

**"VICTOR BABEȘ" UNIVERSITY OF
MEDICINE AND PHARMACY FROM TIMIȘOARA
DOCTORAL SCHOOL
MEDICINE DOMAIN**



HABILITATION THESIS

A HOLISTIC APPROACH TO THE CARDIO-RENO- METABOLIC CONTINUUM, FROM THE NEPHROLOGIST'S PERSPECTIVE

A B S T R A C T

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ABSTRACT

I chose Nephrology as my specialty of based on the conviction developed during my time at medical school that it is an essential branch of internal medicine, situated on top of medical knowledge, requiring a thorough understanding of the pathophysiological principles of human organ function and medical theory for their practical integration in various pathological cases.

The beginning of my academic career provided me with the opportunity to develop extensively in this specialty, combining scientific research with teaching skills and clinical acumen. Following the defense of my PhD thesis entitled "Atherosclerotic Disease and Chronic Kidney Disease: Clinical and Biological Correlations," supervised by Prof. Dr. Gaiță Dan, in November 2013 with the qualification of "Summa Cum Laude," a prolific period ensued for me both personally and professionally. Notable achievements were attained in academia, and the recognition of research efforts came through invitations as a lecturer to prestigious conferences and congresses, along with the publication of articles in journals with high impact factors. Certainly, all these achievements were celebrated in collaboration with the team with whom I conducted the studies and published the results.

Throughout my academic and professional career, I continued to be dedicated to studying the relationship between Chronic Kidney Disease (CKD) and cardiovascular pathology, both in dialysis and pre-dialysis CKD patients. Scientific activity, encompassing clinical studies on diverse patient categories with multiple pathologies, systematic research, and reviews of specialized literature, led to scientific outcomes disseminated through books, book chapters, and articles published in prestigious scientific journals.

As of August 19, 2023, the statistics of my scientific publications, according to Clarivate-Web of Knowledge are as follows: Hirsch index of 10, a total of 51 indexed publications with a total of 251 citations, published in 11 subfields, and a cumulative impact factor as the principal author (FCIAP) of 31,104.

The Habilitation Thesis aims to be a synthesis of my professional, academic, and scientific activities, prepared according to the recommendations of the Ministry of Education, the National Council for the Certification of Titles, Diplomas, and University Certificates (CNATDCU), adhering to the Guide for the Preparation and

Writing of the Habilitation Thesis, approved by the Council for Doctoral Studies at the "Victor Babeș" University of Medicine and Pharmacy Timișoara.

Chapter 1, titled "**Scientific Activity**," encompasses the most significant research results obtained during the postdoctoral period until the present, spanning a duration of 10 years. The chapter synthesizes the three main research directions that I focused on, categorized into three subchapters:

1.1 - Pathology of G1-G5 pre-dialysis CKD Patients: Analyzing specific epidemiological, diagnostic, progression, and treatment aspects for CKD patients.

- Detailed research assessing the prevalence, peculiarities, and prognosis of CKD patients with neoplastic diseases.
- Addressing the prevention and treatment of *Clostridioides difficile* infection in CKD patients through a systematic review of relevant literature.
- A systematic evaluation of evidence from relevant clinical studies on interventions to improve nutritional status in elderly CKD patients (over 65 years old).
- Early diagnosis of Gitelman syndrome in a patient, using cutting-edge genetic diagnostic techniques in collaboration with colleagues from the genetics discipline.
- Studying s-Klotho levels in patients with diabetic kidney disease (DKD), correlating them with renal function decline markers and interstitial fibrosis markers.
- Investigating the bidirectional communication between the liver and kidney (kidney-liver cross-talk) by analyzing the relationship between CKD and Metabolic-Associated Fatty Liver Disease (MAFLD).

1.2 - Pathology of G5 dialysis CKD Patients: Evaluating prognosis, complications, comorbidities, and the impact of specific therapeutic interventions on the quality and duration of life of CKD patients on chronic hemodialysis.

- Analyzing comorbidity trends and mortality in Romanian patients on chronic hemodialysis, highlighting improved survival in diabetic patients until the initiation of dialysis at older ages.
- Studying structural and functional changes in the left ventricle of hemodialysis patients using echocardiography, demonstrating that cardiovascular disease progresses over time in these patients.
- Addressing the issue of hepatitis B and C infections in chronically hemodialyzed patients, assessing the prevalence and trends of infection in response to preventive measures.
- Investigating vitamin D deficiency in hemodialysis patients and its association with mortality, indicating that severe vitamin D deficiency predicts increased all-cause mortality.
- Evaluating the effects of intradialytic exercise over three months on cardiovascular parameters and body composition in chronic hemodialysis patients.

1.3 - Atherosclerotic Cardiovascular Disease in Patients with Acute or Chronic Renal Impairment: Particular aspects of atherosclerotic diseases at various levels (peripheral vessels, cerebral vessels, heart) in patients with kidney damage.

- Evaluating the acute kidney injury (AKI) impact on patients with peripheral arterial disease, revealing a significant association between AKI and mortality and major cardiovascular events after surgery.
- Studying the relationship between AKI and cerebrovascular disease, showing that AKI presence or CKD increases mortality within 30 days after stroke.
- Investigating the bidirectional relationship between cardiovascular disease and CKD, highlighting the increased prevalence of cardiovascular disease in CKD patients, with a direct relationship to renal impairment severity.

Chapter 2, titled "**Academic Activity**," provides a chronological overview of my academic journey. In 2013, as a doctoral student, I began my career as a temporary assistant professor, having already been a nephrology specialist since

2009. Following the completion of my PhD in 2013, I successfully competed for an indefinite-term assistant professor position in 2014 at the Nephrology discipline of the "Victor Babeș" University of Medicine and Pharmacy Timișoara. In 2020, I obtained the title of "Șef de lucrări" (Lecturer), and since 2022, I have advanced further to the position of "Conferențiar Universitar" (Associate Professor) in the same discipline.

During my decade-long tenure as a teaching staff member at the Nephrology discipline, I continually improved my pedagogical skills by attending specialized teaching courses. I completed levels I and II of postgraduate pedagogical training modules, equivalent to a pedagogy master's degree, earned Competency Certificates in English and French, and participated in scientific and academic skills development courses organized by the Romanian Society of Nephrology and the European Renal Association.

My teaching activities have been divided into two major areas: university and post-university teaching. My university teaching activities include delivering courses, supervising practical internships, and mentoring research projects for medical students. I am involved in both Romanian and English-language study groups, and my mentorship extends to residents as well. I participate in courses, conferences, and scientific debates as a lecturer or moderator and am involved in organizing postgraduate courses (director of the postgraduate course "Doctor-Patient Communication"). In terms of post-university activities, I engage in coordinating the medical training of residents, presenting case studies, and reviewing significant medical and scientific subjects.

Chapter 3, titled "Professional Activity," offers a synthesis of my journey as a medical practitioner. I graduated from the Faculty of Medicine at the "Victor Babeș" University of Medicine and Pharmacy Timișoara in 2003 and became a resident in anesthesiology and intensive care at the Emergency Clinical County Hospital Timișoara. In 2004, I switched my residency specialty to nephrology and pursued residency training from 2004 to 2009.

During my residency, I had the opportunity to complete a 6-month training period at Imperial Renal and Transplant Centre in Hammersmith Hospital, Imperial College London, one of the largest nephrology centers in Europe, as a fellow of the International Society of Nephrology.

After successfully defending my PhD thesis in 2009, I became a nephrology specialist and practiced in the Nephrology Clinic at the County Hospital Timișoara. I also worked in outpatient nephrology clinics and private practices, as well as two private dialysis centers. I obtained a Competency Certificate in General Ultrasound in 2009. From 2015 until now, I have been practicing as a nephrology consultant in various medical settings.

I pursued a second paid residency in internal medicine at the Timișoara University Center, and since 2022, I have been a specialist in internal medicine following the successful completion of the specialty exam.

From March 2020 to June 2021, I was appointed as the medical coordinator of the temporary "Red Zone" non-critical COVID area, where I engaged in medical and organizational management activities for a 50-bed section treating patients with severe COVID and multiple comorbidities.

Chapter 4, titled "**Academic and Scientific Perspectives**," outlines my plans for future academic development. In terms of scientific research projects, I intend to continue collaborating with the Diabetes Clinic to evaluate preventive possibilities for chronic kidney disease development in light of new therapies. I aim to study non-proteinuric diabetic kidney disease through proteomic and/or genomic assessments.

Additionally, I plan to continue researching vascular calcifications in CKD patients, assessing the serum calcium propensity (T50) test in correlation with biological, clinical, and imaging calcification markers. Another collaborative national project focuses on evaluating the impact of immunosuppression on the intestinal microbiome of kidney patients, whether they are transplant recipients or have active systemic or isolated renal immune diseases.

I intend to continue studying the liver-kidney cross-talk, detecting and measuring biological markers to further understand the humoral pathways through which the liver and kidney influence each other. I also plan to initiate a research project with oncologists to assess the impact of new anti-neoplastic therapies on the kidney.

Regarding academic perspectives, I aim to enhance teaching methods through efficient integration of emerging technologies, create a comprehensive "nephrology internship guide" to enhance student practical training, and establish

collaborative "nephrology meetings" involving students and nephrology residents in interdisciplinary and practical discussions on medical topics.

I plan to participate in national and international conferences and congresses, organize and partake in interdisciplinary roundtable discussions, maintain membership in nephrology societies (Romanian Society of Nephrology, European Renal Association, International Society of Nephrology), and contribute to the publication and revision of nephrology guidelines.

I believe it is essential to be constantly engaged in a research team alongside nephrology colleagues and experts from various disciplines in Timișoara and other academic centers, contributing with my continuously improving professional, academic, and organizational skills to joint research.

The list of references completes the Habilitation Thesis, which also includes a list of the most significant scientific works published after the defense of the PhD Thesis.

LIST OF 10 REPRESENTATIVE SCIENTIFIC PAPERS

1. Chisavu, Lazar; **Mihaescu, Adelina**; Bob, Flaviu; Motofelea, Alexandru; Schiller, Oana; Marc, Luciana; Dragota-Pascota, Razvan; Chisavu, Flavia; Schiller, Adalbert - Trends in mortality and comorbidities in hemodialysis patients between 2012 and 2017 in an East-European Country: a retrospective study, INTERNATIONAL UROLOGY AND NEPHROLOGY, 2023, doi:10.1007/s11255-023-03549-6 (**FI 2**) <https://rdcu.be/djXsf>
2. Marc, Luciana; **Mihaescu, Adelina**; Lupusoru, Raluca; Schiller, Oana; Bob, Flaviu; Chisavu, Lazar; Bende, Felix; Sirli, Roxana; Schiller, Adalbert - Hepatitis C and hepatitis B virus infection in hemodialysis patients after nationwide direct antiviral agents therapy-experience of 10 Romanian HD centers, INTERNATIONAL UROLOGY AND NEPHROLOGY, 2023, doi 10.1007/s11255-023-03587-0 (**FI 2**) <https://rdcu.be/djXrP>
3. Marc, Luciana; **Mihaescu, Adelina**; Lupusoru, Raluca; Grosu, Iulia; Gadalean, Florica; Bob, Flaviu; Chisavu, Lazar; Olariu, Nicu; Tucicovschi, Vlad; Timar, Bogdan; Sporea, Ioan; Timar, Romulus; Schiller, Adalbert - Liver Steatosis: Better Predictor of CKD in MAFLD Than Liver Fibrosis as Determined by Transient Elastography With Controlled Attenuation Parameter, FRONTIERS IN MEDICINE, 2022, 8:788881. doi: 10.3389/fmed.2021.788881 (**FI 5,058**) <https://doi.org/10.3389/fmed.2021.788881>
4. Ciorcan, Mircea; Chisavu, Lazar; **Mihaescu, Adelina**; Gadalean, Florica; Bob, Flaviu Raul; Negru, Serban; Marina Schiller, Oana; Dana Grosu, Iulia; Marc, Luciana; Chisavu, Flavia; Dragota Pascota, Razvan; Apostol, Adrian; Ivan, Viviana; Schiller, Adalbert - Chronic kidney disease in cancer patients, the analysis of a large oncology database from Eastern Europe, PlosOne, 2022, 17(6), 10.1371/journal.pone.0265930 (**FI 3,752**) <https://doi.org/10.1371/journal.pone.0265930>
5. **Mihaescu, Adelina**; Augustine, Arlyn Maria; Khokhar, Hassan Tahir; Zafran, Mohammed; Masood, Syed Shah Mohammed Emmad; Gilca-Blanariu, Georgiana-Emmanuela; Covic, Adrian; Nistor, Ionut - Clostridioides difficile Infection in Patients with Chronic Kidney Disease: A Systematic Review,

BIOMED RESEARCH INTERNATIONAL, 2021, DOI:10.1155/2021/5466656;
WOS:000700336000001 (**FI 3,411**) <https://doi.org/10.1155/2021/5466656>

6. **Mihaescu, Adelina**; Masood, Emmad; Zafran, Mohammed; Khokhar, Hassan Tahir; Augustine, Arlyn Maria; Filippo, Aucella; Van Biesen, Wim; Farrington, Ken; Carrero, Juan Jesus; Covic, Adrian; Nistor, Ionut - Nutritional status improvement in elderly CKD patients: a systematic review, INTERNATIONAL UROLOGY AND NEPHROLOGY, 2021, 53(8): 1603-1621; DOI 10.1007/s11255-020-02775-6 (**FI 2,37**) <https://rdcu.be/djXuP>

7. Chisavu, Lazar A.; Apostol, Adrian; Pop, Gheorghe N.; Ivan, Viviana; Schiller, Oana; Bob, Flaviu; Marc, Luciana; **Mihaescu, Adelina**; Gadalean, Florica; Grosu, Iulia; Timar, Bogdan; Schiller, Adalbert - Exploring the relation between mortality and left ventricular structure and function in stable hemodialysis treated patients, a longitudinal multicenter cohort study, SCIENTIFIC REPORTS, 2021; 11 (1); DOI:10.1038/s41598-021-91431-9 (**FI 4,38**) <https://rdcu.be/djXuI>

8. Gug, Cristina; **Mihaescu, Adelina**; Mozos, Ioana - Two mutations in the thiazide-sensitive NaCl co-transporter gene in a Romanian Gitelman syndrome patient: case report, THERAPEUTICS AND CLINICAL RISK MANAGEMENT, 2018;14:149-155; DOI10.2147/TCRM.S150483 (**FI 1,82**) <https://doi.org/10.2147/TCRM.S150483>

9. Schiller, Adalbert; Gadalean, Florica; Schiller, Oana; Timar, Romulus; Bob, Flaviu; Munteanu, Mircea; Stoian, Dana; **Mihaescu, Adelina**; Timar, Bogdan - Vitamin D Deficiency-Prognostic Marker or Mortality Risk Factor in End Stage Renal Disease Patients with Diabetes Mellitus Treated with Hemodialysis-A Prospective Multicenter Study, PLOS ONE; 2015; 10(5):e0126586. doi: 10.1371/journal.pone.0126586. eCollection 201 (**FI 4,41**) <https://doi.org/10.1371/journal.pone.0126586>

10. Gaita, Dan; Gaita, Laura; **Mihaescu, Adelina** - Non-HDL cholesterol series: PCSK9 inhibitor new season! EUROPEAN JOURNAL OF PREVENTIVE CARDIOLOGY; 2020;27(15):1661-1662; ISSN2047-4873, DOI10.1177/2047487320913375 (**FI 7,804**) <https://doi.org/10.1177/2047487320913375>