LUMEN ET VIRTUS
ISSN: 2177-2789

MULTISYSTEM TOXICITY OF CANCER THERAPIES: INTERACTIONS BETWEEN CARDIAC, RENAL, AND METABOLIC PATHWAYS

TOXICIDADE MULTISSISTÊMICA DE TERAPIAS CONTRA O CÂNCER: INTERAÇÕES ENTRE AS VIAS CARDÍACA, RENAL E METABÓLICA

TOXICIDAD MULTISISTÉMICA DE LAS TERAPIAS CONTRA EL CÁNCER: INTERACCIONES ENTRE LAS VÍAS CARDÍACA, RENAL Y METABÓLICA

https://doi.org/10.56238/levv16n53-094

Submission date: 09/23/2025 **Publication date:** 10/23/2025

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ABSTRACT

Introduction: The growing success of oncological therapies has redefined cancer as a chronic disease, yet these advances are increasingly accompanied by cardiovascular, renal, and metabolic complications that threaten long-term survival and quality of life. The interaction between these systems creates a complex clinical scenario in which injury to one organ often amplifies dysfunction in others.

Objective: To analyze the mechanisms, clinical manifestations, and diagnostic strategies associated with the multisystem toxicity of cancer therapies, emphasizing the interconnection between cardiac, renal, and metabolic alterations and the implications for integrated management.

Methods: A narrative systematic review was performed through searches in PubMed, Scopus, Web of Science, Cochrane Library, and Google Scholar, including studies published between 2015 and 2025 that investigated cardiotoxic, nephrotoxic, or metabolic side effects of chemotherapy, targeted therapy, and immunotherapy.

Results and Discussion: Anthracyclines, HER2 inhibitors, tyrosine kinase inhibitors, and immune checkpoint inhibitors remain the most frequent agents linked to cardiovascular dysfunction, while cisplatin, ifosfamide, and VEGF inhibitors are prominent in renal injury. Metabolic complications such as insulin resistance, dyslipidemia, and sarcopenic obesity have been increasingly recognized as interconnected sequelae. Recent studies demonstrate that biomarkers and multimodal imaging facilitate early detection, whereas multidisciplinary

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management—combining cardio-oncology, nephrology, and endocrinology—reduces adverse outcomes.

Conclusion: The multisystem toxicity of oncological treatments constitutes a major challenge for contemporary oncology. An integrated approach is essential to maintain therapeutic efficacy while minimizing organ damage and preserving patient longevity and well-being.

Keywords: Cardio-oncology. Nephrotoxicity. Metabolic Dysregulation. Cancer Therapy.

RESUMO

Introdução: O crescente sucesso das terapias oncológicas redefiniu o câncer como uma doença crônica, mas esses avanços são cada vez mais acompanhados por complicações cardiovasculares, renais e metabólicas que ameaçam a sobrevida e a qualidade de vida a longo prazo. A interação entre esses sistemas cria um cenário clínico complexo, no qual a lesão em um órgão frequentemente amplifica a disfunção em outros.

Objetivo: Analisar os mecanismos, as manifestações clínicas e as estratégias diagnósticas associadas à toxicidade multissistêmica das terapias contra o câncer, com foco na interconexão entre alterações cardíacas, renais e metabólicas e nas implicações para o manejo integrado.

Métodos: Uma revisão sistemática narrativa foi realizada por meio de buscas no PubMed, Scopus, Web of Science, Biblioteca Cochrane e Google Acadêmico, incluindo estudos publicados entre 2015 e 2025 que investigaram os efeitos colaterais cardiotóxicos, nefrotóxicos ou metabólicos da quimioterapia, terapia direcionada e imunoterapia.

Resultados e Discussão: Antraciclinas, inibidores de HER2, inibidores de tirosina quinase e inibidores de checkpoint imunológico continuam sendo os agentes mais frequentemente associados à disfunção cardiovascular, enquanto cisplatina, ifosfamida e inibidores de VEGF são proeminentes na lesão renal. Complicações metabólicas, como resistência à insulina, dislipidemia e obesidade sarcopênica, têm sido cada vez mais reconhecidas como sequelas interconectadas. Estudos recentes demonstram que biomarcadores e exames de imagem multimodal facilitam a detecção precoce, enquanto o tratamento multidisciplinar — combinando cardio-oncologia, nefrologia e endocrinologia — reduz desfechos adversos.

Conclusão: A toxicidade multissistêmica dos tratamentos oncológicos constitui um grande desafio para a oncologia contemporânea. Uma abordagem integrada é essencial para manter a eficácia terapêutica, minimizando os danos aos órgãos e preservando a longevidade e o bem-estar do paciente.

Palavras-chave: Cardio-oncologia. Nefrotoxicidade. Desregulação Metabólica. Terapia do Câncer.

RESUMEN

Introducción: El creciente éxito de las terapias oncológicas ha redefinido el cáncer como una enfermedad crónica. Sin embargo, estos avances se acompañan cada vez más de complicaciones cardiovasculares, renales y metabólicas que amenazan la supervivencia a largo plazo y la calidad de vida. La interacción entre estos sistemas crea un escenario clínico complejo en el que la lesión de un órgano a menudo amplifica la disfunción en otros.

Objetivo: Analizar los mecanismos, las manifestaciones clínicas y las estrategias diagnósticas asociadas con la toxicidad multisistémica de las terapias oncológicas,

centrándose en la interconexión entre las alteraciones cardíacas, renales y metabólicas y las implicaciones para el manejo integral.

Métodos: Se realizó una revisión sistemática narrativa mediante búsquedas en PubMed, Scopus, Web of Science, Cochrane Library y Google Scholar, incluyendo estudios publicados entre 2015 y 2025 que investigaron los efectos secundarios cardiotóxicos, nefrotóxicos o metabólicos de la quimioterapia, la terapia dirigida y la inmunoterapia.

Resultados y discusión: Las antraciclinas, los inhibidores de HER2, los inhibidores de la tirosina quinasa y los inhibidores de puntos de control inmunitario siguen siendo los agentes más frecuentemente asociados con la disfunción cardiovascular, mientras que el cisplatino, la ifosfamida y los inhibidores del VEGF son importantes en la lesión renal. Las complicaciones metabólicas, como la resistencia a la insulina, la dislipidemia y la obesidad sarcopénica, se reconocen cada vez más como secuelas interconectadas. Estudios recientes demuestran que los biomarcadores y la imagen multimodal facilitan la detección temprana, mientras que el manejo multidisciplinario —que combina cardiooncología, nefrología y endocrinología— reduce los resultados adversos.

Conclusión: La toxicidad multisistémica de los tratamientos oncológicos constituye un desafío importante para la oncología contemporánea. Un enfoque integrado es esencial para mantener la eficacia terapéutica, minimizar el daño orgánico y preservar la longevidad y el bienestar del paciente.

Palabras clave: Cardiooncología. Nefrotoxicidad. Desregulación Metabólica. Terapia Oncológica.

1 INTRODUCTION

The expanding therapeutic arsenal in oncology has substantially improved cancer survival but has also led to a significant rise in treatment-related organ toxicities, particularly involving the cardiovascular, renal, and metabolic systems[1]. Anthracyclines, HER2-targeted therapies, tyrosine kinase inhibitors, and immune checkpoint inhibitors (ICIs) represent key contributors to these adverse events[2]. Their cumulative toxicity poses a major clinical challenge, transforming the focus of oncological care from short-term remission to long-term survivorship and chronic disease management[3]. This paradigm shift has given rise to cardio-oncology and onconephrology as emerging interdisciplinary fields that aim to balance efficacy with safety[4].

Anthracyclines remain indispensable for the treatment of hematologic malignancies, sarcomas, and breast cancer, yet their well-documented cardiotoxic potential continues to be a limiting factor[5]. Mechanistic studies indicate that oxidative stress, mitochondrial injury, and interference with topoisomerase IIβ (topoisomerase II beta) pathways are central to myocardial damage[6]. Despite the use of preventive agents such as dexrazoxane and liposomal formulations, subclinical injury can persist and evolve into heart failure over time[7]. The cumulative dose-dependent nature of anthracycline toxicity highlights the need for stringent surveillance and risk stratification protocols[8].

HER2-targeted monoclonal antibodies, particularly trastuzumab and pertuzumab, have revolutionized breast cancer therapy but introduced new cardiovascular concerns[9]. The inhibition of neuregulin-1/ErbB signaling impairs cardiomyocyte repair and contractility, often resulting in reversible left ventricular dysfunction[10]. Long-term follow-up studies, however, suggest that repeated HER2 blockade can lead to chronic remodeling and recurrent heart failure episodes[11]. Therefore, serial echocardiography and cardiac biomarker assessments are recommended throughout and after treatment[12].

Tyrosine kinase inhibitors (TKIs) used in hematologic and solid tumors—such as imatinib, sunitinib, and sorafenib—have been associated with hypertension, ischemia, and heart failure through mechanisms involving endothelial dysfunction and inhibition of vascular endothelial growth factor (VEGF) signaling[13]. These adverse effects can be compounded by traditional cardiovascular risk factors such as diabetes and dyslipidemia[14]. Persistent hypertension during TKI therapy not only predicts cardiovascular events but also correlates with renal injury and microvascular damage[15].

Immunotherapy, particularly with ICIs targeting programmed death receptor 1 (PD-1) or cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), has redefined cancer treatment but introduced a new spectrum of immune-mediated toxicities[16]. Immune-related myocarditis,

although rare, carries a high fatality rate, and its early diagnosis relies on troponin surveillance and cardiac magnetic resonance imaging[17]. These agents can also induce systemic inflammation that extends to the kidneys and metabolic pathways, producing overlapping toxic effects across organ systems[18]. Recognizing these interrelations has become vital for patient safety in the immuno-oncology era[19].

Renal toxicity remains an equally significant concern across oncological therapies[20]. Cisplatin, methotrexate, and ifosfamide are classical nephrotoxic agents, while VEGF inhibitors and checkpoint inhibitors have emerged as novel contributors[21]. Nephrotoxicity mechanisms include ischemic tubular injury, endothelial dysfunction, and immune-mediated glomerulonephritis[22]. Chronic kidney disease following chemotherapy can limit further oncological options and increase mortality from cardiovascular causes[23]. Thus, early recognition of renal involvement is critical for optimizing therapy[24].

Metabolic disturbances such as insulin resistance, hyperglycemia, and dyslipidemia are increasingly reported in patients undergoing cancer therapy[25]. Corticosteroids, mammalian target of rapamycin (mTOR) inhibitors, and androgen deprivation therapy contribute to these metabolic derangements[26]. Emerging evidence indicates that metabolic toxicity not only affects quality of life but also predisposes survivors to accelerated cardiovascular aging[27]. Consequently, multidisciplinary interventions involving endocrinology have become central to survivorship programs[28].

The concept of the “cardio-renal-metabolic axis” has gained relevance as studies reveal that injury to one organ system can precipitate dysfunction in others[29]. For instance, cardiotoxicity can lead to renal hypoperfusion, while renal dysfunction exacerbates hypertension and metabolic dysregulation[30]. These intertwined pathophysiological pathways demand an integrated management strategy beyond isolated organ-based approaches[31]. Multimodal monitoring—combining biomarkers, imaging, and functional testing—has been proposed to detect early multisystem involvement[32].

Advancements in biomarkers such as high-sensitivity troponin, N-terminal pro–B-type natriuretic peptide (NT-proBNP), cystatin C, and kidney injury molecule-1 (KIM-1) now allow for earlier identification of subclinical damage[33]. Likewise, global longitudinal strain (GLS) and cardiac magnetic resonance provide enhanced sensitivity for detecting myocardial changes before left ventricular ejection fraction declines[34]. Integration of these diagnostic modalities has strengthened the foundation of preventive cardio-oncology[35].

Ultimately, the recognition of multisystem toxicity represents a shift from compartmentalized medicine to systemic precision oncology[36]. By understanding the molecular crosstalk among cardiac, renal, and metabolic systems, clinicians can tailor

therapies and reduce long-term sequelae[37]. Future research must focus on risk prediction, real-time monitoring, and pharmacological innovation to mitigate these toxicities without compromising antitumor efficacy[38]. The need for collaboration among oncologists, cardiologists, nephrologists, and endocrinologists has never been more evident[39].

2 OBJECTIVES

The primary objective of this review is to analyze the multisystem toxicities induced by oncological therapies, with particular emphasis on the interconnected mechanisms underlying cardiac, renal, and metabolic dysfunctions. This work aims to delineate how these adverse effects interact pathophysiologically, identify diagnostic and monitoring strategies that enable early detection, and propose integrative approaches for clinical management.

Specific objectives:

1. To identify the main classes of chemotherapeutic, targeted, and immunotherapeutic agents associated with cardiovascular, renal, and metabolic toxicity.
2. To describe the cellular and molecular mechanisms involved in the development of multisystem injury during cancer therapy.
3. To evaluate diagnostic tools, including imaging and biomarkers, for the early identification of subclinical dysfunction.
4. To discuss preventive and therapeutic strategies that mitigate treatment-related organ damage without compromising oncological efficacy.
5. To highlight the relevance of multidisciplinary collaboration—combining oncology, cardiology, nephrology, and endocrinology—in reducing morbidity and improving long-term outcomes.

3 METHODOLOGY

This study was designed as a narrative systematic review integrating clinical, experimental, and translational evidence from the contemporary literature. The methodological framework followed the standards for qualitative synthesis used in biomedical research and aimed to provide a critical overview of recent advances in the field of cardio-oncology and onconephrology.

3.1 SEARCH STRATEGY

A comprehensive search was conducted in the databases PubMed, Scopus, Web of Science, Cochrane Library, and Google Scholar. The search included articles published between January 2015 and March 2025. The following controlled terms and free-text

combinations were applied using Boolean operators: ("cardiotoxicity" OR "cardio-oncology") AND ("nephrotoxicity" OR "onconephrology") AND ("metabolic complications" OR "metabolic disorders") AND ("cancer therapy" OR "chemotherapy" OR "targeted therapy" OR "immunotherapy"). Filters were applied to include only studies conducted in humans and published in English, Portuguese, or Spanish.

3.2 INCLUSION AND EXCLUSION CRITERIA

Studies were included if they (1) evaluated cardiovascular, renal, or metabolic adverse effects of oncological therapies; (2) presented clinical, observational, or experimental data; and (3) discussed preventive or monitoring strategies. Eligible study types comprised randomized controlled trials, cohort and case-control studies, systematic reviews, meta-analyses, and clinical guidelines. Exclusion criteria included case reports, editorials, letters, and studies focusing exclusively on radiotherapy or surgical outcomes.

4 RESULTS

A total of **26 studies** published between 2015 and 2025 met the eligibility criteria. After screening 1,247 initial records, 1,061 were excluded based on title and abstract and 160 after full-text evaluation. The final sample comprised **clinical trials, observational cohorts, reviews, and international guidelines** that explored the cardiovascular, renal, and metabolic toxicities of oncological therapies.

Most studies addressed cardiotoxicity associated with **anthracyclines, HER2 inhibitors, and tyrosine kinase inhibitors (TKIs)**. A substantial number evaluated **renal impairment** related to **platinum-based agents, VEGF inhibitors, and immune checkpoint inhibitors (ICIs)**. Others focused on **metabolic disturbances**, including dyslipidemia, insulin resistance, and sarcopenic obesity, secondary to corticosteroids, mTOR inhibitors, and endocrine therapy.

Table 1

Summarizes the key studies included, ordered chronologically by publication year, highlighting the main findings and clinical conclusions

Author / Year	Study Type / Objective	Main Results	Conclusion
Curigliano et al., 2022	ESC Guidelines on cancer therapy-related cardiovascular toxicity	Defined mechanisms, risk stratification, and structured monitoring algorithms	Multidisciplinary management reduces treatment interruptions and adverse outcomes
Pudil et al., 2023	Review on biomarker-based surveillance in cardio-oncology	Validated troponin and NT-proBNP for early cardiotoxicity detection	Biomarker-guided monitoring improves outcomes
Zhang et al., 2021	Cohort on anthracycline-induced cardiomyopathy	Confirmed cumulative dose-dependent LV dysfunction	Dose limitation and cardioprotective strategies remain essential
Wallace et al., 2021	Mechanistic review of oxidative and mitochondrial damage	Identified mitochondrial ROS as central to anthracycline toxicity	Targeting oxidative stress may enhance cardioprotection
Parrella et al., 2023	Prospective study on HER2-targeted therapy	LV dysfunction occurred in 9% of patients, mostly reversible	Regular imaging and biomarker follow-up recommended
Eschenhagen et al., 2021	Translational research on VEGF inhibition	Demonstrated endothelial injury as mechanism of hypertension and renal dysfunction	BP control and renal monitoring mitigate toxicity
Moslehi et al., 2021	Review on immune checkpoint inhibitor myocarditis	Reported ~1% incidence with high lethality	Early diagnosis via troponin and MRI improves survival
Mahmood et al., 2022	Registry of ICI-related cardiotoxicity	Identified high-risk subgroups with combined therapies	Cardiac surveillance should be mandatory in ICI protocols
Kitchlu et al., 2022	Cohort on cisplatin nephrotoxicity	25–30% developed acute kidney injury	Hydration and dose adjustment remain crucial
Perazella et al., 2022	Narrative review on onconephrology	Emphasized overlap between renal and cardiovascular toxicities	Integrative onco-nephrology approach needed
Namba et al., 2023	Review on targeted therapy nephrotoxicity	VEGF inhibitors associated with proteinuria and hypertension	Early detection via urinalysis and KIM-1 suggested

Author / Year	Study Type / Objective	Main Results	Conclusion
Bottinor et al., 2020	Review on immune-mediated renal toxicity	Described glomerulonephritis in ICI-treated patients	Corticosteroids effective in most immune nephritis cases
Gonçalves et al., 2023	Clinical study on metabolic dysfunction post-therapy	Identified increased insulin resistance and lipid alterations	Lifestyle and pharmacologic interventions reduce morbidity
Saad et al., 2021	Review on endocrine toxicity in oncology	Described mTOR- and steroid-induced metabolic syndromes	Routine metabolic monitoring recommended
Blaes et al., 2023	Review on chronic cardiovascular risk in cancer survivors	Highlighted persistent CV risk decades post-treatment	Lifelong surveillance warranted for all survivors
López-Fernández et al., 2022	Study on imaging in cardio-oncology	Showed GLS detects early dysfunction before LVEF decline	GLS recommended in serial cardiac assessment
Zhang et al., 2020	Study on cardiac strain imaging	Confirmed predictive role of GLS in anthracycline users	Subclinical dysfunction detectable before symptoms
Lyon et al., 2023	Prospective cardio-oncology program	Reduced hospitalizations and improved adherence	Multidisciplinary care improves cancer outcomes
Herrmann et al., 2020	Cohort on multi-organ toxicity	Reported overlapping cardiac, renal, and metabolic dysfunction	Reinforced need for integrated follow-up
de Boer et al., 2021	Review on cardio-renal-metabolic axis	Proposed triadic model linking cardiac, renal, and metabolic injury	Advocated systemic rather than isolated management
Adão et al., 2022	Experimental study on endothelial dysfunction	Demonstrated cross-talk between heart and kidney pathways	Endothelial protection may limit multi-organ injury
Thavendiranathan et al., 2020	Imaging-based follow-up study	Early GLS changes predicted cardiac events	Supports preventive screening in high-risk patients
Pudil et al., 2024	Translational review	Integrated biomarkers with imaging for early detection	Multimodal surveillance improves precision medicine
Mir et al., 2021	Study on immune-mediated metabolic syndrome	Reported autoimmune diabetes and dyslipidemia after ICIs	Interdisciplinary management essential
Gonçalves et al., 2023	Review on inflammation-driven metabolic toxicity	Identified cytokine-mediated insulin resistance	Anti-inflammatory therapy may reduce sequelae

Author / Year	Study Type / Objective	Main Results	Conclusion
Lyon et al., 2024	Prospective evaluation of integrated care model	Demonstrated reduction in mortality and treatment interruption	Cardio-onco-nephrology clinics improve survival

The data synthesis across these studies reveals a **convergent pattern of multisystem toxicity**, emphasizing that oncological agents rarely affect a single organ system in isolation. Cardiovascular dysfunction frequently coincided with renal impairment and metabolic dysregulation, reinforcing the existence of a **cardio-renal-metabolic axis**.

The results also highlight a clear **evolution in diagnostic precision**, with biomarkers such as high-sensitivity troponin, NT-proBNP, cystatin C, and KIM-1 enabling earlier identification of subclinical damage. Likewise, advanced echocardiography (GLS) and cardiac magnetic resonance have become indispensable for surveillance, often detecting dysfunction before the onset of symptoms.

Preventive measures, including **dose adjustment, hydration protocols, antioxidant therapy, and dexrazoxane**, proved effective in reducing cardiotoxicity, though heterogeneity among studies limits definitive conclusions. Most importantly, **multidisciplinary care programs** were consistently associated with reduced hospitalization rates, improved treatment adherence, and lower morbidity, confirming the need for integrative cardio-onco-nephrology models in modern oncology.

5 DISCUSSION

The integration of cardiovascular, renal, and metabolic toxicities as a unified field of study has transformed the understanding of adverse events associated with oncological therapies. Recent evidence demonstrates that these toxicities rarely occur in isolation and frequently interact through shared molecular pathways involving oxidative stress, inflammation, and endothelial dysfunction. Such overlap explains why damage to one organ system often propagates dysfunction in others, leading to what is now described as the cardio-renal-metabolic syndrome in oncology.

The updated European Society of Cardiology (ESC) guidelines by Curigliano et al. established a critical foundation for structured prevention and surveillance in cardio-oncology. These recommendations emphasize risk stratification before treatment initiation, periodic cardiac monitoring, and the inclusion of cardioprotective agents when indicated. Subsequent multicenter cohorts, such as those by Lyon and colleagues, confirmed that multidisciplinary cardio-oncology programs significantly reduce treatment interruptions and mortality, highlighting the impact of organized care delivery models.

Anthracyclines remain a cornerstone of cancer treatment but continue to represent one of the most studied causes of chemotherapy-induced cardiotoxicity. Investigations by Zhang and Wallace revealed that cumulative dose, oxidative stress, and mitochondrial injury are central to myocardial damage. Mitochondrial ROS accumulation disrupts ATP production and triggers apoptosis, explaining the progressive nature of left ventricular dysfunction. Advances in molecular imaging now allow subclinical changes to be detected before symptomatic heart failure develops. Preventive measures such as dexrazoxane and liposomal doxorubicin have shown consistent efficacy in limiting injury without compromising tumor response, yet their implementation remains inconsistent across centers.

HER2-directed agents such as trastuzumab and pertuzumab have dramatically improved outcomes in breast cancer but introduced distinct patterns of cardiac dysfunction. Parrella and colleagues demonstrated that left ventricular ejection fraction declines in nearly one in ten patients, often reversible after therapy discontinuation. However, recurrent or late dysfunction has also been reported, indicating possible incomplete myocardial recovery. Integration of global longitudinal strain (GLS) in echocardiographic monitoring allows earlier identification of subtle myocardial impairment, reducing the likelihood of permanent damage.

Tyrosine kinase inhibitors (TKIs) introduce additional cardiovascular risks, particularly hypertension, ischemia, and heart failure. Eschenhagen's translational studies revealed that these effects arise primarily from endothelial injury secondary to VEGF pathway inhibition, leading to capillary rarefaction and increased afterload. The combination of TKIs with pre-existing cardiovascular comorbidities magnifies this risk. Strict blood pressure control and early cardiology co-management are now recommended standard practices for all patients receiving VEGF inhibitors.

The introduction of immune checkpoint inhibitors (ICIs) represented a paradigm shift in oncology but simultaneously exposed patients to new immune-mediated toxicities. Moslehi and Mahmood identified immune-related myocarditis as one of the most severe, albeit infrequent, complications, with mortality rates approaching 50% in certain series. The pathophysiology involves autoimmune infiltration of cardiac tissue, which can also affect renal glomeruli and endocrine organs. Cardiac magnetic resonance imaging and high-sensitivity troponin testing are now integral to early detection. Prompt initiation of corticosteroids has been associated with improved survival, underscoring the importance of clinical vigilance.

Renal complications remain a major determinant of treatment discontinuation. Kitchlu and Perazella described cisplatin-induced nephrotoxicity as one of the most prevalent and preventable adverse effects in oncology. The mechanisms include tubular necrosis, mitochondrial dysfunction, and renal vasoconstriction, all potentiated by dehydration and

concurrent nephrotoxins. Preventive measures such as aggressive hydration and magnesium supplementation remain the mainstay of management, though residual chronic kidney disease persists in a subset of patients.

Emerging therapies such as VEGF inhibitors, ICIs, and CAR-T cell therapy have expanded the spectrum of immune-mediated renal injury. Namba and Bottinor documented patterns of glomerulonephritis and interstitial nephritis secondary to immune activation, frequently coexisting with cardiovascular or metabolic disorders. Corticosteroid therapy remains effective in most cases, though the growing number of affected patients calls for standardized diagnostic and therapeutic algorithms.

Metabolic disturbances induced by cancer therapies have gained increased recognition as long-term contributors to morbidity. Gonçalves and Saad identified a high prevalence of insulin resistance, hyperlipidemia, and sarcopenic obesity among survivors, often exacerbated by corticosteroids and mTOR inhibitors. These changes accelerate vascular aging and predispose patients to atherosclerosis and type 2 diabetes. Interventional studies support lifestyle modification, structured exercise, and pharmacologic metabolic control as effective strategies to mitigate these effects.

The long-term perspective provided by Blaes and colleagues underscores that cardiovascular and metabolic risk persists for decades after the end of treatment. This finding reinforces the need for lifelong follow-up of cancer survivors, integrating oncological and cardiometabolic care. López-Fernández and Thavendiranathan advanced the field further by validating imaging modalities such as GLS and cardiac magnetic resonance for early identification of subclinical dysfunction, providing opportunities for preemptive intervention before irreversible structural changes occur.

Herrmann and de Boer expanded the concept of the cardio-renal-metabolic axis, highlighting that the heart, kidneys, and metabolic pathways form an interdependent system. Dysregulation in one component triggers compensatory but ultimately deleterious adaptations in others. For instance, renal impairment exacerbates hypertension and left ventricular remodeling, while hyperglycemia and dyslipidemia amplify oxidative stress. This interconnection explains why multisystem monitoring yields superior outcomes compared to organ-specific approaches.

Adão's experimental work further elucidated endothelial dysfunction as the central link between cardiac and renal injury. Damaged endothelium disrupts nitric oxide signaling and microvascular homeostasis, predisposing to fibrosis and inflammation. These mechanistic insights are critical for the development of novel endothelium-protective therapies capable of simultaneously mitigating cardiac and renal damage.

6 CONCLUSION

The progressive integration of biomarkers, imaging, and clinical risk models has ushered in a new era of precision medicine in cardio-oncology. Studies by Pudil and Lyon demonstrated that multimodal surveillance combining troponin, NT-proBNP, cystatin C, and imaging parameters markedly improves detection accuracy and reduces adverse event rates. Implementation of these programs, however, remains uneven across healthcare systems, often limited by resource availability and lack of interdisciplinary infrastructure.

The collective evidence across these studies confirms that multidisciplinary care models are not merely advantageous but essential. Coordinated collaboration between oncology, cardiology, nephrology, and endocrinology results in fewer treatment interruptions, better control of comorbidities, and improved overall survival. Lyon's 2024 multicenter evaluation provided quantitative support for this approach, demonstrating significant reductions in hospitalization and mortality when cardio-onco-nephrology services were embedded in cancer centers.

Despite remarkable progress, challenges remain. The heterogeneity of study populations and endpoints limits generalizability, and many clinical trials exclude patients with pre-existing cardiac or renal disease, underestimating real-world risk. Furthermore, most available studies are short-term, whereas chronic sequelae often manifest years after therapy. Future research must prioritize longitudinal multicenter studies capable of capturing late toxicities and evaluating novel protective interventions such as genetic risk profiling, antioxidant therapies, and AI-driven monitoring systems.

In summary, the reviewed literature reinforces that oncological therapies exert a complex, interconnected pattern of injury across the cardiac, renal, and metabolic systems. Understanding and addressing these interactions requires a paradigm shift from compartmentalized to systemic, integrative care. The ultimate goal is to achieve effective cancer control while preserving long-term organ health and quality of life.

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