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TIMISOARA**

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Department VII

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PHD THESIS

**MORTALITY RISK IN HAEMODIALYSIS: THE OBESITY
PARADOX, OVERWEIGHT VERSUS OBESITY, AND MACHINE
LEARNING APPROACHES**

A B S T R A C T

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ABSTRACT

1. INTRODUCTION AND RESEARCH MOTIVATION

Chronic kidney disease (CKD) represents one of the most pressing global public health challenges of the twenty-first century, with approximately 788 million adults affected worldwide and an age-standardised prevalence of 14.2%. End-stage renal disease (ESRD) requiring haemodialysis (HD) carries substantial morbidity and mortality, with annual costs representing 2-3% of total healthcare expenditure in high-income countries despite affecting less than 0.1% of the population. In Romania, data from the PREDATORR study (2012-2014) indicated a CKD prevalence of 6.74%, although detailed epidemiological information remains limited, and recent screening data demonstrate a concerning upward trend in the burden of advanced-stage disease among patients with cardiometabolic comorbidities.

The conventional wisdom in the general population that higher body mass index (BMI) confers increased mortality risk has been challenged in dialysis populations since the early observations of reverse epidemiology reported in the 1980s. This paradoxical phenomenon, wherein overweight and obese haemodialysis patients exhibit lower mortality compared with normal-weight patients, has stimulated considerable research interest and clinical debate over four decades. Early explanations centred on reverse causality (malnutrition-inflammation complex syndrome), haemodynamic stability, altered cytokine dynamics, and metabolic reserve during catabolic stress.

The contemporary landscape of nephrology has transformed markedly since the obesity paradox was first identified. The average age of incident dialysis patients has risen substantially; the prevalence of diabetes mellitus in dialysis populations has increased; and guideline-directed medical therapies - particularly sodium-glucose cotransporter-2 inhibitors (SGLT2i), GLP-1 receptor agonists (GLP-1 RA), and mineralocorticoid receptor antagonists (MRA) - have been implemented in predialysis CKD management. The CREDENCE trial demonstrated that canagliflozin reduced the composite endpoint by 30%; the DAPA-CKD trial showed dapagliflozin reduced CKD progression or cardiovascular death by 39%; and the EMPA-KIDNEY trial confirmed empagliflozin reduced kidney disease progression or cardiovascular death by 28%. These interventions have substantially altered the cardiorenal risk profile of patients transitioning to dialysis.

Concurrently, the integration of machine learning (ML) and artificial intelligence into clinical nephrology has opened transformative possibilities for mortality risk stratification and personalised medicine. Unlike conventional regression-based models, ML algorithms can identify complex nonlinear interactions among clinical, biochemical, and demographic predictors, potentially enhancing prognostic accuracy and enabling precision interventions. Despite promising early results, the clinical translation of ML models in dialysis populations

remains constrained by methodological heterogeneity, limited external validation, and insufficient risk-of-bias assessments.

2. RESEARCH OBJECTIVES

The present thesis aimed to address three central research questions derived from identified gaps in the literature:

- Is the obesity paradox reproducible in contemporary Romanian haemodialysis cohorts in the era of modern cardiometabolic prevention (SGLT2i, GLP-1 RA, MRA)?
- Can machine learning approaches enhance mortality prediction beyond conventional statistical models in this population, and which algorithms demonstrate superior performance?
- What is the differential prognostic impact of overweight (BMI 25-29.9 kg/m²) versus obesity (BMI $\geq$ 30 kg/m²) at dialysis initiation in Eastern European incident patients?

3. THESIS STRUCTURE

The thesis is structured in two main parts. Part I - General Overview - comprises four theoretical chapters: (1) CKD Epidemiology - global prevalence, KDIGO classification, cardiovascular complications, and Romanian Renal Registry data; (2) Clinical Aspects of Haemodialysis - principles (diffusion, convection, ultrafiltration), vascular access types, dialysis adequacy (Kt/V, URR), nutritional status (protein-energy wasting), and the impact of key comorbidities; (3) The Obesity Paradox in CKD - definition and conceptual framework, evidence from large international cohorts, body composition versus BMI, proposed mechanistic explanations; (4) Machine Learning in Nephrology - fundamentals of ML paradigms, principal algorithms (Logistic Regression, Random Forest, XGBoost, SVM, ANN/LSTM), and clinical applications in dialysis.

Part II - Original Contributions - presents three independent research studies (Chapters 6, 7, and 8), followed by general conclusions, personal contributions, and future research directions. The thesis is underpinned by three scientific articles published or in press in ISI-indexed journals (Journal of Clinical Medicine x2, Applied Sciences x1).

4. STUDY 1 - ROMANIAN MULTICENTRE COHORT (CHAPTER 6)

4.1. Study design and population

The first original study was a multicentre, observational, prospective cohort study with 5-year survival follow-up. A total of 679 adult patients undergoing maintenance haemodialysis were enrolled from eight dialysis centres across Romania, covering all historical regions of the country (Muntenia, Moldova, Dobrogea, Oltenia, Banat, Transylvania, Crisana-Maramures). Inclusion criteria were: age $\geq$ 18 years, thrice-weekly haemodialysis ($\geq$ 12 h/week) using high-flux, high-surface-area dialysers, and clinical stability at enrolment. Patients with

documented active or prior malignancy, aged < 18 years, or lacking essential clinical, laboratory, or follow-up data were excluded.

4.2. Data collection and study variables

Variables collected included: demographic (age, sex), clinical (dialysis vintage, primary nephropathy, comorbidities: diabetes mellitus, arterial hypertension, cardiovascular disease, peripheral vascular disease), biochemical (serum albumin, haemoglobin, ferritin, CRP, phosphorus, calcium, bicarbonate, pre-dialysis creatinine and urea, dialysis adequacy: eKt/V by online clearance monitoring OCM/Adimea, URR), anthropometric (post-dialysis weight, height, BMI), and comprehensive echocardiographic parameters. Annual echocardiographic assessment included two-dimensional, M-mode, continuous and pulsed Doppler evaluation performed between the 2nd and 3rd hours of dialysis by the same operator per cohort, using comparable equipment to minimise inter-observer variability. The operator recorded valvular calcifications, measured left ventricular hypertrophy, and evaluated LVEF using Simpson method.

BMI categories were defined according to WHO classification: normal weight (18.5-24.9 kg/m²), overweight (25-29.9 kg/m²), and obese (≥ 30 kg/m²). The cohort was stratified into three groups: normal weight (< 25 kg/m²), overweight (25-29.9 kg/m²), and obese (≥ 30 kg/m²). Notably, no patients met criteria for underweight (BMI < 18.5 kg/m²). The primary outcome was all-cause mortality over the 5-year follow-up period.

4.3. Statistical analysis

Statistical analysis included: Shapiro-Wilk test for normality, Levene test for equality of variances, independent t-tests and ANOVA for continuous variables, chi-square and Fisher exact tests for categorical variables. Survival was assessed by Kaplan-Meier method, with between-group comparisons by log-rank and Gehan-Wilcoxon tests (more sensitive to early differences). Cox proportional hazards regression, both univariable and multivariable, was used to calculate adjusted risk estimates for all-cause mortality. All analyses were performed in RStudio version 4.4.3, with a significance threshold of $p < 0.05$.

4.4. Baseline cohort characteristics

Cohort distribution by BMI was: normal weight 52.7% (mean BMI 21.5 $\pm$ 2.3 kg/m², n=358), overweight 28.9% (mean BMI 27.6 $\pm$ 1.4 kg/m², n=196), and obese 18.4% (mean BMI 34.7 $\pm$ 4.1 kg/m², n=125). Mean cohort age was 57.2 $\pm$ 12.9 years, with 59.1% males. Age differed significantly across BMI groups ($p = 0.002$), with normal-weight patients being younger than both overweight and obese individuals. Dialysis vintage decreased progressively with increasing BMI ($p < 0.001$), ranging from 5.1 $\pm$ 4.5 years in normal-weight to 3.2 $\pm$ 2.7 years in obese patients. Coronary artery disease was significantly more prevalent among overweight and obese patients ($p = 0.001$ and $p = 0.011$). Diabetes mellitus was more common in

overweight and obese groups ($p = 0.001$ and $p < 0.001$). Dialysis adequacy (eKt/V) was significantly lower in obese patients ($p < 0.001$ vs. normal weight).

4.5. Key survival and mortality predictor results

Kaplan-Meier analysis demonstrated median survival of 7.56 dialysis years in normal-weight patients, 4.56 years in overweight patients, and lowest in obese patients. Survival curves diverged from months 12-18 and remained separated throughout the follow-up period, suggesting a persistent BMI effect on long-term mortality.

Multivariable Cox regression identified the following independent predictors of all-cause mortality:

- Obesity (BMI ≥ 30 kg/m²): HR 1.411, 95% CI 1.008-1.976, $p = 0.045$ - independent predictor of increased mortality
- Overweight (BMI 25-29.9 kg/m²): HR 1.022, $p = 0.873$ - no significant mortality association
- Advanced age: HR 1.028 per year, $p < 0.001$
- Elevated CRP: HR 1.781, $p < 0.001$ - strongest independent predictor
- eKt/V < 1.2 : HR 1.343, $p = 0.029$ - inadequate dialysis delivery
- Presence of cardiovascular disease: significant in univariable models

These findings contradict the classical obesity paradox, demonstrating that obesity - not overweight - is independently associated with increased mortality in this Romanian cohort. Overweight conferred neither a significant survival advantage nor disadvantage.

4.6. Discussion

The present findings align more closely with studies that have challenged the obesity paradox in contemporary settings. Normal-weight patients were younger and had a markedly lower prevalence of traditional cardiovascular risk factors (CAD 64.4% vs. 78.1% in overweight and 76.8% in obese; DM 15.7% vs. 28.8% and 37.6%; PVD 24.0% vs. 33.6%), which may partly explain the survival gradient. An important alternative explanation is survivor bias: patients with longer dialysis exposure progressively lost weight from protein-energy wasting, artificially enriching the normal-weight group with long-term survivors and inflating their apparent survival advantage.

The use of eKt/V measured by online clearance monitoring (OCM/Adimea system) to correct for urea rebound represents a methodological strength: lower delivered eKt/V in obese patients partially but incompletely explains the obesity-mortality association, supporting the need for individualised dialysis prescriptions. The absence of body composition data

(bioimpedance, CT, DEXA) remains the principal limitation, as BMI cannot distinguish between sarcopenic obesity and robust obesity - two phenotypes with markedly different prognoses.

5. STUDY 2 - ML SYSTEMATIC REVIEW AND META-ANALYSIS (CHAPTER 7)

5.1. Design and methodology

The second original study was a systematic review and meta-analysis of ML models for mortality prediction in haemodialysis patients, conducted according to PRISMA 2020 guidelines. Systematic searches were performed in four databases (PubMed, Scopus, Web of Science, Cochrane CENTRAL) up to March 2023. Inclusion criteria covered studies assessing ML model predictive capabilities for mortality in adult HD patients. Risk of bias was assessed using the QUADAS-2 tool across four domains: patient selection, index test, reference standard, and flow/timing. Meta-analysis was performed using Review Manager software version 5.4.1.

5.2. Included studies and characteristics

Eleven retrospective cohort studies were included, published between 2012 and 2023, with data collection spanning 1995-2019. ML algorithms investigated included: Logistic Regression, Adaptive Boosting, Decision Tree, Gradient Boosting, K-Nearest Neighbour, Random Forest, XGBoost, and Support Vector Machine. Cohorts ranged from 345 to 345,305 patients originating from the USA (3 studies), Spain (2), China (2), Taiwan (1), Iran (1), and multinational settings (2). Mean patient age ranged from 50.29 +/- 15.73 to 68.7 +/- 11.2 years; most patients were male. Key included studies: Garcia-Montemayor 2020 (Spain, n=1,571, RF vs. LR); Chaudhuri 2023 (multi-centre, n=95,142, XGBoost); Sheng 2020 (China, n=5,828, multiple algorithms); Akbilgic 2019 (USA, n=27,615, RF); Rankin 2022 (USA, n=345,305, XGBoost for 90-day mortality); Wang 2021 (China, n=1,200, SVM and LSTM).

5.3. Meta-analysis results

The meta-analysis demonstrated the following predictive performance at 1-year follow-up:

- Random Forest: pooled AUC 0.78 (95% CI 0.72-0.82); predicted true positive mortality rate 9.93% vs. actual rate 13.73%
- Logistic Regression: pooled AUC 0.77 (95% CI 0.72-0.82); predicted rate 8.23% vs. actual rate 10.53%
- XGBoost: AUC 0.80 at 3-year follow-up (Chaudhuri 2023, n=95,142)
- Gradient Boosting and LightGBM: individual AUC 0.83-0.85 (Sheng 2020)
- Difference between Random Forest and Logistic Regression: $p = 0.82$ - statistically non-significant

The SROC curve demonstrated that Random Forest achieved the highest AUC, followed by XGBoost, while Logistic Regression demonstrated slightly lower but clinically meaningful performance. QUADAS-2 risk-of-bias assessment: low risk in flow/timing and reference standard domains for most studies; unclear risk in index test domain for 4 studies; Garcia-Montemayor 2020 showed high risk of bias. A critical limitation identified across the literature: only 3 of 11 studies reported any external validation, substantially limiting current clinical applicability.

5.4. Clinical implications

The systematic review identified common important mortality predictors in haemodialysis: age, serum albumin, haemoglobin, creatinine, dialysis adequacy (Kt/V), presence of diabetes mellitus and cardiovascular disease, and dialysis vintage. The principal clinical implication is that ML models do not currently provide a substantial discriminatory advantage over well-calibrated logistic regression in dialysis populations using structured tabular data. Their potential advantage lies in integrating large longitudinal data volumes and identifying subtle nonlinear interactions - a capability that becomes increasingly relevant as clinical databases grow in size and quality, and as electronic health record integration advances.

6. STUDY 3 - INCIDENT HAEMODIALYSIS COHORT (CHAPTER 8)

6.1. Study design and population

The third original study was a retrospective single-centre cohort study including 268 incident patients who initiated haemodialysis at the County Emergency Clinical Hospital Pius Branzeu Timisoara between January 2022 and December 2025 - a period representative of the modern cardiometabolic prevention era. Follow-up data at 3, 6, 12, 24, and 36 months were obtained from the dialysis centres to which patients were referred for maintenance haemodialysis. The study protocol was approved by the Institutional Ethics Committee of Pius Branzeu Hospital (approval no. 591, January 8, 2026) and conducted in accordance with the Declaration of Helsinki.

6.2. Cohort characteristics and CKD aetiology

Median cohort age was 66 years (IQR: 54-72) with 61% male predominance (164 males). At dialysis initiation, kidney function was severely compromised, with median eGFR of 6.4 mL/min/1.73 m² (IQR: 4.6-8.9). Diabetic kidney disease was the leading cause of CKD (116 patients, 43%), followed by hypertensive nephrosclerosis (53 patients, 20%) and glomerulonephritis (51 patients, 19%). Aetiology remained undetermined in 76 patients (28%), predominantly due to late referral without available renal biopsy data. BMI distribution: normal weight 46.6%, overweight 34.7%, obese 18.7%.

A particularly concerning finding in this cohort: 61% of patients presented as very late referrals (< 3 months of pre-dialysis nephrology follow-up), reflecting a major gap in the CKD care

pathway in Romania. This figure substantially exceeds recommended targets (European guidelines advocate ≥ 6 months of nephrology follow-up before dialysis initiation) and has direct implications for patient outcomes, as demonstrated by the independent survival benefit of longer pre-dialysis nephrology follow-up identified in this study.

6.3. Statistical analysis

All statistical analyses were performed using Python 3.12. Data manipulation used pandas; statistical testing used SciPy; survival analyses used lifelines; visualisation used matplotlib and seaborn. Continuous variables were assessed for normality using the Shapiro-Wilk test. Non-normally distributed continuous variables are presented as median [IQR]; categorical variables as n (%). Kaplan-Meier method was used for survival analysis, with Cox proportional hazards regression for multivariable mortality prediction. Survival probabilities were estimated at 3, 6, 12, 24, and 36 months with 95% confidence intervals. Missing data were not imputed; complete-case methods were used throughout.

6.4. Key results

The overweight paradox - not the obesity paradox:

Overweight status (BMI 25-29.9 kg/m²) was independently associated with reduced mortality at ALL evaluated time horizons:

- HR 0.22 (significant 95% CI) at 3 months versus normal weight
- HR 0.29 at 1 year versus normal weight
- HR 0.31 at 3 years versus normal weight ($p < 0.05$ at all time horizons)

Obesity (BMI ≥ 30 kg/m²) did not confer significant mortality protection at any timepoint (HR 1.13-1.51, all $p > 0.5$), indicating that the survival benefit attributed to higher BMI in the dialysis population is driven by moderate excess weight (overweight), not by obesity per se. This finding supports an "overweight paradox" rather than a broad obesity paradox, with clinically and prognostically meaningful distinctions between the two BMI categories.

Temporal patterns of risk factors:

Risk factors followed distinct temporal patterns suggesting different pathogenic mechanisms:

- At 3 months: advanced age (≥ 65 years) dominated (HR 11.77) - early mortality reflects acute physiological vulnerability at dialysis initiation
- At 1 year: diabetes mellitus (HR 2.75) and COPD (HR 2.49) began to contribute significantly - cumulative comorbid burden
- At 3 years: cumulative comorbid burden becomes the principal determinant; pre-dialysis nephrology follow-up remains independently protective (HR 0.70 per year, $p < 0.001$)

Late referral - a modifiable determinant:

Each additional year of pre-dialysis nephrology follow-up independently reduced 3-year mortality by 30% (HR 0.70, $p < 0.001$). Given that 61% of patients were referred very late (< 3 months of nephrology follow-up), this result underscores the enormous impact of early nephrology engagement - representing the most powerful modifiable predictor identified in this cohort, and one that is directly amenable to healthcare system intervention.

7. GENERAL CONCLUSIONS

- In the Romanian multicentre maintenance haemodialysis cohort ($n = 679$, Chapter 6), obesity (BMI ≥ 30 kg/m²) was independently associated with increased all-cause mortality (HR 1.411, 95% CI 1.008-1.976, $p = 0.045$), whereas overweight was not independently associated with excess mortality (HR 1.022, $p = 0.873$) - contradicting the traditional obesity paradox and providing the first Eastern European multicentre evidence on this topic. Published J Clin Med 2026;15(1):357.
- In the incident haemodialysis cohort ($n = 268$, Chapter 8), overweight status was independently protective across all time horizons (HR 0.22-0.31 at 3 months to 3 years), while obesity conferred no significant protection (HR 1.13-1.51, all $p > 0.5$) - supporting an "overweight paradox" and confirming that obesity and overweight carry distinct prognostic implications at dialysis initiation. In press J Clin Med 2025.
- Taken together, the two Romanian cohort studies provide convergent Eastern European evidence that BMI should not be treated as a homogeneous continuous variable in dialysis outcome studies; the distinction between overweight and obesity is clinically and prognostically meaningful, and should be reflected in clinical guidelines and nutritional counselling of dialysis patients.
- The systematic review and meta-analysis (Chapter 7) demonstrated that ML models hold considerable potential for mortality risk prediction in HD patients (pooled AUC 0.77-0.78 at 1-year follow-up), but significant heterogeneity and near-universal absence of external validation currently limit clinical implementation. The absence of discriminatory superiority of complex ML over logistic regression in moderate-sized clinical datasets suggests that interpretability and external validation should be prioritised over model complexity in future ML research in nephrology. Published Appl Sci 2025;15(10):5776.
- Longer pre-dialysis nephrology follow-up was independently protective at dialysis initiation (HR 0.70 per year at 3 years, $p < 0.001$), whereas 61% of incident patients presented as very late referrals (< 3 months), underscoring the critical importance of early nephrology

engagement to improve survival outcomes in Romania - the most powerful modifiable determinant of outcome identified in the incident cohort.

- Future prospective studies should incorporate direct body composition measurement (BIA, DEXA, waist circumference), standardised ML datasets with mandatory external validation, and longer follow-up to fully characterise the overweight-obesity-mortality relationship and validate risk stratification tools in Eastern European dialysis populations.

8. PERSONAL CONTRIBUTIONS

- CONTRIBUTION 1: First Romanian multicentre cohort study (8 dialysis centres, all historical regions of Romania, n = 679 patients, 5-year follow-up) demonstrating that obesity but not overweight is independently associated with increased all-cause mortality in maintenance haemodialysis, with comprehensive echocardiographic characterisation. Published: J Clin Med 2026;15(1):357. doi:10.3390/jcm15010357
- CONTRIBUTION 2: First systematic review of ML-based mortality prediction models in haemodialysis patients with comprehensive QUADAS-2 risk-of-bias appraisal across 11 included studies, demonstrating equivalent pooled AUC for Random Forest and Logistic Regression (0.78 vs. 0.77, p = 0.82) at 1-year follow-up, and identifying the absence of external validation as the primary barrier to clinical implementation. Published: Appl Sci 2025;15(10):5776. doi:10.3390/app15105776
- CONTRIBUTION 3: First Eastern European single-centre incident haemodialysis cohort study (n = 268, Pius Branzeu Hospital, Timisoara, 2022-2025) characterising mortality at dialysis initiation in the modern cardiometabolic prevention era, demonstrating an "overweight paradox" (HR 0.22-0.31) distinct from classical obesity paradox, and identifying distinct temporal patterns of risk factor contribution. In press: J Clin Med. doi:10.3390/jcm15082856
- CONTRIBUTION 4: Identification of eKt/V < 1.2 measured by online clearance monitoring (OCM/Adimea) as an independent predictor of all-cause mortality (HR 1.343, p = 0.029) even after adjustment for body size and nutritional parameters, supporting the need for individualised dialysis prescriptions in obese patients (Chapter 6).
- CONTRIBUTION 5: Demonstration that very late nephrology referral (< 3 months, 61% of incident patients) is the norm rather than the exception in the Eastern European setting, and that each additional year of pre-dialysis nephrology follow-up independently reduces 3-year mortality by 30% (HR 0.70, p < 0.001; Chapter 8) - identifying late referral as the single most impactful modifiable determinant of outcome at dialysis initiation.

9. SCIENTIFIC PUBLICATIONS

- Motofelea Alexandru Catalin, Olariu N., Pecingina R., Marc L., Chisavu L., Bob F., Mihaescu A., Apostol A., Schiller O., Motofelea N., Pop G.N., Crintea A., Schiller A. BMI Category and Survival in Incident Hemodialysis Patients: The Overweight Advantage in an Eastern European Cohort. *J Clin Med*. 2026;15(8):2856. doi:10.3390/jcm15082856
- Motofelea Alexandru Catalin, Pecingina R., Olariu N., Marc L., Chisavu L., Bob F., Mihaescu A., Apostol A., Schiller O., Motofelea N., Schiller A. The Obesity Paradox Reconsidered: Evidence from a Multicenter Romanian Hemodialysis Cohort. *J Clin Med*. 2026;15(1):357. doi:10.3390/jcm15010357
- Motofelea Alexandru Catalin, Mihaescu A., Olariu N., Marc L., Chisavu L., Pop G.N., Crintea A., Jura A.M.C., Ivan V.M., Apostol A., Schiller A. Machine Learning Models for Predicting Mortality in Hemodialysis Patients: A Systematic Review. *Appl Sci*. 2025;15(10):5776. doi:10.3390/app15105776

10. FUTURE RESEARCH DIRECTIONS

- Prospective longitudinal study with direct body composition measurement (BIA, DEXA, waist circumference, CT imaging) to disentangle contributions of fat mass and lean mass to the obesity/overweight paradox in Romanian HD patients, and to test whether the overweight paradox persists after body composition adjustment - the most critical next methodological step.
- External prospective validation of the best-performing ML models identified in the systematic review using an independent Romanian or Eastern European HD cohort, with TRIPOD-compliant reporting, sufficient sample size for subgroup analyses (diabetic vs. non-diabetic, incident vs. prevalent), and real-world electronic health record integration.
- Development and clinical piloting of a prospective registry of incident haemodialysis patients in Romania, integrating nutritional, inflammatory, body composition, dialysis adequacy, and medication parameters to enable longitudinal ML-based risk stratification and real-time clinical decision support.
- Investigation of the impact of modern cardiometabolic therapies (SGLT2 inhibitors, GLP-1 RAs, MRAs) on the risk profile at dialysis initiation and the obesity paradox in contemporary incident cohorts, through prospective cohort studies with medication use data collected longitudinally.
- Analysis of the interaction between body composition, inflammatory status (CRP, IL-6, TNF-alpha), and the obesity paradox in haemodialysis, using repeated longitudinal measurements and time-varying models, to test the metabolic reserve hypothesis and elucidate the mechanisms underlying the overweight paradox.

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TEZĂ DE DOCTORAT

**RISCUL DE MORTALITATE ÎN HEMODIALIZĂ: PARADOXUL
OBEZITĂȚII, SUPRAPONDERALITATEA VERSUS OBEZITATEA ȘI
ABORDĂRILE PRIN ÎNVĂȚARE AUTOMATĂ**

R E Z U M A T

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REZUMAT

1. INTRODUCERE SI MOTIVATIA CERCETARII

Boala cronică de rinichi (BCR) reprezintă una dintre cele mai importante provocări de sănătate publică ale secolului XXI, cu aproximativ 788 de milioane de adulți afectați la nivel mondial și o prevalență standardizată de 14,2%. Boala renală în stadiu terminal (BSRT) necesitând hemodializă (HD) este asociată cu morbiditate și mortalitate substanțiale, costurile anuale reprezentând 2-3% din cheltuielile totale de sănătate în țările cu venituri ridicate, în ciuda faptului că afectează mai puțin de 0,1% din populație. În România, date din studiul PREDATORR (2012-2014) au indicat o prevalență a BCR de 6,74%, deși informațiile epidemiologice detaliate rămân limitate, iar tendințele recente indică o creștere a povarării bolii avansate în rândul pacienților cu comorbiditate cardiometabolică.

Înțelegerea convențională conform căreia un indice de masă corporală (IMC) mai ridicat conferă risc crescut de mortalitate în populația generală a fost contestată în populațiile dializate încă din observațiile timpurii de epidemiologie inversă raportate în anii 1980. Acest fenomen paradoxal, în care pacienții supraponderali și obezi dializați prezintă mortalitate mai scăzută comparativ cu pacienții normoponderali, a stimulat un considerabil interes de cercetare și dezbateri clinice pe parcursul a patru decenii. Explicațiile timpurii s-au centrat pe cauzalitate inversă (sindromul malnutriție-inflamație, stabilitate hemodinamică, dinamică alterată a citokinelor și rezerva metabolică în stres catabolic).

Peisajul contemporan al nefrologiei s-a transformat semnificativ. Vârsta medie a pacienților incidenti la dializă a crescut substanțial; prevalența diabetului zaharat în populațiile dializate a crescut; iar terapiile cardiometabolice moderne - în special inhibitorii cotransportorului sodiu-glucoză de tip 2 (iSGLT2), agonistii receptorilor GLP-1 (GLP-1 RA) și antagoniștii receptorilor mineralocorticoizi (ARM) - au fost implementate în managementul BCR predialitice. Aceste intervenții au modificat demonstrabil profilul de risc cardiorenal al pacienților care tranzitează spre dializă: studiul CREDENCE a demonstrat reducerea cu 30% a endpointului compozit (BSRT, dublarea creatininei serice sau deces renal/cardiovascular) cu canagliflozin; studiul DAPA-CKD a arătat reducerea cu 39% a progresiei BCR cu dapagliflozin; iar EMPA-KIDNEY a confirmat reducerea cu 28% a progresiei bolii renale cu empagliflozin.

Concomitent, integrarea machine learning (ML) si a inteligentei artificiale in nefrologia clinica a deschis posibilitati transformatoare pentru stratificarea riscului de mortalitate si medicina de precizie. Spre deosebire de modelele conventionale bazate pe regresie, algoritmi ML pot identifica interactiuni neliniare complexe intre predictorii clinici, biochimici si demografici, imbunatatind potential acuratetea prognostica si permitand interventii de precizie. In ciuda rezultatelor promitoare timpurii, translarea clinica a modelelor ML in populatiile dializate ramane limitata de heterogenitatea metodologica, validarea externa limitata si evaluarile insuficiente ale riscului de bias.

2. OBIECTIVELE CERCETARII

Teza de fata a urmarit sa raspunda la trei intrebari centrale de cercetare, derivate din lacunele identificate in literatura de specialitate:

- Este paradoxul obezitatii reproductibil in cohortele contemporane romanesti de hemodializa, in era prevenirii cardiometabolice moderne (iSGLT2, GLP-1 RA, ARM)?
- Pot abordarile de machine learning sa imbunatateasca predictia mortalitatii fata de modelele statistice conventionale in aceasta populatie, si care algoritmi demonstreaza performanta superioara?
- Care este impactul prognostic diferential al supraponderalitatii (IMC 25-29,9 kg/m²) fata de obezitate (IMC $\geq$ 30 kg/m²) la initierea dializei, in contextul pacientilor incidenti din Europa de Est?

3. STRUCTURA TEZEI

Teza este structurata in doua parti principale. Partea I - Cadrul general - cuprinde patru capitole teoretice: (1) Epidemiologia BCR - prevalenta globala, clasificare KDIGO, complicatii cardiovasculare si Registrul Renal Roman; (2) Aspecte clinice ale hemodializei - principii (difuzie, convecție, ultrafiltrare), accesul vascular, adecvarea dializei (Kt/V, URR), starea nutritionala si comorbiditatile; (3) Paradoxul obezitatii in BCR - definitie, dovezi din cohorte internationale mari, compozitie corporala versus IMC, mecanisme propuse; (4) Machine learning in nefrologie - fundamente, algoritmi principali (Regresie Logistica, Random Forest, XGBoost, SVM, ANN/LSTM), aplicatii in dializa.

Partea a II-a - Contributii originale - prezinta trei studii de cercetare independente (Capitolele 6, 7 si 8), urmate de concluzii generale, contributii personale si directii viitoare de cercetare. Teza se bazeaza pe trei articole stiintifice publicate/in curs de publicare in reviste indexate ISI (Journal of Clinical Medicine x2, Applied Sciences x1).

4. STUDIUL 1 - COHORTA MULTICENTRICA ROMANEASCA (CAPITOLUL 6)

4.1. Design si populatia studiului

Primul studiu original a constat dintr-un studiu de cohorta multicentric, observational, prospectiv, cu 5 ani de urmarire a supravietuirii. Au fost inclusi 679 de pacienti adulti cu hemodializa de intretinere din opt centre de dializa din Romania, acoperind toate regiunile istorice ale tarii (Muntania, Moldova, Dobrogea, Oltenia, Banat, Ardeal, Crisana-Maramures). Criteriile de includere au vizat: varsta ≥ 18 ani, tratament cu hemodializa de trei ori pe saptamana (≥ 12 ore/saptamana) utilizand dializoare de flux inalt si suprafata mare, si stabilitate clinica la momentul inrolarii. Pacientii cu diagnostic documentat de malignitate activa sau antecedenta, sub 18 ani, sau cu date clinice, de laborator sau de urmarire incomplete au fost exclusi.

4.2. Colectarea datelor si variabilele studiului

Variabilele colectate au cuprins date demografice (varsta, sex), clinice (vintaj de dializa, nefropatie primara, comorbiditate - diabet zaharat, hipertensiune arteriala, boala cardiovasculara, boala arteriala periferica), biochimice (albumina serica, hemoglobina, feritina, CRP, fosfor, calciu, bicarbonat, creatinina si uree predialitice, indici de adecvare a dializei: eKt/V masurat prin monitorizare online a clearance-ului OCM/Adimea, URR), antropometrice (greutate post-dializa, inaltime, IMC), si ecocardiografice complete. Evaluarea ecocardiografica anuala a inclus: ecografie bidimensionala, M-mod, Doppler continuu si pulsat, efectuata intre orele 2-3 ale sedintei de dializa de catre acelasi operator pentru fiecare cohorta, folosind echipamente comparabile (pentru a evita variabilitatea interobservator). Operatorul a inregistrat prezenta si cantitatea calcificarilor valvulare, a masurat hipertrofia ventriculara stanga si a evaluat fractia de ejectie a ventriculului stang (FEVS) prin metoda Simpson.

Categoriile IMC au fost definite conform clasificarii Organizatiei Mondiale a Sanatatii: normoponderal (18,5-24,9 kg/m²), supraponderal (25-29,9 kg/m²) si obez (≥ 30 kg/m²).

Cohorta a fost stratificata in trei grupuri: normoponderal ($< 25 \text{ kg/m}^2$), supraponderal ($25\text{-}29,9 \text{ kg/m}^2$) si obez ($\geq 30 \text{ kg/m}^2$). Remarcabil, niciun pacient din cohorta nu a indeplinit criteriile pentru subponderalitate ($\text{IMC} < 18,5 \text{ kg/m}^2$). Endpointul primar a fost mortalitatea de orice cauza pe parcursul perioadei de urmarire de 5 ani.

4.3. Analiza statistica

Analiza statistica a inclus: testul Shapiro-Wilk pentru normalitate, testul Levene pentru egalitatea variantelor, teste t independente si ANOVA pentru variabile continui, chi-patrat si testul exact Fisher pentru variabile categoriale. Supravietuirea a fost evaluata prin metoda Kaplan-Meier, cu comparatii intre grupuri prin testul log-rank si Gehan-Wilcoxon (mai sensibil la diferentele timpurii). Regresia proportionala Cox, atat univariabila cat si multivariabila, a fost utilizata pentru calculul estimarilor de risc ajustate pentru mortalitatea de orice cauza. Toate analizele au fost efectuate in RStudio versiunea 4.4.3, cu un prag de semnificatie de $p < 0,05$.

4.4. Caracteristicile de baza ale cohortei

Distributia cohortei pe categorii IMC a fost: normoponderali 52,7% (IMC mediu $21,5 \pm 2,3 \text{ kg/m}^2$, $n=358$), supraponderali 28,9% (IMC mediu $27,6 \pm 1,4 \text{ kg/m}^2$, $n=196$) si obezi 18,4% (IMC mediu $34,7 \pm 4,1 \text{ kg/m}^2$, $n=125$). Varsta medie a cohortei a fost $57,2 \pm 12,9$ ani, cu 59,1% barbati. Varsta a diferit semnificativ intre grupurile IMC ($p = 0,002$), pacientii normoponderali fiind mai tineri decat cei supraponderali si obezi.

Caracteristicile legate de dializa au variat in functie de grupul IMC. Vintajul de dializa a scazut progresiv odata cu cresterea IMC ($p < 0,001$), durata cea mai lunga inregistrandu-se la pacientii normoponderali ($5,1 \pm 4,5$ ani) si cea mai scurta la cei obezi ($3,2 \pm 2,7$ ani). Volumul de ultrafiltrare per sedinta a fost semnificativ mai mare la pacientii supraponderali si obezi comparativ cu grupul normoponderali ($p = 0,032$ si $p = 0,018$). Adecvarea dializei (eKt/V) a fost semnificativ mai scazuta la pacientii obezi comparativ cu celelalte doua grupuri ($p = 0,040$ vs. supraponderali si $p < 0,001$ vs. normoponderali). Comorbiditati cardiovasculare: boala arteriala coronariana a fost semnificativ mai prevalenta la supraponderali si obezi fata de normoponderali ($p = 0,001$ si $p = 0,011$). Diabetul zaharat a fost mai frecvent la supraponderali si obezi ($p = 0,001$ si $p < 0,001$).

4.5. Rezultatele principale - supravietuire si predictorii de mortalitate

Analiza Kaplan-Meier a demonstrat o supravietuire mediiana de 7,56 ani (pe dializa) la pacientii normoponderali, 4,56 ani la supraponderali si cea mai scazuta la obezi. Curbele de

supravietuire au divergat incepand cu lunile 12-18 si au ramas separate pe toata perioada de urmarire, sugerand un efect persistent al IMC asupra mortalitatii pe termen lung.

Regresia Cox multivariabila

a identificat urmatorii predictorii independenti ai mortalitatii de orice cauza:

- Obezitate (IMC ≥ 30 kg/m²): HR 1,411, IC 95% 1,008-1,976, $p = 0,045$ - predictor independent de mortalitate crescuta
- Supraponderalitate (IMC 25-29,9 kg/m²): HR 1,022, $p = 0,873$ - fara asociere semnificativa cu mortalitatea
- Varsta avansata: HR 1,028 per an, $p < 0,001$
- CRP crescut: HR 1,781, $p < 0,001$ - cel mai puternic predictor independent
- eKt/V $< 1,2$: HR 1,343, $p = 0,029$ - adecvanta insuficienta a dializei
- Boala cardiovasculara prezenta: HR semnificativ in modele univariabile

Aceste rezultate contrazic paradoxul obezitatii clasic, demonstrand ca obezitatea - nu supraponderalitatea - este asociata cu mortalitate crescuta in aceasta cohorta romaneasca. Supraponderalitatea nu a conferit nici avantaj, nici dezavantaj semnificativ de supravietuire.

4.6. Discutii

Rezultatele prezentului studiu se aliniaza mai degraba cu dovezile care au contestat paradoxul obezitatii in contextul contemporan. Pacientii normoponderali au fost mai tineri si au prezentat o prevalenta semnificativ mai scazuta a factorilor de risc cardiovascular traditionali (CAD 64,4% vs. 78,1% la supraponderali si 76,8% la obezi; DZ 15,7% vs. 28,8% si 37,6%; BAP 24,0% vs. 33,6%), ceea ce ar putea explica partial gradientul de supravietuire. O explicatie alternativa este aceea ca pacientii cu expunere mai lunga la dializa au pierdut progresiv greutate din cauza deperditiei proteico-energetice, imbogatind artificial grupul normoponderali cu supravietuitorii pe termen lung - o forma de bias de supravietuitor.

Adecvanta dializei a variat de asemenea in functie de categoriile IMC, pacientii obezi demonstrand valori eKt/V mai scazute. Deoarece ecuatiile Kt/V bazate pe cinetica ureei nu sunt instrumente ideale pentru evaluarea adecvantei dializei la pacientii obezi (volumul de distributie al ureei putand fi crescut odata cu dimensiunea corporala mai mare), am utilizat

eKt/V echilibrat determinat prin monitorizare online a clearance-ului (OCM, sisteme Adimea) pentru a corecta reboundul ureei. eKt/V < 1,2 a ramas predictor independent al mortalitatii crescute (HR 1,343, p = 0,029), subliniind necesitatea prescriptiilor de dializa individualizate la pacientii obezi.

5. STUDIUL 2 - REVIZUIRE SISTEMATICA SI META-ANALIZA ML (CAPITOLUL 7)

5.1. Design si metodologie

Al doilea studiu original a constatat dintr-o revizuire sistematica si meta-analiza a modelelor ML pentru predictia mortalitatii la pacientii hemodializati, efectuata conform ghidurilor PRISMA 2020. Cautarea sistematica a fost realizata in patru baze de date (PubMed, Scopus, Web of Science, Cochrane CENTRAL) pana in martie 2023. Criteriile de includere au vizat studii ce au evaluat capabilitatile predictive ale modelelor ML pentru mortalitate la pacientii adulti HD. Evaluarea riscului de bias a utilizat instrumentul QUADAS-2 in patru domenii: selectia pacientilor, testul index, standardul de referinta, si flux/timing.

5.2. Studii incluse si caracteristici

Au fost incluse 11 studii de cohorta retrospective, publicate intre 2012 si 2023, cu date colectate intre 1995 si 2019. Algoritmii ML investigati au inclus: Regresia Logistica, Adaptive Boosting, Arborele de Decizie, Gradient Boosting, K-Nearest Neighbour, Random Forest, XGBoost si Support Vector Machine. Cohortele au variat de la 345 la 345.305 pacienti, provenind din SUA (3 studii), Spania (2), China (2), Taiwan (1), Iran (1), si cohorte multinationale (2). Varsta medie a pacientilor inclusi a variat intre 50,29 +/- 15,73 si 68,7 +/- 11,2 ani; majoritatea pacientilor au fost de sex masculin.

5.3. Rezultatele meta-analizei

Meta-analiza a demonstrat urmatoarele performante predictive la urmarire de 1 an:

- Random Forest: AUC grupat 0,78 (IC 95% 0,72-0,82); rata de mortalitate prezisa 9,93% vs. rata reala 13,73%

- Regresia Logistica: AUC grupat 0,77 (IC 95% 0,72-0,82); rata de mortalitate prezisa 8,23% vs. rata reala 10,53%
- XGBoost: AUC de 0,80 la urmarire de 3 ani (studiul Chaudhuri 2023, n=95.142)
- Gradient Boosting si LightGBM: AUC 0,83-0,85 in studii individuale (Sheng 2020)
- Diferenta intre Random Forest si Regresia Logistica: $p = 0,82$ - nesemnificativa statistic

Curba SROC (Summary ROC) a demonstrat ca Random Forest a prezentat cel mai ridicat AUC, urmat de XGBoost, in timp ce Regresia Logistica a demonstrat performanta usor mai scazuta dar semnificativa clinic. O limitare majora identificata a fost absenta aproape universala a validarii externe - doar 3 din 11 studii au raportat validare externa - limitand aplicabilitatea clinica actuala a acestor modele. Riscul de bias a fost scazut la majoritatea studiilor in domeniile flux/timing si standardul de referinta, dar neclar la 4 studii pentru testul index.

5.4. Implicatii clinice

Revizuirea sistematica a identificat ca predictorii comuni importanti ai mortalitatii in hemodializa: varsta, albumina serica, hemoglobina, creatinina, adecvanta dializei (Kt/V), prezenta diabetului zaharat si a bolii cardiovasculare, si durata de dializa. Implicatia clinica principala este ca modelele ML nu aduc, in prezent, un avantaj discriminatoriu substantial fata de regresia logistica bine calibrata in populatiile dializate; avantajul lor potential consta in capacitatea de a integra volume mari de date longitudinale si de a identifica interactiuni neliniare subtile, ceea ce devine relevant pe masura ce bazele de date clinice cresc in dimensiune si calitate.

6. STUDIUL 3 - COHORTA INCIDENTA LA HEMODIALIZA (CAPITOLUL 8)

6.1. Design si populatia studiului

Al treilea studiu original a constat dintr-un studiu de cohorta retrospectiv monocentric, incluzand 268 de pacienti incidenti care au initiat hemodializa la Spitalul Clinic Judetean de Urgenta Pius Branzeu Timisoara intre ianuarie 2022 si decembrie 2025 - perioada reprezentativa pentru era moderna a prevenirii cardiometabolice. Datele de urmarire la 3, 6, 12, 24 si 36 de luni au fost obtinute din centrele de dializa spre care au fost transferati pacientii

pentru hemodializa de intretinere. Protocolul a fost aprobat de Comitetul de Etica al Spitalului Pius Branzeu (nr. 591, 8 ianuarie 2026) si condus in conformitate cu Declaratia de la Helsinki.

6.2. Caracteristicile cohortei si etiologia BCR

Varsta mediana a cohortei a fost 66 de ani (IQR: 54-72) cu predominanta masculina de 61% (164 barbati). La initierea dializei, functia renala era sever compromisa, cu eRFG median de 6,4 mL/min/1,73 m² (IQR: 4,6-8,9). Nefropatia diabetica a reprezentat cauza principala a BCR (116 pacienti, 43%), urmata de nefroangioscleroza hipertensiva (53 pacienti, 20%) si glomerulonefritele (51 pacienti, 19%). Etiologia a ramas nedeterminata la 76 de pacienti (28%), predominant din cauza prezentarii tardive fara biopsie renala disponibila.

Un aspect deosebit de ingrijorator identificat in aceasta cohorta: 61% dintre pacienti s-au prezentat ca trimeri foarte tardive (< 3 luni de urmarire nefrologica predializatica), ceea ce reflecta o lacuna majora in traseul de ingrijire al pacientilor cu BCR in Romania. Distributia pe categorii IMC a cohortei incidente a fost: normoponderal 46,6%, supraponderal 34,7%, obez 18,7% - o distributie similara cu cohorta multicentrica, dar cu o proportie mai mare de supraponderali.

6.3. Analiza statistica

Toate analizele statistice au fost efectuate in Python 3.12, utilizand: pandas si SciPy pentru manipularea datelor si testarea statistica, lifelines pentru analize de supravietuire si vizualizare, matplotlib si seaborn pentru vizualizare. Variabilele continue au fost evaluate pentru normalitate cu testul Shapiro-Wilk. Metodele Kaplan-Meier si regresia Cox proportionala au fost utilizate pentru analiza de supravietuire, cu estimari de probabilitate la 3, 6, 12, 24 si 36 de luni. Datele lipsa nu au fost imputate; metodele complete-case au fost utilizate pe parcurs.

6.4. Rezultatele principale

Paradoxul supraponderalitatii - nu al obezitatii:

Supraponderalitatea (IMC 25-29,9 kg/m²) a fost asociata independent cu mortalitate redusa la TOATE orizonturile de timp evaluate:

- HR 0,22 (IC 95% semnificativ) la 3 luni vs. normoponderali
- HR 0,29 la 1 an vs. normoponderali
- HR 0,31 la 3 ani vs. normoponderali ($p < 0,05$ la toate orizonturile)

Obezitatea ($\text{IMC} \geq 30 \text{ kg/m}^2$) nu a conferit protectie semnificativa la niciunul dintre orizonturile de timp (HR 1,13-1,51, $p > 0,5$ la toate), indicand ca beneficiul de supravietuire atribuit IMC crescut in populatia dializata este determinat de excesul moderat de greutate (supraponderalitate), nu de obezitate ca atare.

Tipare temporale ale factorilor de risc:

Factorii de risc au urmat tipare temporale distincte, sugerand mecanisme patogene diferite:

- La 3 luni: varsta avansata (≥ 65 ani) a dominat (HR 11,77) - mortalitatea timpurie reflecta vulnerabilitate fiziologica acuta
- La 1 an: diabetul zaharat (HR 2,75) si BPOC (HR 2,49) au inceput sa contribuie semnificativ
- La 3 ani: povara comorbida cumulativa devine determinanta; urmarire nefrologica prelungita ramane protectiva (HR 0,70 per an, $p < 0,001$)

Referire tardiva - un factor modificabil:

Fiecare an suplimentar de urmarire nefrologica predializatica a redus independent mortalitatea la 3 ani cu 30% (HR 0,70, $p < 0,001$). In contextul in care 61% din pacienti au fost trimisi extrem de tarziu (< 3 luni de urmarire nefrologica), acest rezultat subliniaza impactul enorm al implicarii nefrologice timpurii, reprezentand cel mai puternic factor modificabil identificat in aceasta cohorta.

7. CONCLUZII GENERALE

- In cohorta multicentrica romaneasca de hemodializa de intretinere ($n = 679$, Capitolul 6), obezitatea ($\text{IMC} \geq 30 \text{ kg/m}^2$) a fost asociata independent cu mortalitate de orice cauza crescuta (HR 1,411, IC 95% 1,008-1,976, $p = 0,045$), in timp ce supraponderalitatea nu a fost asociata independent cu mortalitate in exces (HR 1,022, $p = 0,873$) - contradictand paradoxul obezitatii traditional si furnizand prima dovada multicentrica est-europeana pe aceasta tema (publicat J Clin Med 2026;15(1):357).

- In cohorta de hemodializa incidenta ($n = 268$, Capitolul 8), supraponderalitatea (IMC 25-29,9 kg/m²) a fost independent protectiva la toate orizonturile de timp (HR 0,22-0,31), in timp ce obezitatea nu a conferit protectie semnificativa - sustinand un "paradox al supraponderalitatii" si confirmand ca obezitatea si supraponderalitatea au implicatii prognostice distincte (in press J Clin Med 2025).
- Cele doua studii de cohorta furnizeaza impreuna dovezi convergente ca IMC nu trebuie tratat ca o variabila continua omogena in studiile de outcome la pacientii dializati; distinctia dintre supraponderalitate si obezitate este relevanta clinic si prognostic, si ar trebui reflectata in ghidurile clinice si in consilierea nutritionala a pacientilor.
- Revizuirea sistematica si meta-analiza (Capitolul 7) au demonstrat ca modelele ML, in special Random Forest si Regresia Logistica, prezinta potential considerabil pentru predictia riscului de mortalitate la pacientii HD (AUC grupat 0,77-0,78 la urmarire de 1 an), dar heterogenitatea semnificativa si absenta aproape universala a validarii externe limiteaza in prezent implementarea clinica (publicat Appl Sci 2025;15(10):5776).
- Urmărirea nefrologica predializatica prelungita a fost independent protectiva la initierea dializei (HR 0,70 per an la 3 ani, $p < 0,001$), in timp ce 61% dintre pacientii incidenti s-au prezentat ca trimiteri foarte tardive (< 3 luni), subliniind importanta critica a implicarii nefrologice timpurii pentru imbunatatirea rezultatelor de supravietuire in Romania.
- Studiile viitoare prospective ar trebui sa incorporeze masurarea directa a compozitiei corporale (BIA, DEXA, circumferinta taliei), seturi de date ML standardizate, urmarire mai indelungata si cohorte multicentrice extinse, pentru a caracteriza pe deplin relatia supraponderalitate-obezitate-mortalitate si a valida instrumentele de stratificare a riscului in populatiile dializate din Europa de Est.

8. CONTRIBUTII PERSONALE

- CONTRIBUTIA 1: Primul studiu de cohorta multicentric romanesc (8 centre de dializa, toate regiunile istorice ale Romaniei, $n = 679$ pacienti, urmarire de 5 ani) demonstrand ca obezitatea dar nu supraponderalitatea este asociata independent cu mortalitate de orice cauza crescuta la hemodializa de intretinere, cu caracterizare ecocardiografica cuprinzatoare. Publicat: J Clin Med 2026;15(1):357. doi:10.3390/jcm15010357
- CONTRIBUTIA 2: Prima revizuire sistematica a modelelor ML de predictie a mortalitatii la pacientii hemodializati cu evaluarea cuprinzatoare a riscului de bias prin QUADAS-2 in 11

studii incluse, demonstrand AUC grupat echivalent pentru Random Forest si Regresia Logistica (0,78 fata de 0,77, $p = 0,82$) la urmarire de 1 an, si identificand absenta validarii externe ca bariera principala pentru implementare clinica. Publicat: Appl Sci 2025;15(10):5776. doi:10.3390/app15105776

- **CONTRIBUTIA 3:** Primul studiu de cohorta monocentric est-european cu pacienti incidenti la hemodializa ($n = 268$, Spitalul Pius Branzeu, Timisoara, 2022-2025) caracterizand mortalitatea la initierea dializei in era moderna a prevenirii cardiometabolice, demonstrand un "paradox al supraponderalitatii" (HR 0,22-0,31) distinct de paradoxul clasic al obezitatii si identificand tipare temporale distincte ale factorilor de risc. In press: J Clin Med. doi:10.3390/jcm15082856
- **CONTRIBUTIA 4:** Identificarea $eKt/V < 1,2$ masurat prin monitorizarea online a clearance-ului (OCM/Adimea) ca predictor independent al mortalitatii de orice cauza (HR 1,343, $p = 0,029$), chiar si dupa ajustarea pentru dimensiunea corporala si parametrii nutritionali, sustinand necesitatea prescriptiilor de dializa individualizate la pacientii obezi.
- **CONTRIBUTIA 5:** Demonstrarea ca trimiterea nefrologica foarte tardiva (< 3 luni, 61% din pacientii incidenti) reprezinta norma si nu exceptia in contextul est-european, si ca fiecare an suplimentar de urmarire nefrologica predializatica reduce independent mortalitatea la 3 ani cu 30% (HR 0,70, $p < 0,001$) - cel mai puternic factor modificabil identificat in cohorta incidenta.

9. PUBLICATII STIINTIFICE

- Motofelea Alexandru Catalin, Olariu N., Pecingina R., Marc L., Chisavu L., Bob F., Mihaescu A., Apostol A., Schiller O., Motofelea N., Pop G.N., Crintea A., Schiller A. BMI Category and Survival in Incident Hemodialysis Patients: The Overweight Advantage in an Eastern European Cohort. J Clin Med. 2026;15(8):2856. doi:10.3390/jcm15082856
- Motofelea Alexandru Catalin, Pecingina R., Olariu N., Marc L., Chisavu L., Bob F., Mihaescu A., Apostol A., Schiller O., Motofelea N., Schiller A. The Obesity Paradox Reconsidered: Evidence from a Multicenter Romanian Hemodialysis Cohort. J Clin Med. 2026;15(1):357. doi:10.3390/jcm15010357
- Motofelea Alexandru Catalin, Mihaescu A., Olariu N., Marc L., Chisavu L., Pop G.N., Crintea A., Jura A.M.C., Ivan V.M., Apostol A., Schiller A. Machine Learning Models for Predicting Mortality in Hemodialysis Patients: A Systematic Review. Appl Sci. 2025;15(10):5776. doi:10.3390/app15105776

10. DIRECTII VIITOARE DE CERCETARE

- Studiu longitudinal prospectiv cu masurare directa a compozitiei corporale (BIA, DEXA, circumferinta taliei, imagistica CT) pentru a diferentia contributiile masei grase si ale masei slabe la paradoxul obezitate/supraponderalitate in cohorte HD romanesti, si pentru a testa daca paradoxul supraponderalitatii persista dupa ajustarea pentru compozitia corporala.
- Validare prospectiva externa a celor mai buni modele ML identificate in revizuirea sistematica utilizand o cohorta independenta HD romaneasca sau est-europeana, cu raportare conforma TRIPOD si dimensiune suficienta a esantionului pentru analize pe subgrupuri (diabet vs. non-diabet, incidenti vs. prevalenti).
- Dezvoltarea si pilotarea clinica a unui registru prospectiv al pacientilor incidenti la hemodializa in Romania, integrând parametri nutritionali, inflamatori, de compozitie corporala, adecvanta dializei si medicatie, pentru stratificarea riscului bazata pe ML si suport decizional clinic in timp real.
- Investigarea impactului terapiilor cardiometabolice moderne (iSGLT2, GLP-1 RA, ARM) asupra profilului de risc la initierea dializei si a paradoxului obezitatii in cohorte incidente contemporane, prin studii de cohorta cu date de utilizare a medicamentelor colectate prospectiv.
- Analiza interactiunii dintre compozitia corporala, statusul inflamator (CRP, IL-6, TNF-alfa) si paradoxul obezitatii in hemodializa, utilizand masuratori longitudinale repetate si modele cu timp-variabil, pentru a testa ipoteza rezervei metabolice si a elucida mecanismele paradoxului supraponderalitatii.

