn:*** validation, data curation, writing – review & editing;

***Yevhen Skliarov:*** validation. Resources. writing – review & editing, supervision.

All authors have read and agreed to the published version of the manuscript.

**Data availability statement.** Due to strict patient privacy regulations and restrictions imposed by the local Ethics Committee, the clinical dataset generated and analyzed during the current study is not publicly available. However, the anonymized data that support the findings of this study are available from the corresponding author upon reasonable request, subject to ethical approval and a formal data-sharing agreement. The complete analytical pipeline and R scripts used for the statistical analysis are fully open-source and publicly available on GitHub at https://github.com/NefroStat/mm-ngal-fgf23-score. A persistent, citable archive of the code corresponding to this manuscript is available on Zenodo at https://doi.org/10.5281/zenodo.19665490

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