Ukrainian Journal of Nephrology and Dialysis
Scientific and Practical, Medical Journal

Founder:
- National Kidney Foundation of Ukraine

ISSN 2304-0238;
eISSN 2616-7352

Journal homepage: https://ukrjnd.com.ua

Research article

doi: 10.31450/ukrjnd.3(87).2025.04

Natalia Stepanova, Svitlana Fomina, Mykola Kolesnyk

Magnesium status and clinical outcomes in kidney transplant recipients: Systematic review and meta-analysis

State Institution "O.O. Shalimov National Scientific Center of Surgery and Transplantology of the National Academy of Medical Science of Ukraine," Kyiv, Ukraine

Citation: Stepanova N, Fomina S, Kolesnyk M. Magnesium status and clinical outcomes in kidney transplant recipients: Systematic review and meta-analysis. Ukr J Nephrol Dialys. 2025;3(87):34-44. doi: 10.31450/ukrjnd.3(87).2025.04.

Abstract. *Kidney transplant recipients (KTRs) remain at risk for metabolic, cardiovascular, and infectious complications. Magnesium abnormalities are common but their prognostic significance remains unclear.*

Objectives. To systematically review and meta-analyze the association between serum magnesium status and clinical outcomes in KTRs.

Methods. We searched PubMed, Embase, Web of Science, Cochrane Library, and ClinicalTrials.gov (by May 31, 2025). Eligible studies were observational cohorts in adult KTRs reporting outcomes by magnesium categories. The primary outcome was all-cause mortality; secondary outcomes were cardiovascular events, graft outcomes, and infections. Data were synthesized using random-effects meta-analysis where ≥3 studies were available, complemented by Bayesian analysis. Risk of bias was assessed with the Newcastle–Ottawa Scale (NOS), and certainty of evidence was graded using GRADE. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO, ID: CRD420251055485).

Results. Eight studies (n=7,026 KTRs) met the inclusion criteria. Five studies assessed all-cause mortality, and four provided adjusted estimates for pooling. Higher/normal magnesium (≥1.7–1.8 mg/dL) vs. lower was associated with increased mortality (HR 1.17, 95% CI 1.06–1.29; I^2=59.5%). Sensitivity analysis excluding one null study yielded HR 1.18 (95% CI 1.03–1.34). Bayesian modeling produced consistent but uncertain estimates (posterior HR 1.22, 95% CrI 0.94–1.68; BF_{10}=0.88). Evidence for cardiovascular, graft, and infection outcomes was inconsistent and heterogeneous, precluding pooling. Certainty of evidence was low for the all-cause mortality outcome and very low for secondary outcomes.

Conclusions: Current evidence from a small number of heterogeneous observational studies suggests that higher/normal serum magnesium status may be associated with a modest increase in all-cause mortality among KTRs. However, the certainty of evidence is low, and associations with cardiovascular, graft, and infection outcomes remain inconclusive. Prospective multicenter cohorts and interventional trials are needed to determine whether magnesium status is a causal and modifiable factor and to define the optimal post-transplant magnesium range.

Keywords: *kidney transplantation, magnesium, all-cause mortality, cardiovascular outcomes, graft survival, infections, systematic review, meta-analysis.*

Article history:
Received August 13, 2025
Received in revised form September 03, 2025
Accepted September 04, 2025

Conflict of interest. The authors declare no conflict of interest.

Correspondence should be addressed to Natalia Stepanova: nmstep@ukr.net

УДК: 616.61-089.843:546.46]-036.8

Наталя Степанова, Світлана Фоміна, Микола Колесник

Статус магнію та клінічні наслідки у реципієнтів ниркового трансплантата: систематичний огляд та метааналіз

ДУ «Національний центр хірургії та трансплантології імені О.О. Шалімова НАМН України», Київ, Україна

Резюме. *Реципієнти ниркового трансплантата (РНТ) мають високий ризик метаболічних, серцево-судинних та інфекційних ускладнень. Порушення концентрації магнію сироватки є поширеним явищем, проте його прогностичне значення залишається невизначеним.*

Мета. Систематично оцінити та провести мета-аналіз асоціації між рівнем сироваткового магнію та клінічними результатами у РНТ.

Методи: Пошук літератури виконано у PubMed, Embase, Web of Science, Cochrane Library та ClinicalTrials.gov (до 31 травня 2025 р.). До аналізу включено обсерваційні дослідження за участю дорослих РНТ (≥18 років), в яких оцінювався зв'язок між рівнем магнію в сироватці або плазмі та клінічними наслідками. Первинна кінцева точка – загальна смертність; вторинні – серцево-судинні події, функція трансплантата та інфекції. Для об'єднання результатів ≥3 досліджень застосовано модель випадкових ефектів; додатково проведено баєсівський аналіз. Ризик упередженості оцінювали за шкалою Ньюкасл–Оттави (NOS), достовірність доказів – за системою GRADE. Протокол дослідження зареєстрований у Міжнародному проспективному реєстрі систематичних оглядів (PROSPERO, ID: CRD420251055485).

Результати. Включено 8 досліджень (n=7026 РНТ). П'ять робіт оцінювали смертність, чотири – надали скориговані показники для мета-аналізу. Вищий/нормальний рівень магнію (≥1,7–1,8 мг/дл) порівняно з нижчим асоціювався з підвищеним ризиком смерті (HR 1,17; 95% CI 1,06–1,29; I^2=59,5%). Аналіз чутливості, з виключенням одного дослідження без статистично значущої асоціації, продемонстрував HR 1,18 (95% CI 1,03–1,34). Баєсівська модель мета-аналізу підтвердила напрямок зв'язку, але з широкими довірчими інтервалами (HR 1,22; 95% CrI 0,94–1,68; BF_{10}=0,88). Дані щодо серцево-судинних подій, функції трансплантата й інфекційних ускладнень були суперечливими та гетерогенними, що унеможливило мета-аналіз. Достовірність доказів оцінена як низька для загальної смертності та дуже низька для вторинних кінцевих точок.

Ключові слова: *трансплантація нирки, магній, смертність від усіх причин, серцево-судинні наслідки, виживання трансплантата, інфекції, систематичний огляд, метааналіз.*

Introduction. Kidney transplantation is a life-saving treatment for patients with end-stage kidney disease (ESKD), offering superior survival and improved quality of life compared to long-term dialysis [**1–3**]. Despite advances in surgical technique and immunosuppressive management, kidney transplant recipients (KTRs) remain at risk for a range of metabolic, cardiovascular, and immunological complications that can compromise graft function and patient survival [**3, 4**].

Among these complications, disturbances in magnesium homeostasis are increasingly recognized as clinically relevant [**5, 6**]. Magnesium is a vital intracellular cation that plays key roles in numerous physiological processes, including cardiovascular regulation, immune function, glucose metabolism, neuromuscular transmission, and renal physiology [**7**]. In the non-transplant chronic kidney disease (CKD) population, higher serum magnesium levels have been associated with protective effects, including reduced vascular calcification and lower cardiovascular risk [**8, 9**]. However, the significance of magnesium status in KTRs is less clear, as magnesium metabolism is altered by both the transplanted kidney and immunosuppressive therapies [**10**].

Hypomagnesemia is the most frequently reported electrolyte abnormality in KTRs, affecting 30–50% of patients [**5, 6, 10**]. Its underlying causes include altered renal magnesium handling due to impaired graft function and the use of calcineurin inhibitors (CNIs), which reduce tubular magnesium reabsorption [**5, 8, 10**].

Emerging evidence suggests that abnormalities in serum magnesium levels may contribute to adverse outcomes in KTRs. Hypomagnesemia has been associated with an increased risk of new-onset diabetes after transplantation (NODAT) [**11**], heightened susceptibility to infections [**12**], and potential endothelial dysfunction [**13**]. However, despite these recognized risks, the current literature on magnesium status and clinical outcomes in KTRs has reported paradoxical or protective associations. One observational study has reported a U-shaped relationship between serum magnesium levels and mortality [**14**], while others have shown linear or

Natalia Stepanova
nmstep@ukr.net

even inverse associations [15–17]. These discrepancies, coupled with heterogeneity in exposure definitions and outcome measures, have prevented clear clinical recommendations.

Therefore, this systematic review and meta-analysis aimed to synthesize available evidence to clarify the relationship between post-transplant magnesium status and key clinical outcomes, such as all-cause mortality, MACE or cardiovascular mortality, graft function decline or loss, and infection risk in adult KTRs.

Materials and Methods. This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO, ID: CRD420251055485).

Eligibility criteria. We used the PICOTS framework to define inclusion and exclusion criteria:

- Population: adult KTRs (≥18 years). Exclusions: pediatric recipients, multiorgan transplants, or studies not reporting kidney-only outcomes.
- Intervention/Exposure: serum or plasma magnesium concentrations, categorized as "higher or normal magnesium" vs. "lower" according to study-specific thresholds.
  - Higher or normal magnesium was most often defined as ≥1.7–1.8 mg/dL, the upper quartile, or the highest exposure category. Where explicitly reported, true hypermagnesemia (>2.4 mg/dL, >1.0 mmol/L) was noted separately.
  - Lower magnesium was generally defined as <1.7 mg/dL (<0.70 mmol/L) or study-specific "low" categories.
- Comparator: because exposure definitions varied, we harmonized study contrasts into (i) higher/normal magnesium vs lower and (ii) hypomagnesemia vs higher-normal, analyzing them separately.
- Outcomes:
  - Primary outcome: All-cause mortality.
  - Secondary outcomes:
    1. Cardiovascular outcomes – major adverse cardiovascular events (MACE) or cardiovascular mortality.
    2. Graft outcomes – graft loss, death with functioning graft, estimated GFR <60 mL/min/1.73 m^2, or accelerated renal function decline.
    3. Infection outcomes – bacterial (urinary tract infections [UTI]) or viral (CMV, EBV, BK) infections, or infection-related mortality.
- Timing: magnesium concentrations measured at any time post_-transplantation, with follow-up ranging from 1 to 7 years.
- Study design: observational studies (prospective or retrospective cohort, case-control). Randomized controlled trials were excluded, as none reported relevant associations.

Information sources and search strategy. A comprehensive search was performed across PubMed, Embase, Web of Science, Cochrane Library, and ClinicalTrials.gov from inception to May 2025. No language restrictions were applied. Non-English studies were screened and, when eligible, translated. Search terms combined controlled vocabulary (e.g., MeSH) and free-text keywords related to "magnesium," "kidney transplantation," "mortality," "graft function," "cardiovascular outcomes," and "infection." The full search strategy is provided in Supplementary Table S1.

Study Selection. Two reviewers (NS, SF) independently screened titles and abstracts, followed by a full-text review of potentially eligible studies. Disagreements were resolved by consensus or third-party adjudication (MK). Search results were imported into EndNote X9 for deduplication.

Data extraction and management. The following data were collected:

- Study characteristics (author, year, country, design, sample size, follow-up).
- Participant characteristics (age, sex, immunosuppression regimen, donor type).
- Exposure assessment (magnesium cutoff, categories, timing of measurement, analytic approach).
- Outcomes (mortality, cardiovascular, graft, infection).
- Effect estimates (hazard ratios (HRs), with 95% confidence interval (CI)) and number of events.
- Covariates adjusted in multivariable models.

Where effect measures were not directly reported, we derived ORs or HRs using raw event data where available. No assumptions were made to impute missing data.

Risk of bias assessment. Risk of bias was evaluated using the Newcastle-Ottawa Scale (NOS) for observational studies, covering domains of selection, comparability, and outcome ascertainment. Studies scoring ≥7 were considered low risk; those scoring <6 were considered high risk. No eligible RCTs were identified.

Data synthesis and statistical analysis. We synthesized data separately by outcome domain. When ≥3 studies reported comparable effect estimates (all-cause mortality for the higher/normal magnesium vs lower contrast), we conducted quantitative meta-analysis. When ≤2 studies were available, we synthesized findings qualitatively in the narrative review without statistical pooling.

Effect measures. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were the preferred effect measure. We extracted the most fully adjusted HRs reported in each study. Log-transformed HRs were pooled in meta-analyses. Where HRs were unavailable, odds ratios (ORs) were considered separately.

For quantitative pooling, we used a random-effects model with the Paule–Mandel estimator for between-study variance (τ^2). Because of the small number of studies, we applied the Hartung–Knapp–Sidik–Jonk-

man (HKSJ) adjustment and used a t-test with k−1 degrees of freedom to test for overall effects.

Between-study heterogeneity was summarized using Cochran's Q ($p < 0.10$ indicating statistical significance) and the I^2 statistic, interpreted as low (<25%), moderate (25–50%), or substantial (>50%). Heterogeneity was not calculated when fewer than three studies were available.

Sensitivity analyses. We performed leave-one-out analyses to assess individual study influence. Predefined subgroup and sensitivity analyses included: exclusion of lower-quality studies (NOS <7), exclusion of studies lacking covariate adjustment, comparison of continuous vs categorical magnesium exposures, and harmonization to common cutoffs (<1.7 mg/dL vs ≥1.7–1.8 mg/dL).

Publication bias. We did not evaluate small-study effects or conduct meta-regression because <10 studies were available, consistent with PRISMA recommendations.

Subgroup and sensitivity analyses. We prespecified subgroups by timing of magnesium measurement (early vs late post-transplant) and predominant calcineurin inhibitor (tacrolimus vs cyclosporine). However, these could not be performed because each subgroup was represented by only a single study, precluding meaningful comparison. Differences in exposure definitions (categorical vs continuous; varying cutoffs) were instead considered qualitatively in the narrative synthesis.

To test the robustness of findings for all-cause mortality (high/normal magnesium vs lower), we excluded the study with fair quality (NOS <7), and compared results across harmonized magnesium cutoffs (<1.7 mg/dL vs ≥1.7–1.8 mg/dL).

Bayesian analysis. To complement frequentist analyses and account for small-sample uncertainty, we conducted a Bayesian random-effects meta-analysis for all-cause mortality, specifying weakly informative priors. We report posterior means, 95% credible intervals, and Bayes factors.

Certainty of evidence. Certainty of evidence was assessed using the GRADE framework, considering risk of bias (based on NOS), consistency, directness, precision, and publication bias. As all included studies were observational, evidence for each outcome started at low certainty by default. Each outcome was rated as high, moderate, low, or very low certainty.

Results. Study selection. The database search identified 1,248 records. After deduplication, 978 records were screened; 68 full texts were assessed, and 8 studies met the inclusion criteria. Three studies contributed adjusted estimates suitable for quantitative synthesis of all-cause mortality; other outcomes were summarized narratively due to heterogeneity of effect measures/definitions. PRISMA flow shown in Fig. 1.

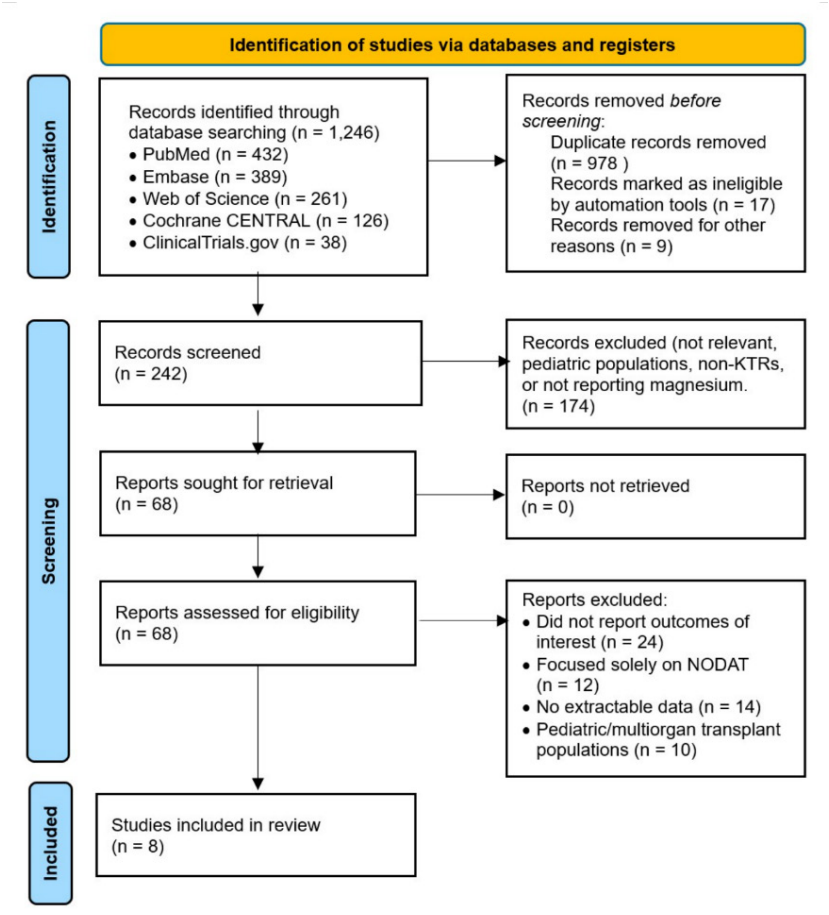

Fig. 1. Flow diagram of the study selection process.

Study characteristics. Eight single-center retrospective cohort studies published between 2005 and 2025 were included, encompassing 7,026 KTRs (per-study sample size range 60–3,680) [12, 14, 16–21]. The patients' age was reported in six studies, with the median values of 49.8 (47.9-52.0) years. The median proportion of male participants among the six studies reporting sex distribution was 56% (range 34.7%–68.6%). Follow-up durations ranged from approximately 3.0 to 6.7 years, with a median of 5.0 years across the eight studies. Maintenance immunosuppression was predominantly calcineurin-inhibitor-based. Serum magnesium was measured post-transplant in all studies; five used a 1.7 mg/dL threshold, one analyzed quartiles, one used three categories (≤1.5, 1.5–1.8, >1.8 mg/dL), and one applied a 2.0 mg/dL threshold at biopsy. Two single-centre Israeli cohorts each reported n=726 in overlapping eras; sample overlap is possible but cannot be confirmed from the available reports. All included studies were of moderate to good quality, with NOS scores ranging from 6 to 9 (Supplementary Tables S2). Detailed study characteristics, including NOS scores, are presented in Table 1.

Outcomes reported across studies. All-cause mortality was reported by five studies, of which three provided adjusted HRs amenable to pooling. Cardiovascular outcomes (MACE or cardiovascular death) were reported by two studies. Graft outcomes (graft loss, death with functioning graft, eGFR <60 mL/min/1.73 m^2, or eGFR slope) were reported by three studies. Infection outcomes (urinary tract infection, viral infections, or infection-related mortality) were reported by three studies. Although graft and infection outcomes each appeared in three reports, definitions and effect measures were heterogeneous (e.g., continuous eGFR slope vs. odds of eGFR <60; any viral infection vs. UTI), precluding statistical pooling.

All-cause mortality. Five studies evaluated all-cause mortality according to magnesium status in KTRs. Four reported adjusted HRs were included in the quantitative synthesis, comprising 5,230 patients and 838 deaths. Three of the four studies reported higher mortality in patients with relatively higher magnesium categories compared to lower categories [14, 16, 18], whereas one study [21] found no significant difference between groups. To allow harmonization across studies, the exposure contrast was aligned as higher/normal vs. lower magnesium.

The random-effects meta-analysis demonstrated that higher/normal magnesium status was associated with a 17% increase in all-cause mortality (HR 1.17, 95% CI 1.06–1.29; p = 0.013) with moderate heterogeneity (I^2 = 59.5%) (Fig. 2).

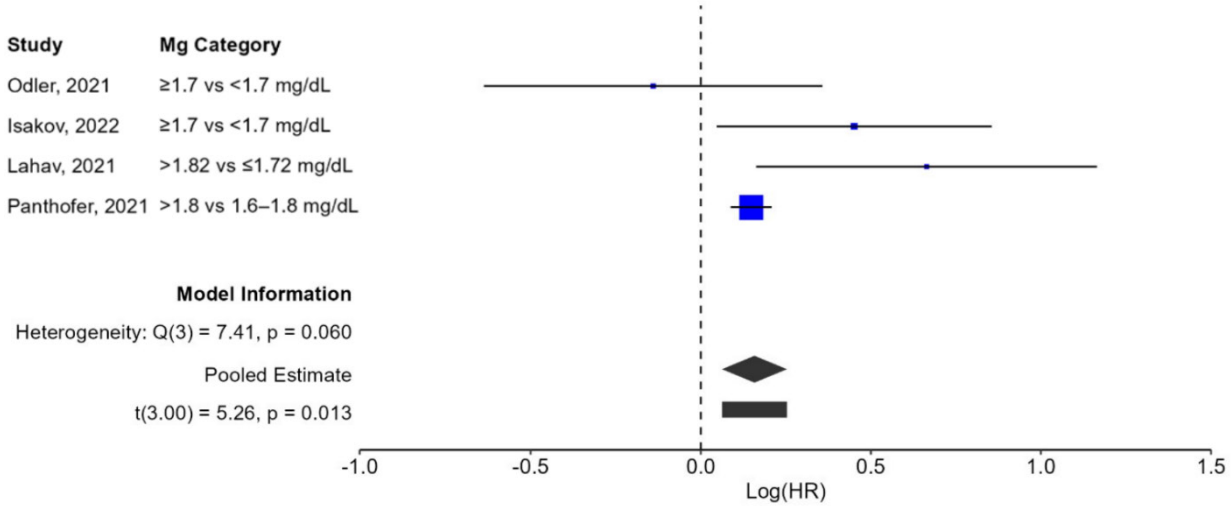

Fig. 2. Forest plot of the association between magnesium status and all-cause mortality in KTRs. Pooled estimates are based on a random-effects meta-analysis of four studies (Panthofer 2021, Lahav 2021, Isakov 2022, Odler 2021), harmonized as higher/normal vs. lower magnesium categories.

Clinically, this corresponds to nearly one additional death for every six deaths otherwise expected in recipients with lower magnesium status.

To test the robustness of findings, we repeated the analysis excluding the study by Odler et al (the only study reporting no association, and with shorter follow-up compared to the others). This sensitivity analysis of three studies (Panthofer, Lahav, Isakov) showed that higher magnesium was associated with an 18% increase in mortality risk (HR 1.18, 95% CI 1.03–1.34; p = 0.033), although heterogeneity remained statistically significant (p = 0.049).

Table 1

Characteristics of the included studies

Study	Country and setting	Design	Sample size	Population characteristics	Follow-up duration	Magnesium measurement	Outcomes assessed	Findings	Confounders Adjusted	Event Numbers	NOS score (AHRQ standards)
Panthofer et al, 2021 [14]	USA, single-center	Retrospective cohort	3,680 (Mg ≤1.5 mg/dL: 347, 1.5–1.8 mg/dL: 1,433, >1.8 mg/dL: 1,547)	Mean age 49.5 years, 59.9% male, CNI-based immunosuppression (65.8% tacrolimus, 25.8% cyclosporine)	5.1 (2.3-5.8) years	Serum Mg, categorized as ≤1.5 mg/dL, 1.5–1.8 mg/dL, >1.8 mg/dL, measured outpatient post-6 months	All-cause mortality, CVD-related mortality, infection-related mortality	All-cause mortality: U-shaped association; Mg ≤1.5 mg/dL HR 1.17 (95% CI 1.07–1.28), Mg >1.8 mg/dL HR 1.16 (95% CI 1.09–1.23); CVD-related mortality: Mg ≤1.5 mg/dL HR 1.31 (95% CI 1.03–1.68), Mg >1.8 mg/dL non-significant; Infection-related mortality: Mg ≤1.5 mg/dL HR 1.28 (95% CI 1.09–1.51), Mg >1.8 mg/dL non-significant	Age, sex, race, cause of ESKD, BMI, prior transplant, ischemic heart disease, arrhythmias, heart failure, living donor, induction immunosuppression, maintenance immunosuppression, transplant year, eGFR, CNI levels	All-cause mortality: 657 deaths (Mg ≤1.5 mg/dL: 73, 1.5–1.8 mg/dL: 211, >1.8 mg/dL: 373); CVD-related mortality: 129 deaths (Mg ≤1.5 mg/dL: 9, 1.5–1.8 mg/dL: 42, >1.8 mg/dL: 78); Infection-related mortality: 131 deaths (Mg ≤1.5 mg/dL: 16, 1.5–1.8 mg/dL: 39, >1.8 mg/dL: 76)	9 (Good)
Lahav, 2021 [18]	Israel, single-center	Retrospective cohort	498 (Q1: <1.62; Q2: 1.62–1.77; Q3: 1.77–1.82; Q4: >1.82)	Median age 47.9 years, 34.7% male, CNI use common	5.26 (4.21-7.37) years	Serum Mg as TWA quartiles	All-cause mortality, MACE (CVD death, ACS, HF hospitalization)	Q3 vs Q1: HR 2.37 (1.14–3.91) for all-cause mortality; Q4 vs Q1: HR 1.88 (1.14–3.11) for death-censored CVD endpoint	Age, sex, BMI, IHD before transplantation, serum calcium, albumin, LDL, treatment with PPI, beta-blockers, ACEi	Deaths: 47; MACE: 98; Graft loss: 24 (by quartile not shown)	9 (Good)
Isakov, 2022 [16]	Israel, single-center	Retrospective cohort	726 (Mg <1.7 mg/dL: 407, Mg ≥1.7 mg/dL: 319)	Mean age 50.7 ± 13.6 years, 55.7% male	Mean 50.1 months (median 76 months for low Mg, 47 months for high Mg)	Median serum Mg from 1 month to 1 year post-transplant, categorized as <1.7 mg/dL or ≥1.7 mg/dL; also analyzed as continuous variable (per 0.1 mg/dL increase)	Mortality, graft loss, death with functioning graft	Higher Mg (≥1.7 mg/dL) is associated with increased mortality (HR 1.57, 95% CI 1.04–2.38). Per 0.1 mg/dL increase in Mg, risk of death increased by 14% (HR 1.14, 95% CI 1.04–1.23), graft loss or death by 11% (HR 1.11, 95% CI 1.04–1.19), and death with functioning graft by 12% (HR 1.12, 95% CI 1.02–1.23).	Age, sex, race, transplant type, induction therapy, diabetes, Mg coefficient of variation, median CNI trough levels, presence of SGF, baseline eGFR at 3 months	Graft loss: 84 events (low Mg: 49, high Mg: 35); Deaths: 119 events (low Mg: 65, high Mg: 54);	8 (Good)

Продовження таблиці 1

Study	Country and setting	Design	Sample size	Population characteristics	Follow-up duration	Magnesium measurement	Outcomes assessed	Findings	Confounders Adjusted	Event Numbers	NOS score (AHRQ standards)
Odler, 2021 [21]	Austria, single-center	Retrospective cohort	376 (Mg <1.7 mg/dL: 229, Mg ≥1.7 mg/dL: 147)	Median age 52 (41.0-62.0) years, 68.6% male, CNI use	Up to 2 years (primary outcomes within 1 year), all-cause mortality 6.7 (4.9-9.3) years	Serum Mg, cutoff 1.7 mg/dL, measured post-Tx	UTIs, viral infections (CMV, EBV, polyoma), hospitalization due to infections, all-cause mortality	Mg <1.7 mg/dL significantly associated with UTI risk (OR 1.73, 95% CI 1.04–2.86), viral infection (OR 2.05, 95% CI 1.23–3.41), Mortality: HR 1.15, 95% CI 0.70–1.89	Age, sex, CNI, GFR, albumin, diabetes	Mortality: ~50 deaths; Infection: ~40 events	6 (Good)
Hod, 2020 [17]	Israel, single-center	Retrospective cohort	726 (High Mg ≥1.7: NR, Low Mg <1.7: NR)	Median age NR, CNI use common, 2000–2013	Up to 5 years	Median serum Mg, cutoff 1.7 mg/dL, measured 1–12 months post-Tx	GFR at 3/5 years, GFR <60 mL/min	Per 0.1 mg/dL Mg increase: GFR 1.1 mL/min at 3 years (p<0.01), 1.5 mL/min at 5 years; GFR <60 mL/min: OR ~2.0 (high vs. low Mg)	Age, sex, CNI, baseline GFR	GFR <60 mL/min: NR	8 (Good)
Van Laecke, 2016 [19]	Belgium,single-center	Retrospective cohort	873 (High Mg: NR, Low Mg: NR)	Median age 50 years, 57% male, CNI-based immunosuppression	Up to 5 years	Serum Mg, cutoff 1.7 mg/dL, measured post-Tx	Mortality, infection	Mortality: HR 1.25 (95% CI 1.03–1.52); Infection: No significant association	Age, sex, CNI, diabetes, GFR	Mortality: ~100 deaths; Infection: NR	6 (Good)
Ratiu, 2025 [12]	Romania,single-center	Retrospective cohort	87 (High Mg: NR, Low Mg: NR)	Median age 48 years, 54% male, CNI use	Up to 3 years	Serum Mg, cutoff 1.7 mg/dL, measured post-Tx	Infection	Infection: OR 0.62 (95% CI 0.20–1.92, p=0.394)	Age, sex, CNI, limited adjustments	Infection: ~10 events	5 (Fair)
Holzmacher, 2005 [20]	USA, single-center	Retrospective cohort	60 (Low Mg: 29, Normal Mg: 31)	Cyclosporin nephrotoxicity cohort, median age NR, CNI-based	Up to 5 years	Serum Mg at biopsy, cutoff 2 mg/dL (low 1.8, normal 2.2 mg/dL)	Graft loss, creatinine clearance slope	Low Mg: Faster decline (8.9±3.5 vs. 1±2.7 mL/min/year, p=0.02); Reduced graft survival (p=0.02)	CNI, limited adjustments	Graft loss: NR	5 (Fair)

Abbreviations: Mg, magnesium; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular events; CVD, cardiovascular disease; ACS, acute coronary syndrome; HF, heart failure; TWA, time-weighted average; HR, hazard ratio; OR, odds ratio; CI, confidence interval; UTI, urinary tract infection; CMV, cytomegalovirus; EBV, Epstein–Barr virus; polyoma, polyomavirus (BK virus); LDL, low-density lipoprotein; PPI, proton-pump inhibitor; ACEi, angiotensin-converting enzyme inhibitor; IHD, ischemic heart disease; ESKD, end-stage kidney disease; BMI, body mass index; SGF, slow graft function; Tx, transplant; post-Tx, post-transplant; NOS, Newcastle–Ottawa Scale; AHRQ, Agency for Healthcare Research and Quality; NR, not reported.

The Bayesian random-effects meta-analysis produced a posterior mean HR of 1.22 (95% CrI 0.94–1.68), consistent with the frequentist estimate but with wider uncertainty. The Bayes factor (BF_{10} = 0.88) indicated only weak evidence in favor of an association (**Supplementary Table S3 and Fig. S1**).

Taken together, these analyses suggest that KTRs with relatively higher magnesium categories experience a 15–20% higher risk of death compared with those in lower categories. The effect persisted across sensitivity analyses and was consistent across analytic frameworks. However, statistical heterogeneity and wide Bayesian credible intervals limit certainty. Accordingly, the overall certainty of evidence for all-cause mortality was rated low.

Cardiovascular outcomes. Only two studies reported the association between serum magnesium level and cardiovascular outcomes. Panthofer et al. observed that recipients with lower magnesium (≤1.5 mg/dL) had a 31% higher risk of cardiovascular mortality (HR 1.31, 95% CI 1.03–1.68), while higher/normal magnesium levels (>1.8 mg/dL) were not associated with cardiovascular death [**14**]. In contrast, Lahav reported that recipients in the highest magnesium quartile had an 88% increased risk of MACE compared to those in the lowest quartile (HR 1.88, 95% CI 1.14–3.11) [**18**]. Given the small number of studies and differing outcome definitions (MACE vs. cardiovascular mortality), meta-analysis was not performed. The available evidence, therefore, suggests that both lower and relatively higher magnesium status may contribute to adverse cardiovascular outcomes, but the direction of risk differs by cohort. Certainty of evidence was rated very low due to inconsistency, indirectness, and imprecision.

Graft outcomes. Three studies assessed graft function and loss, but outcome definitions were heterogeneous. Isakov et al. found that higher magnesium was associated with an 11% increased risk of graft loss or death per 0.1 mg/dL increase (HR 1.11, 95% CI 1.04–1.19) [**16**]. Hod et al. demonstrated that higher magnesium was associated with a more rapid decline in kidney function, with each 0.1 mg/dL increase linked to a 1.1–1.5 mL/min reduction in eGFR at 3–5 years ($p < 0.01$) [**17**]. Holzmacher et al. showed that lower magnesium at biopsy was associated with faster creatinine clearance decline (-8.9 ± 3.5 vs. -1.0 ± 2.7 mL/min/year, $p = 0.02$) and shorter graft survival [**20**]. Because of differing metrics (continuous eGFR decline vs. time-to-event graft loss vs. biopsy-defined function), results could not be pooled. Taken together, these studies suggest that deviations in magnesium status, whether higher or lower, may adversely affect graft function. Certainty of evidence was rated very low, reflecting heterogeneity and limited sample size.

Infection outcomes. Three studies investigated the association between serum magnesium status and infection risk in kidney transplant recipients. Odler et al. demonstrated that low magnesium (<1.7 mg/dL) was associated with a 73% increased risk of UTI (OR 1.73, 95% CI 1.04–2.86) and a two-fold higher risk of viral infections, including CMV, EBV, and polyomavirus (OR 2.05, 95% CI 1.23–3.41) [**21**]. Panthofer et al. found that low magnesium was associated with a 28% higher risk of infection-related mortality (HR 1.28, 95% CI 1.09–1.51) [**14**]. Ratiu et al. revealed no significant association between magnesium status and infection risk (OR 0.62, 95% CI 0.20–1.92) [**12**]. Due to heterogeneity in outcomes (UTI, viral infections, infection-related death), quantitative synthesis was not feasible. Overall, the evidence suggests that lower magnesium may predispose to infection, but results remain inconsistent. Certainty of evidence was graded very low, downgraded for inconsistency and imprecision.

A consolidated overview of effect estimates and certainty ratings is presented in Supplementary Table S4. Formal tests for publication bias (Egger's and Begg's) did not suggest asymmetry, although these analyses are underpowered with fewer than ten studies, and publication bias cannot be excluded.

Discussion. This systematic review and meta-analysis synthesized available evidence on the association between serum magnesium status and clinical outcomes in KTRs. Five studies reported on all-cause mortality, of which four contributed adjusted hazard ratios suitable for pooling. The main analysis demonstrated that relatively higher magnesium status was associated with a 17% increase in all-cause mortality compared with lower categories, with consistent findings in sensitivity analyses. Bayesian modelling produced similar estimates, although uncertainty was substantial. Evidence for secondary outcomes (cardiovascular events, graft outcomes, and infections) was limited and heterogeneous, precluding meta-analysis. Overall, the certainty of evidence was rated low for all-cause mortality and very low for other outcomes.

Our findings add to a growing but inconsistent body of literature on magnesium in the post-transplant setting. In non-transplant CKD, higher serum magnesium has generally been associated with favorable outcomes, including lower vascular calcification and reduced cardiovascular risk [**22–24**]. By contrast, in KTRs, the direction of association appears reversed: in three of four cohorts included in our meta-analysis, recipients with relatively higher magnesium status had increased mortality [**14, 16, 18**].

This apparent paradox may be explained by transplant-specific physiology. Calcineurin inhibitor therapy typically induces hypomagnesemia [**10, 25**]; therefore, recipients with higher magnesium concentrations represent an atypical group in whom impaired tubular excretion or early graft dysfunction may predominate. In this context, elevated magnesium may act as a surrogate marker of declining graft function and CKD-mineral bone disorder activity rather than a direct toxic exposure [**14, 18**]. Clinical data outside transplantation also show that hypermagnesemia predicts short-term mortality in hospitalized patients [**26**], supporting the view that higher magnesium often reflects underlying

systemic illness or reduced renal clearance. This divergence reflects transplant-specific factors, such as immunosuppressive therapy, altered tubular handling of magnesium, or competing risks of infection and metabolic complications [18, 21].

The U-shaped relationship observed by Panthofer et al. suggests that both lower and higher magnesium levels may be harmful, a pattern also seen in population-based cohorts outside transplantation [14, 24]. This raises the possibility that an "optimal" magnesium range exists for KTRs, narrower than the conventional laboratory reference interval.

Several biological mechanisms may underlie these associations. While higher magnesium may indicate impaired renal clearance and mineral–bone axis dysregulation, low magnesium has been implicated in immune dysregulation, endothelial dysfunction, and increased susceptibility to infection, potentially contributing to graft injury and adverse [6, 12, 18, 27]. In addition, disturbances in magnesium homeostasis may influence broader metabolic pathways. Hypomagnesemia has been linked to impaired insulin signaling and an increased risk of NODAT [28, 29]. Although NODAT was excluded from our present analysis because a separate systematic review has addressed this outcome [11], it remains a relevant mechanism linking low magnesium to adverse prognosis. Furthermore, low magnesium may contribute to disordered calcium–oxalate handling and other metabolic derangements, with potential implications for nephrolithiasis, tubular toxicity, and vascular calcification [30–32]. These possible metabolic effects, while not captured by the included studies, warrant further investigation.

From a clinical standpoint, these results suggest that routine monitoring of serum magnesium in KTRs is important not only to detect hypomagnesemia, which is common under calcineurin inhibitor therapy [25, 27], but also to identify persistently higher values that may carry prognostic significance. The observed 15–20% increase in mortality risk associated with relatively higher magnesium status is clinically relevant and may warrant closer evaluation of patients with upward deviations from the lower-normal range.

However, it remains unclear whether magnesium status is a modifiable risk factor or a marker of underlying graft or cardiovascular dysfunction. Interventional studies of magnesium supplementation in KTRs have primarily focused on hypomagnesemia and metabolic complications, not mortality or graft survival [6, 13]. Until such trials are available, no evidence-based recommendations can be made regarding magnesium correction beyond standard clinical thresholds.

This review has several strengths, including a comprehensive search strategy without language restrictions, rigorous data extraction, and the use of both frequentist and Bayesian approaches to account for small-sample uncertainty. By harmonizing exposure contrasts as "higher vs. lower magnesium," we were able to pool data across studies with different categorizations.

Nonetheless, important limitations must be acknowledged. All included studies were observational, single-center cohorts, limiting causal inference and generalizability. Heterogeneity in exposure definitions, timing of magnesium measurement, and outcome ascertainment precluded pooling for most endpoints. Potential residual confounding by graft function, immunosuppressive regimen, or nutritional status can also not be excluded. The number of studies contributing to each outcome was small, limiting the power to assess publication bias or dose–response relationships.

Future studies should aim to clarify the optimal range of serum magnesium in KTRs, ideally through large, multicenter prospective cohorts with standardized exposure definitions and long-term follow-up. Randomized controlled trials of magnesium supplementation, stratified by baseline magnesium status and immunosuppressive regimen, are needed to determine whether correction of hypomagnesemia or avoidance of higher levels can improve patient or graft outcomes. Studies integrating biomarkers of tubular function, magnesium transport, and cardiovascular risk may help to disentangle causality from association.

Conclusions. In summary, this systematic review and meta-analysis indicates that KTRs with relatively higher serum magnesium levels (>1.8 mg/dL) may experience an increased risk of all-cause mortality compared with those in lower categories. However, the available studies are few, heterogeneous, and observational in design, and the certainty of evidence remains low. Associations with cardiovascular, graft, and infection outcomes are inconsistent and inconclusive. At present, these findings should be considered hypothesis-generating rather than practice-changing. Further large, prospective studies and interventional trials are required to clarify whether magnesium status represents a causal and modifiable risk factor, and to define the optimal post-transplant magnesium range.

Ethics approval and consent to participate. Not applicable. This study is a systematic review and meta-analysis of previously published data and does not involve direct participation of human subjects or animals.

Supplementary file. Stepanova N, Fomina S, Kolesnyk M. Magnesium status and clinical outcomes in kidney transplant recipients: Systematic review and meta-analysis. Mendeley Data, V2, doi: 10.17632/kxbf6vbg2r.2.

Data availability. All data generated or analyzed in this review are included in this published article and its supplementary files. Additional details are available from the corresponding author on reasonable request.

Competing interests. The authors declare that they have no competing interests.

Funding. This work was carried out within the framework of the research project 'Identification of immunological, inflammatory, and metabolic determinants of kidney graft survival and development of strategies to prolong its function' (State registration number

0124U003704). No external funding was received for this study.

Authors' contributions.

Natalia Stepanova: conceptualization, methodology, literature search, data curation, formal analysis, writing – original draft.

Svitlana Fomina: literature search, data curation, writing – review & editing.

Mykola Kolesnyk: supervision, validation, writing – review & editing.

All authors contributed to the analysis and interpretation of data, approved the final version of the manuscript, and agree to be accountable for all aspects of the work.

References:

1. *Strohmaier S, Wallisch C, Kammer M, Geroldinger A, Heinze G, Oberbauer R, et al.* Survival Benefit of First Single-Organ Deceased Donor Kidney Transplantation Compared With Long-term Dialysis Across Ages in Transplant-Eligible Patients With Kidney Failure. JAMA Netw Open. 2022;5(10):e2234971. doi: 10.1001/jamanetworkopen.2022.34971.
2. *de Boer SE, Knobbe TJ, Kremer D, van Munster BC, Nieuwenhuijs-Moeke GJ, Pol RA, et al.* Kidney Transplantation Improves Health-Related Quality of Life in Older Recipients. Transpl Int. 2024;37:12071. doi: 10.3389/ti.2024.12071.
3. *Khan I, Wani M, Wani I, Rather JI, Bhat MA, Wani MM, et al.* Incidence of complications and outcome in live kidney transplant recipients at 1 year—a single center experience. Egypt J Intern Med. 2025;37:30. doi: 10.1186/s43162-025-00414-z.
4. *Thongprayoon C, Hansrivijit P, Leeaphorn N, Acharya P, Torres-Ortiz A, Kaewput W, et al.* Recent Advances and Clinical Outcomes of Kidney Transplantation. J Clin Med. 2020;9(4):1193. doi: 10.3390/jcm9041193.
5. *Riaza Ortiz C, Fernández Fernández C, Pujol Pujol M, Muñiz Rincón M, Aiffil Meneses AS, Pérez Flores IM, et al.* Prevalence, Risk Factors and Potential Protective Strategies for Hypomagnesemia in Kidney Transplant Recipients. Int J Mol Sci. 2025;26(13):6528. doi: 10.3390/ijms26136528.
6. *Bocchi F, Schietzel S, Huynh-Do U, Vogt B, Sidler D.* Magnesium matters: unveiling hidden risks in kidney transplant patients through total and ionized magnesium profiling. Front Nephrol. 2024;4:1385447. doi: 10.3389/fneph.2024.1385447.
7. *Van Laecke S.* An Update on Hypomagnesemia and Hypermagnesemia. Kidney and Dialysis. 2024;4(1):1-14. doi: 10.3390/kidneydial4010001.
8. *Díaz-Tocados JM, Lloret MJ, Domínguez-Coral JD, Tinoco Aranda AP, Fayos de Arizón L, Massó Jiménez E, et al.* Magnesium Balance in Chronic Kidney Disease: Mineral Metabolism, Immunosuppressive Therapies and Sodium-Glucose Cotransporter 2 Inhibitors. Int J Mol Sci. 2025;26(12):5657. doi: 10.3390/ijms26125657.
9. *Correa S, Guerra-Torres XE, Waikar SS, Mc Causland FR.* Serum Magnesium, Blood Pressure, and Risk of Hypertension and Chronic Kidney Disease Progression in the CRIC Study. Hypertension. 2021;78(6):1771-1780. doi: 10.1161/HYPERTENSIONAHA.121.17694.
10. *Elsayed MM, Elgohary IE, Abouelnaga SF, Elian FAS, Zeid MM.* Hypomagnesemia and its association with calcineurin inhibitor use in renal transplant recipients. J Egyptian So Nephrol Transplant. 2023;23(3):106-110. doi: 10.4103/jesnt.jesnt_30_22.
11. *Cheungpasitporn W, Thongprayoon C, Harindhanavudhi T, Edmonds PJ, Erickson SB.* Hypomagnesemia linked to new-onset diabetes mellitus after kidney transplantation: A systematic review and meta-analysis. Endocr Res. 2016;41(2):142-7. doi: 10.3109/07435800.2015.1094088.
12. *Ratiu IA, Moisa C, Marc L, Olariu N, Ratiu CA, Bako GC, et al.* The Impact of Hypomagnesemia on the Long-Term Evolution After Kidney Transplantation. Nutrients. 2024;17(1):50. doi: 10.3390/nu17010050.
13. *Garnier AS, Duveau A, Planchais M, Subra JF, Sayegh J, Augusto JF.* Serum Magnesium after Kidney Transplantation: A Systematic Review. Nutrients. 2018;10(6):729. doi: 10.3390/nu10060729.
14. *Panthofer AM, Lyu B, Astor BC, Singh T, Aziz F, Mandelbrot D, et al.* Post-kidney transplant serum magnesium exhibits a U-shaped association with subsequent mortality: an observational cohort study. Transpl Int. 2021;34(10):1853-1861. doi: 10.1111/tri.13932.
15. *Van Laecke S, Nagler EV, Verbeke F, Van Biesen W, Vanholder R.* Hypomagnesemia and the risk of death and GFR decline in chronic kidney disease. Am J Med. 2013;126(9):825-31. doi: 10.1016/j.amjmed.2013.02.036.
16. *Isakov O, Patibandla BK, Christopher KB, Chandraker A, Hod T.* Impact of Post-Transplantation Hypomagnesemia on Long-Term Graft and Patient Survival after Transplantation. Kidney Blood Press Res. 2022;47(5):341-353. doi: 10.1159/000522233.

17. *Hod T, Isakov O, Patibandla BK, Christopher KB, Hershkoviz R, Schwartz IF, Chandraker A.* Posttransplantation Hypomagnesemia as a Predictor of Better Graft Function after Transplantation. Kidney Blood Press Res. 2020;45(6):982-995. doi: 10.1159/000510797.
18. *Lahav I, Steinmetz T, Molcho M, Lev N, Agur T, Nesher E, et al.* The Association Between Exposure to Low Magnesium Blood Levels After Renal Transplantation and Cardiovascular Morbidity and Mortality. Front Med (Lausanne). 2021;8:690273. doi: 10.3389/fmed.2021.690273.
19. *Van Laecke S, Vermeiren P, Nagler EV, Caluwe R, De Wilde M, Van der Vennet M, et al.* Magnesium and infection risk after kidney transplantation: An observational cohort study. J Infect. 2016;73(1):8-17. doi: 10.1016/j.jinf.2016.04.007.
20. *Holzmacher R, Kendziorski C, Michael Hofman R, Jaffery J, Becker B, Djamali A.* Low serum magnesium is associated with decreased graft survival in patients with chronic cyclosporin nephrotoxicity. Nephrol Dial Transplant. 2005;20(7):1456-62. doi: 10.1093/ndt/gfh831.
21. *Odler B, Deak AT, Pregartner G, Riedl R, Bozic J, Trummer C, et al.* Hypomagnesemia Is a Risk Factor for Infections after Kidney Transplantation: A Retrospective Cohort Analysis. Nutrients. 2021;13(4):1296. doi: 10.3390/nu13041296.
22. *Hayes W, Boyle S, Carroll A, Bockenhauer D, Marks SD.* Hypomagnesemia and increased risk of new-onset diabetes mellitus after transplantation in pediatric renal transplant recipients. Pediatr Nephrol. 2017;32(5):879-884. doi: 10.1007/s00467-016-3571-6.
23. *Panta R, Regmi S.* Role of Magnesium, Effects of Hypomagnesemia, and Benefits of Magnesium Supplements in Cardiovascular and Chronic Kidney Diseases. Cureus. 2024;16(7):e64404. doi: 10.7759/cureus.64404.
24. *Negrea L, DeLozier SJ, Janes JL, Rahman M, Dobre M.* Serum Magnesium and Cardiovascular Outcomes and Mortality in CKD: The Chronic Renal Insufficiency Cohort (CRIC). Kidney Med. 2021;3(2):183-192.e1. doi: 10.1016/j.xkme.2020.10.010.
25. *Stefanelli LF, Alessi M, Bertoldi G, Rossato V, Di Vico V, Nalesso F, et al.* Calcineurin-Inhibitor-Induced Hypomagnesemia in Kidney Transplant Patients: A Monocentric Comparative Study between Sucrosomial Magnesium and Magnesium Pidolate Supplementation. J Clin Med. 2023;12(3):752. doi: 10.3390/jcm12030752.
26. *Haider DG, Lindner G, Ahmad SS, Sauter T, Wolzt M, Leichtle AB, et al.* Hypermagnesemia is a strong independent risk factor for mortality in critically ill patients: results from a cross-sectional study. Eur J Intern Med. 2015;26(7):504-7. doi: 10.1016/j.ejim.2015.05.013.
27. *Osorio JM, Bravo J, Pérez A, Ferreyra C, Osuna A.* Magnesemia in renal transplant recipients: relation with immunosuppression and posttransplant diabetes. Transplant Proc. 2010;42(8):2910-3. doi: 10.1016/j.transproceed.2010.08.016.
28. *Popović L, Bulum T.* New Onset Diabetes After Organ Transplantation: Risk Factors, Treatment, and Consequences. Diagnostics (Basel). 2025;15(3):284. doi: 10.3390/diagnostics15030284.
29. *Carlsen RK, Åsberg A, Svensson M, Birkeland KI, Jørgensen HS, Bressendorff I, et al.* Hypomagnesemia, insulin secretion and action in patients without diabetes, 1 year after kidney transplantation. Front Med (Lausanne). 2025;12:1492871. doi: 10.3389/fmed.2025.1492871.
30. *Stepanova N.* Oxalate Homeostasis in Non-Stone-Forming Chronic Kidney Disease: A Review of Key Findings and Perspectives. Biomedicines. 2023;11(6):1654. doi: 10.3390/biomedicines11061654.
31. *Ter Braake AD, Vervloet MG, de Baaij JHF, Hoenderop JGJ.* Magnesium to prevent kidney disease-associated vascular calcification: crystal clear? Nephrol Dial Transplant. 2022;37(3):421-429. doi: 10.1093/ndt/gfaa222.
32. *Wang J, Xiao Y, Yang Y, Yin S, Cui J, Huang K, et al.* Association between magnesium depletion score and the prevalence of kidney stones in the low primary income ratio: a cross-sectional study of NHANES 2007-2018. Int J Surg. 2024;110(12):7636-7646. doi: 10.1097/JS9.0000000000001822.