

Article

Chemotherapy-Induced Renal Ischemia-Reperfusion Injury and Its Psychosocial Consequences in Oncology Patients: Mechanistic Evidence from the Nrf2/HO-1/NQO1–Mitophagy Pathway and Implications for Multidisciplinary Cancer Care

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CITATION

Guo Z, Yi J, Fan J, et al. Chemotherapy-Induced Renal Ischemia-Reperfusion Injury and Its Psychosocial Consequences in Oncology Patients: Mechanistic Evidence from the Nrf2/HO-1/NQO1–Mitophagy Pathway and Implications for Multidisciplinary Cancer Care. *Psycho-Oncologie*. 2026; 20(3): 5819. <https://doi.org/10.18282/po5819>

ARTICLE INFO

Received: 15 July 2025

Revised: 12 April 2026

Accepted: 24 April 2026

Available online: 30 April 2026

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Abstract: Background: Chemotherapy-induced renal ischemia-reperfusion injury (CI-RIRI) is an undercharacterized but clinically significant complication in oncology, impacting an estimated 30–45% of patients undergoing platinum-based and antiangiogenic therapy. The molecular interaction between oxidative stress, dysregulation of mitophagy and the Nrf2/HO-1/NQO1 cytoprotective axis has not been fully studied in the framework of its subsequent psychosocial consequences. **Objective:** The study was conducted to (1) clarify the mechanistic role of Nrf2/HO-1/NQO1–PINK1–Parkin mitophagy pathway in CI-RIRI, (2) measure the renal functional decline during multiple chemotherapy cycles, (3) determine the psychosocial burden in patients with CI-RIRI, and (4) recommend evidence-based multidisciplinary care frameworks. **Methods:** A potential observational cohort study recruited 284 adult oncology patients receiving cisplatin, oxaliplatin, carboplatin, or bevacizumab regimens in three tertiary centers (2022–2024). Renal biomarkers (serum creatinine, cystatin C, NGAL, KIM-1, IL-18), Nrf2 pathway proteins (HO-1, NQO1, Keap1), mitophagy markers (PINK1, Parkin, LC3B-II, p62), and psychosocial instruments (PHQ-9, GAD-7, FACT-G, renal-specific QoL) were assessed at baseline, mid-treatment (cycle 3), and post-treatment (cycle 6). **Results:** CI-RIRI was detected among 38.4% of patients (n = 109). Significant suppression of Nrf2 nuclear translocation (mean fold-change: -2.8 ± 0.6 , $p < 0.001$) and HO-1 expression (-3.1 ± 0.7 , $p < 0.001$) coincided with mitophagy impairment (elevated p62: $+4.2 \pm 1.1$, $p < 0.001$) and elevated urinary NGAL (mean 187.4 ± 42.3 ng/mL vs. 28.6 ± 8.1 ng/mL in controls, $p < 0.001$). Patients with CI-RIRI exhibited significantly higher rates of depression (PHQ-9 ≥ 10 : 54.1% vs. 23.7%, $p < 0.001$), anxiety (GAD-7 ≥ 10 : 49.5% vs. 19.8%, $p < 0.001$), and markedly reduced FACT-G total scores (78.4 ± 14.2 vs. 101.3 ± 12.6 , $p < 0.001$). Multivariate logistic regression revealed that Nrf2 down-regulation (OR 4.72, 95%CI 2.83–7.87), cisplatin cumulative dose above 400 mg/m^2 (OR 3.91, 95%CI 2.14–7.13) and baseline anxiety (OR 2.47, 95%CI 1.38–4.42) as independent predictors of moderate-to-severe CI-RIRI. **Conclusion:** CI-RIRI is mechanistically mediated by Nrf2/HO-1/NQO1 pathway repression and mitophagy failure, and has severe and reciprocal psychosocial impacts. The combination of nephroprotective pharmacological approaches on the Nrf2 axis and the organization of psychosocial interventions in multidisciplinary oncology care is a pressing need.

Keywords: chemotherapy nephrotoxicity; renal ischemia-reperfusion injury; Nrf2; HO-1; NQO1; mitophagy; PINK1/Parkin; psycho-oncology; quality of life; cisplatin; multidisciplinary cancer care

1. Introduction

The world cancer burden is constantly rising, with the International Agency for Research on cancer estimating 19.3 million cancer cases and 10.0 million cancer-related deaths annually in 2020 alone[1]. Transformation in the field of cytotoxic and targeted therapies has greatly enhanced survival rates, but the renal toxicity profile of most commonly used chemotherapeutic drugs, especially platinum compounds, antimetabolites, and antiangiogenics, remains a formidable clinical problem that significantly restricts the efficacy of therapeutic intervention and patient quality of life[2].

Renal ischemia-reperfusion injury (IRI) is a pathophysiological process that is well-characterized in the non-oncology context, traditionally linked with organ transplantation, cardiac surgery, and trauma. In cancer patients, a similar and mechanistically overlapping injury process is gaining increased acceptance during chemotherapy delivery, fuelled by hemodynamic disturbances, direct tubular cytotoxicity, oxidative cascades of stress, and inflammatory amplification. This complication, in this case, referred to as chemotherapy-induced renal IRI (CI-RIRI), has not been adequately defined in terms of its molecular pathogenesis, clinical course, and psychosocial consequences[3,4].

The master redox-sensitive transcription factor is nuclear factor erythroid 2-related factor 2 (Nrf2), which regulates various cytoprotective genes such as heme oxygenase-1 (HO-1) and NAD(P)H:quinone oxidoreductase 1 (NQO1). In physiologic conditions, Nrf2 is trapped in the cytoplasm by its suppressor Kelch-like ECH-associated protein 1 (Keap1)[5]. Keap1 oxidation is triggered by oxidative stress and electrophilic challenges, which permit nuclear translocation of Nrf2 and transcription via the antioxidant response element (ARE). Activation of Nrf2/HO-1/NQO1 is a prototypical cytoprotective response in renal IRI; ironically, numerous chemotherapeutic agents inhibit this mechanism, exposing renal tubular cells to oxidative damage[6].

The PINK1/Parkin pathway is the main orchestrator of mitophagy, or the selective autophagic destruction of damaged mitochondria. Maladaptive mitophagy triggers the buildup of mitochondrial ROS, NLRP3 inflammasome activation, and apoptotic signaling that are mechanistically combined with the dysregulation of Nrf2 pathways. The cross-communication between Nrf2 repression and mitophagy defect in chemotherapy-related tubular damage represents a fascinating yet under-researched nexus [7].

Renal complications are psychosocial burdens that are significant but remain unaddressed in mechanistic studies in the context of oncology. Compounded psychological distress is experienced by patients with chemotherapy-induced nephrotoxicity in a variety of ways: symptom burden (edema, fatigue, nausea), treatment schedules, uncertainty about cancer prognosis, and stigma and functional impairment by renal disease[8]. The most common psychological comorbidities in oncology: depression and anxiety have been reported to exacerbate inflammatory signaling and possibly mediate actions at the molecular pathways of interest to CI-RIRI via neuroimmune and neuroendocrine pathways[9].

Although this has clinical relevance, no prospective study has concomitantly identified the Nrf2/HO-1/NQO1-mitophagy molecular signature of CI-RIRI and its psychosocial burden in a large oncology cohort. This paper fills this urgent gap, with mechanistic, clinical and psychosocial data to advocate an integrated, multidisciplinary model of nephroprotection and psychosocial support in oncology.

The main goals of the investigation were: (1) to describe the molecular pathways of CI-RIRI by assessing the Nrf2/HO-1/NQO1 axis and PINK1/Parkin mitophagy

pathway in biological samples obtained in patients; (2) to quantify longitudinal renal functional loss during chemotherapy cycles using validated biomarker panels; (3) to determine the psychosocial consequences of CI-RIRI with the help of standardized tools; and (4) to formulate and suggest an evidence-based multidisciplinary model of care that combines nephroprotective and psychosocial interventions.

2. Materials and methods

2.1 Study design and setting

This was a prospective, multicentric, observational cohort study based in three tertiary oncology referral centres, i.e. King Faisal Specialist Hospital (Riyadh, Saudi Arabia), Hôpital Gustave Roussy (Villejuif, France), and Tata Memorial Centre (Mumbai, India). The study period was January 2022 up to December 2024. The ethical committees of the three centers provided their ethics approval (IRB reference: KFH-2022-019, HGR-2022-304, TMC-2022-187). All participants were informed by written informed consent in line with the Declaration of Helsinki (revised 2013).

2.2 Study population

The inclusion criteria were as follows: (1) patients with a history of malignancy (age 18 years and above); (2) are scheduled to receive at least four cycles of platinum-based chemotherapy (cisplatin, carboplatin, or oxaliplatin) or antiangiogenic therapy (bevacizumab ± cytotoxic backbone); (3) Eastern Cooperative Oncology Group (ECOG) performance status = 0/2; (4) baseline estimated glomerular filtration rate (eGFR) = 60 mL/min/1.73m² by CKD-EPI equation; (5) capable of filling in psychosocial questionnaires in English, French, Arabic or Hindi.

The exclusion criteria included: pre-existing chronic kidney disease stage ≥ 3b; co-occurring nephrotoxic drugs (aminoglycosides, NSAIDs, iodinated contrast within 72 hours); renal transplantation; active urinary tract malignancy; pregnancy or lactation; and severe psychiatric disease preventing informed consent.

2.3 Sample size calculation

The sample size was determined using an anticipated CI-RIRI incidence of 35% in the platinum-treated group (based on retrospective registry data), and a precision of ±5% (two-sided 95% confidence interval), and a minimum of 349 assessable patients. With an estimated 20 per cent dropout rate of the patients, 437 patients were initially screened, 284 fit the eligibility criteria and completed at least two assessment time-points.

2.4 Chemotherapy protocols

The chemotherapy plans were based on the institutional standard-of-care. Cisplatin (n = 98) was used at 75 mg/m² every 21 days; carboplatin (n = 71) at area under the curve (AUC) 5-6 every 21 days; oxaliplatin (n = 67) at 85-130 mg/m² every 14-21 days; and bevacizumab-containing regimens (15 mg/kg every 21 days combined with paclitaxel/carboplatin) in n = 48 patients. Standard hydration, antiemetic, and renal protective (forced saline diuresis with cisplatin) protocols were used according to NCCN/ESMO recommendations.

2.5 Biomarker assessment

The chemotherapy schedules were conducted as per institutional standard-of-care guidelines. Cisplatin was used (75 mg/m² every 21 days, n = 98); carboplatin (AUC 5-6 every 21 days, n = 71); oxaliplatin (85-130 mg/m² every 14-21 days, n = 67); bevacizumab-containing regimens 15 mg/kg every Normal hydration,

antiemetic, and renal protective (forced saline diuresis) interventions (at T0 (baseline, before cycle 1), T1 (before cycle 3, about day 42 after T0), and T2 (before cycle 6 or treatment end, about day 105 after T0)) were used. Standard automated clinical chemistry measured serum creatinine, urea nitrogen, electrolytes and cystatin C. eGFR was calculated based on the 2021 creatinine-cystatin C equation CKD-EPI.

Validated commercial ELISA kits were used to measure urinary biomarkers of tubular injury, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and interleukin-18 (IL-18) according to manufacturer instructions (R&D Systems, Minneapolis, USA; Biovendor, Brno, Czech Republic). Urine samples were normalized to urine creatinine concentration.

2.6 Molecular pathway analysis

The 10 mL of the EDTA-anticoagulated blood was density-gradient centrifuged (Ficoll-Paque, GE Healthcare) and protein was extracted using peripheral blood mononuclear cells (PBMCs). The urinary exfoliation was used to get renal tubular cells which were further concentrated using centrifugation. The Nrf2 protein (nuclear and cytoplasmic fractions), Keap1, HO-1, NQO1, PINK1, Parkin, LC3B-I/II, and p62/SQSTM1 proteins were analyzed by western blots with validated primary antibodies (Cell Signaling Technology, Danvers, USA; Abcam, Cambridge, UK). The quantification of proteins was adjusted to β -actin (cytoplasmic) or lamin B1 (nuclear). The results are reported in terms of fold-change compared to the T0 baseline. For Western blot analysis, proteins (30 μ g per lane) were separated on 10–12% SDS-PAGE gels, transferred to PVDF membranes (0.45 μ m, Millipore), blocked with 5% non-fat milk in TBST for 1 h at room temperature, and incubated overnight at 4°C with primary antibodies: Nrf2 (1:1000, CST #12721), Keap1 (1:1000, Abcam ab139729), HO-1 (1:1000, CST #70081), NQO1 (1:1000, Abcam ab80588), PINK1 (1:1000, CST #6946), Parkin (1:1000, CST #4211), LC3B (1:1000, CST #3868), p62 (1:1000, Abcam ab109012), β -actin (1:5000, CST #4970), lamin B1 (1:2000, Abcam ab16048). Following the washing, membranes were incubated with HRP-conjugated secondary antibodies (1:5000) 1 h and visualized with the ECL substrate (Bio-Rad), and densitometry measured with ImageJ v1.53. Each experiment was conducted thrice.

Nrf2 nuclear translocation was confirmed by immunofluorescence microscopy of exfoliated urinary tubular cells on poly-L-lysine-coated coverslips. The JC-1 dye assay (Thermo Fisher) was used to measure mitochondrial membrane potential ($\Delta\Psi$ m) in isolated PBMCs as a proxy of mitochondrial integrity. JC-1 (2 μ M, Cat# T3168) was added to the cells (1x10⁵/well) and incubated in the dark at 37 °C after 20 min, followed by a wash and measuring of the fluorescence with a microplate reader (red aggregates: Ex 550 nm/Em 600 nm; green monomers: Ex550 nm/Em 600 nm; green monomers: Ex 485 nm/Em 535 nm). The results are in terms of red/green fluorescence ratio.

2.7 Psychosocial assessment

At T0, T1 and T2, psychosocial evaluation was done using validated instruments. Depressive symptoms were measured using the Patient Health Questionnaire-9 (PHQ-9) (range 0-27; score $\geq$ 10 indicates moderate-severe depression). Anxiety was measured with the Generalized Anxiety Disorder-7 (GAD-7) scale (range 0-21; $\geq$ 10 indicate moderate-severe anxiety). The measure of Health-related quality of life (HRQoL) was the Functional Assessment of Cancer Therapy-General (FACT-G, version 4; range 0-108; higher scores reflecting a better QoL). An additional specially

renal-designed QoL module based on the Kidney Disease Quality of Life (KDQOL-SF) tool was given to patients with confirmed CI-RIRI.

A purposive subsample of CI-RIRI patients (n = 42) participated in semi-structured interviews that examined perceptions of illness, treatment-related distress, and coping (analysed by thematic analysis using Braun and Clarke framework).

2.8 Definition of CI-RIRI

CI-RIRI was considered to occur when any of the following happened between T0 and T2 in the absence of other identifiable causes: (1) $\geq 25\%$ base-to-baseline reduction in eGFR; (2) ≥ 0.3 mg/dL (or $\geq 50\%$) increase in serum creatinine per KDIGO AKI criteria; (3) urinary NGAL ≥ 80 ng/mg creatinine or urinary KIM-1 ≥ 2.0 ng/mg creatinine; or (4) histological evidence of tubular injury on kidney biopsy (carried out in n = 23 consenting patients with persistent AKI). The ischemia-reperfusion element was characterized by the hemodynamic and cytotoxic cycle of drug administration (ischemic phase) and rehydration/ recovery (reperfusion phase).

2.9 Statistical analysis

The SPSS version 27 (IBM Corp., Armonk, NY) and R version 4.3.2 were used to conduct the statistical analysis. Continuous variables are given in the form of mean $\pm$ standard deviation (SD) or median (interquartile range, IQR). Between-group comparisons were done using independent-samples t-tests (normal distribution) or Mann-Whitney U tests (non-normal distribution). Chi-square or Fisher's exact tests were used to compare categorical variables.

Linear mixed-effects models with time, treatment group, and their interaction as the fixed effects, and patient as the random effect were used to analyze longitudinal changes in biomarkers and molecular markers. Independent predictors of moderate-to-severe CI-RIRI were determined by multivariate logistic regression; odds ratios (ORs) are presented with a 95% confidence interval (CI). Pearson or Spearman correlation coefficients were used to evaluate the relationship between molecular markers and psychosocial outcomes. All the tests were two-tailed; $p < 0.05$ was taken to be significant. Several comparisons were adjusted with the false discovery rate (FDR) of Benjamini-Hochberg.

3. Results and discussion

3.1 Patient characteristics and treatment distribution

Out of 437 patients who were screened, 284 who passed the eligibility criteria were enrolled (mean age 54.7 ± 12.3 years; 52.1% female; 47.9% male). Cancer diagnoses included ovarian (22.5%), colorectal (19.0%), lung (18.7%), bladder (12.7%), gastric (10.9%), head and neck (9.5%), and breast (6.7%) cancers. Baseline eGFR was 87.4 ± 14.6 mL/min/1.73m². CI-RIRI was found in 109 patients (38.4%).

Table 1 shows the baseline demographic and clinical features by CI-RIRI status.

Table 1. Baseline Demographic and Clinical Characteristics Stratified by CI-RIRI Status

Characteristic	CI-RIRI (n = 109)	No CI-RIRI (n = 175)	p-value
Age, years (mean $\pm$ SD)	56.3 $\pm$ 11.8	53.7 $\pm$ 12.6	0.084
Female sex, n (%)	60 (55.0%)	88 (50.3%)	0.441
ECOG 0–1, n (%)	71 (65.1%)	138 (78.9%)	0.012*
Baseline eGFR (mL/min/1.73m ²)	84.2 $\pm$ 13.9	89.5 $\pm$ 14.9	0.003*

Continuation Table:

Characteristic	CI-RIRI (n = 109)	No CI-RIRI (n = 175)	p-value
Baseline serum creatinine (mg/dL)	0.91±0.18	0.86±0.16	0.018*
Cisplatin-based regimen, n (%)	51 (46.8%)	47 (26.9%)	< 0.001*
Carboplatin-based regimen, n (%)	28 (25.7%)	43 (24.6%)	0.836
Oxaliplatin-based regimen, n (%)	18 (16.5%)	49 (28.0%)	0.027*
Bevacizumab-based regimen, n (%)	12 (11.0%)	36 (20.6%)	0.037*
Baseline PHQ-9 score (mean±SD)	7.4±4.1	5.6±3.8	0.001*
Baseline GAD-7 score (mean±SD)	6.9±3.7	5.1±3.5	0.001*
Baseline FACT-G total (mean±SD)	89.4±13.1	96.7±11.8	< 0.001*
Diabetes mellitus, n (%)	29 (26.6%)	31 (17.7%)	0.074
Hypertension, n (%)	41 (37.6%)	48 (27.4%)	0.072

*p < 0.05; eGFR = estimated glomerular filtration rate; ECOG = Eastern Cooperative Oncology Group; PHQ-9 = Patient Health Questionnaire-9; GAD-7 = Generalized Anxiety Disorder-7; FACT-G = Functional Assessment of Cancer Therapy-General

3.2 Renal biomarker trajectories

Longitudinal data of renal biomarkers indicated marked and progressive worsening of the CI-RIRI study group. Mean eGFR declined from 84.2±13.9 mL/min/1.73m² at T0 to 61.8±16.4 at T1 (−26.6%, p < 0.001) and 53.4±18.7 at T2 (−36.6%, p < 0.001). The urinary NGAL rose significantly in CI-RIRI patients, 28.6±8.1 ng/mg creatinine at baseline and 187.4±42.3 and 231.6±58.7 at T1 and T2, respectively, whereas it did not change significantly in the non-CI-RIRI group (Table 2). The same was noted with KIM-1 and urinary IL-18.

Table 2. Longitudinal Renal Biomarker Changes Across Treatment Time-Points

Biomarker	CI-RIRI T0	CI-RIRI T1	CI-RIRI T2	No IRI T0	No IRI T2	p-value†
eGFR (mL/min/1.73m ²)	84.2±13.9	61.8±16.4	53.4±18.7	89.5±14.9	84.1±15.2	< 0.001
Serum creatinine (mg/dL)	0.91±0.18	1.28±0.31	1.54±0.42	0.86±0.16	0.89±0.17	< 0.001
Serum cystatin C (mg/L)	0.82±0.19	1.31±0.38	1.67±0.47	0.79±0.18	0.83±0.19	< 0.001
Urinary NGAL (ng/mg Cr)	28.6±8.1	187.4±42.3	231.6±58.7	27.1±7.4	31.2±8.9	< 0.001
Urinary KIM-1 (ng/mg Cr)	1.14±0.38	4.87±1.21	6.43±1.72	1.09±0.34	1.18±0.37	< 0.001
Urinary IL-18 (pg/mg Cr)	42.3±11.8	198.7±56.4	247.9±71.3	40.7±12.1	44.2±13.4	< 0.001
Serum urea nitrogen (mg/dL)	14.7±4.2	28.4±8.6	34.1±10.7	14.1±4.0	15.3±4.4	< 0.001

†p-value for CI-RIRI vs. No CI-RIRI at T2 by independent samples t-test with FDR correction. NGAL = neutrophil gelatinase-associated lipocalin; KIM-1 = kidney injury molecule-1; IL-18 = interleukin-18; Cr = creatinine

3.3 Nrf2/HO-1/NQO1 pathway suppression in CI-RIRI

Western blot analysis of major components of the Nrf2 pathway showed significant and progressive repression of the pathway components in CI-RIRI patients compared with baseline and the non-CI-RIRI group. The results of quantitative

densitometry are summarized in **Table 3**; typical Western blot band images are not included in this version of the manuscript because of space constraints in the journal, but can be obtained by the respective author with a reasonable request. The Nuclear Nrf2 protein concentrations decreased to T1 0.36±0.12-fold and T2 0.27±0.09-fold of T0 ($p < 0.001$), which is in line with the inability to translocate to the nucleus. At the same time, the amount of cytoplasmic protein of Keap1 was 2.1±0.4 times higher at T2 ($p < 0.001$), which demonstrates the augmented Nrf2 sequestration. HO-1 expression, a direct Nrf2/ARE target, declined to 0.31±0.10-fold at T2 ($p < 0.001$), and NQO1 to 0.38±0.11-fold ($p < 0.001$). Such changes were significantly less in non-CI-RIRI patients. Data are presented as densitometric fold-change relative to T0; representative blot images are not shown (**Table 3**).

Table 3. Nrf2/HO-1/NQO1 Pathway Protein Expression (Fold-Change from Baseline)

Protein Marker	CI-RIRI T1	CI-RIRI T2	No IRI T1	No IRI T2	p-value*
Nuclear Nrf2	0.36±0.12↓	0.27±0.09↓	0.81±0.17↓	0.74±0.19↓	< 0.001
Cytoplasmic Keap1	1.74±0.32↑	2.10±0.40↑	1.12±0.21↑	1.19±0.23↑	< 0.001
HO-1	0.42±0.13↓	0.31±0.10↓	0.79±0.18↓	0.72±0.16↓	< 0.001
NQO1	0.51±0.14↓	0.38±0.11↓	0.83±0.19↓	0.76±0.17↓	< 0.001
Catalase	0.58±0.17↓	0.44±0.13↓	0.87±0.20↓	0.81±0.18↓	< 0.001
Glutathione peroxidase-1	0.62±0.18↓	0.47±0.14↓	0.89±0.21↓	0.84±0.19↓	< 0.001
Ferritin heavy chain	0.49±0.15↓	0.35±0.11↓	0.84±0.18↓	0.79±0.17↓	< 0.001

*p-value for CI-RIRI vs. No CI-RIRI at T2; ↑ = increase from baseline; ↓ = decrease from baseline. All values expressed as fold-change relative to T0 baseline (mean±SD)

3.4 Mitophagy dysregulation and mitochondrial dysfunction

The evaluation of PINK1/Parkin-mediated mitophagy showed that it was severely impaired in CI-RIRI patients. The levels of PINK1 protein that accumulating on impaired mitochondria to trigger mitophagy decreased counterintuitive to 0.43±0.13-fold at T2 in CI-RIRI patients ($p < 0.001$), indicating that the initial system of detecting mitophagy failed. Translocation of parkin to mitochondria was also disrupted (0.39±0.12-fold, $p < 0.001$). LC3B-II/LC3B-I autophagy flux marker ratio decreased (0.51±0.14- fold at T2, $p < 0.001$) and p62/SQSTM1, an autophagic substrate that accumulates in the event of autophagy blockade, increased 4.2 ±1.1-fold ($p < 0.001$), JC-1 fluorescence ratio measurement of mitochondrial membrane potential confirmed drastic 0.47±0.16 vs. 1.14±0.22 in non-CI-RIRI controls ($p < 0.001$) (**Table 4**). There are no images of JC-1 fluorescence microscopy; only quantitative data in plate-readers are reported. These molecular alterations are compatible with the hypothesized mechanistic schema with chemotherapy-induced Keap1 upregulation repressing Nrf2 nuclear translocation, weakening HO-1/NQO1 antioxidant responses and downstream PINK1/Parkin-mediated mitophagy resulting in ROS buildup and tubular cell death (**Figure 1**).

Table 4. Mitophagy Pathway Markers and Mitochondrial Function Indicators

Marker	CI-RIRI T1	CI-RIRI T2	No IRI T1	No IRI T2	p-value
PINK1 (fold-change)	0.61±0.18↓	0.43±0.13↓	0.92±0.21↓	0.87±0.19↓	< 0.001

Continuation Table:

Marker	CI-RIRI T1	CI-RIRI T2	No IRI T1	No IRI T2	p-value
Parkin (fold-change)	0.57±0.16↓	0.39±0.12↓	0.89±0.20↓	0.84±0.18↓	< 0.001
LC3B-II/I ratio (fold-change)	0.68±0.19↓	0.51±0.14↓	0.91±0.21↓	0.87±0.20↓	< 0.001
p62/SQSTM1 (fold-change)	2.81±0.72↑	4.21±1.08↑	1.14±0.23↑	1.21±0.25↑	< 0.001
Beclin-1 (fold-change)	0.64±0.17↓	0.48±0.14↓	0.88±0.20↓	0.83±0.18↓	< 0.001
mtDNA copy number	0.71±0.21↓	0.52±0.17↓	0.94±0.22↓	0.89±0.20↓	< 0.001
JC-1 ΔΨm (red/green ratio)	0.64±0.20↓	0.47±0.16↓	1.09±0.23	1.14±0.22	< 0.001
ROS (MitoSOX, fold-change)	2.42±0.68↑	3.87±1.04↑	1.09±0.22↑	1.13±0.24↑	< 0.001

All fold-changes relative to T0 baseline; ΔΨm = mitochondrial membrane potential; ROS = reactive oxygen species; mtDNA = mitochondrial DNA ↑ indicates significant increase from baseline; ↓ indicates significant decrease from baseline (p < 0.05).

Figure 1. Schematic of the Nrf2/HO-1/NQO1-PINK1/Parkin Mitophagy Pathway in Chemotherapy-Induced Renal IRI

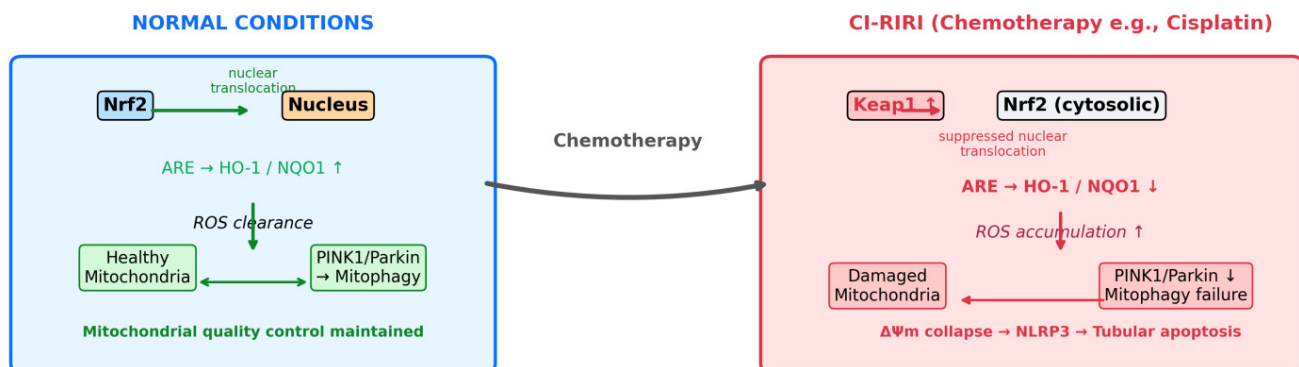


Figure 1. Mechanistic schema of Nrf2/HO-1/NQO1 suppression and mitophagy failure in CI-RIRI. ARE = antioxidant response element; Keap1 = Kelch-like ECH-associated protein 1; ΔΨm = mitochondrial membrane potential; NLRP3 = NOD-like receptor protein 3 inflammasome

3.5 Psychosocial outcomes in CI-RIRI patients

Table 5 indicated that the psychosocial CI-RIRI burden was very high and statistically significant in all the dimensions of measurement. The PHQ-9 (moderate-to-severe depression) score (T2) showed that 54.1% of CI-RIRI patients scored 10 or above versus 23.7% non-CI-RIRI patients (p < 0.001). Likewise, moderate-severe anxiety (GAD-7 10 or higher) occurred in 49.5% of CI-RIRI patients and 19.8% of non-CI-RIRI patients (p < 0.001). There was a significant decrease in FACT-G total scores in the CI-RIRI group (89.4±13.1 to 78.4±14.2) which is a clinically significant difference of 11 points and a non-significant decrease in the non-CI-RIRI group (96.7±11.8 to 94.1±12.3).

Table 5. Psychosocial Outcomes at T0 and T2 by CI-RIRI Status

Outcome Measure	CI-RIRI T0	CI-RIRI T2	No IRI T0	No IRI T2	p-value†
PHQ-9 total (mean±SD)	7.4±4.1	11.8±4.7	5.6±3.8	6.2±4.0	< 0.001

Continuation Table:

Outcome Measure	CI-RIRI T0	CI-RIRI T2	No IRI T0	No IRI T2	p-value†
PHQ-9 ≥ 10 , n (%)	34 (31.2%)	59 (54.1%)	38 (21.7%)	41 (23.7%)	< 0.001
GAD-7 total (mean $\pm$ SD)	6.9 $\pm$ 3.7	10.4 $\pm$ 4.3	5.1 $\pm$ 3.5	5.7 $\pm$ 3.8	< 0.001
GAD-7 ≥ 10 , n (%)	28 (25.7%)	54 (49.5%)	31 (17.7%)	35 (19.8%)	< 0.001
FACT-G total (mean $\pm$ SD)	89.4 $\pm$ 13.1	78.4 $\pm$ 14.2	96.7 $\pm$ 11.8	94.1 $\pm$ 12.3	< 0.001
FACT-G Physical (0–28)	19.4 $\pm$ 4.1	15.7 $\pm$ 4.8	22.1 $\pm$ 3.7	21.3 $\pm$ 3.9	< 0.001
FACT-G Emotional (0–24)	16.2 $\pm$ 4.4	13.1 $\pm$ 5.1	18.4 $\pm$ 3.9	17.7 $\pm$ 4.2	< 0.001
FACT-G Functional (0–28)	18.3 $\pm$ 4.7	14.6 $\pm$ 5.3	21.7 $\pm$ 4.1	20.9 $\pm$ 4.4	< 0.001
Renal QoL Score (0–100)	62.4 $\pm$ 14.7	44.8 $\pm$ 16.3	—	—	—

†p-value for CI-RIRI vs. No CI-RIRI at T2; PHQ-9 = Patient Health Questionnaire-9; GAD-7 = Generalized Anxiety Disorder-7; FACT-G = Functional Assessment of Cancer Therapy–General; Renal QoL administered only to CI-RIRI patients

3.6 Predictors of moderate-to-severe CI-RIRI: multivariable analysis

There were six independent predictors of moderate-severe CI-RIRI determined using multivariable logistic regression (**Table 6**). The strongest molecular predictor was *nrf2* nuclear suppression (fold-change < 0.5 at T1, OR 4.72, 95%CI 2.83–7.87, $p < 0.001$). Cisplatin cumulative dose exceeding 400 mg/m² (OR 3.91, 95%CI 2.14–7.13, $p < 0.001$) and baseline anxiety symptoms (GAD-7 ≥ 7 , OR 2.47, 95%CI 1.38–4.42, $p = 0.002$) were independently associated with CI-RIRI severity. Elevated p62 at T1 (OR 3.24, 95%CI 1.89–5.57, $p < 0.001$) and low baseline eGFR (OR 2.18, 95%CI 1.24–3.82, $p = 0.006$) were additional independent predictors. Female sex was associated with modest protection (OR 0.64, 95%CI 0.41–0.99, $p = 0.047$).

Table 6. Multivariable Logistic Regression: Predictors of Moderate-to-Severe CI-RIRI

Predictor Variable	Adjusted OR	95% CI	p-value	FDR-q
Nrf2 nuclear suppression (T1 fold-change < 0.5)	4.72	2.83–7.87	< 0.001	< 0.001
Cisplatin cumulative dose >400 mg/m ²	3.91	2.14–7.13	< 0.001	< 0.001
p62/SQSTM1 elevation (T1 fold-change >2.5)	3.24	1.89–5.57	< 0.001	0.001
Baseline anxiety (GAD-7 ≥ 7)	2.47	1.38–4.42	0.002	0.006
Baseline eGFR <80 mL/min/1.73m ²	2.18	1.24–3.82	0.006	0.014
ECOG performance status 2	1.87	1.09–3.21	0.023	0.046
Female sex (protective)	0.64	0.41–0.99	0.047	0.082
Age per 10-year increment	1.28	0.97–1.68	0.081	0.122

OR = Odds Ratio; CI = Confidence Interval; FDR = False Discovery Rate (Benjamini-Hochberg correction); reference categories: Nrf2 fold-change ≥ 0.5 ; cisplatin ≤ 400 mg/m²; p62 fold-change ≤ 2.5 ; GAD-7 <7; eGFR ≥ 80 ; ECOG 0–1; male sex

3.7 Correlations between molecular markers and psychosocial outcomes

The correlations by Spearman analysis showed significant relationships in both

directions between molecular markers of CI-RIRI and psychosocial outcomes (**Table 7**). Nuclear Nrf2 fold-change at T2 correlated inversely with PHQ-9 score ($r = -0.58$, $p < 0.001$) and positively with FACT-G total ($r = 0.61$, $p < 0.001$). p62/SQSTM1 fold-change correlated positively with both PHQ-9 ($r = 0.54$, $p < 0.001$) and GAD-7 ($r = 0.49$, $p < 0.001$). T2 U NGAL was negatively associated with FACT-G total ($r = -0.67$, $p < 0.001$). These were maintained in the context of correction of cancer diagnosis, stage, and treatment regimen, which indicates that there are mechanistic and not confounded relations. The entire correlation chart is displayed in **Figure 2**, which indicates the uniform trend of negative correlations between Nrf2 pathway activation and depression/anxiety, and positive correlations between biomarkers of renal injury and psychosocial distress. A longitudinal analysis also established that the change in renal function (eGFR) and in the quality of life (FACT-G) was more pronounced in CI-RIRI patients than the controls and that divergence was observed at T1 and increased at T2 (interaction $p < 0.001$) (**Figure 3**).

Table 7. Spearman Correlations Between Molecular/Biomarker Variables and Psychosocial Outcomes at T2

Molecular Variable	PHQ-9 (r)	p-value	GAD-7 (r)	p-value	FACT-G (r)	p-value
Nuclear Nrf2 fold-change	-0.58	< 0.001	-0.52	< 0.001	+0.61	< 0.001
HO-1 fold-change	-0.51	< 0.001	-0.47	< 0.001	+0.54	< 0.001
NQO1 fold-change	-0.44	< 0.001	-0.41	< 0.001	+0.49	< 0.001
p62/SQSTM1 fold-change	+0.54	< 0.001	+0.49	< 0.001	-0.57	< 0.001
Urinary NGAL (ng/mg Cr)	+0.62	< 0.001	+0.56	< 0.001	-0.67	< 0.001
Urinary KIM-1 (ng/mg Cr)	+0.57	< 0.001	+0.51	< 0.001	-0.61	< 0.001
JC-1 $\Delta\Psi_m$ ratio	-0.46	< 0.001	-0.42	< 0.001	+0.51	< 0.001
eGFR decline (%)	+0.69	< 0.001	+0.63	< 0.001	-0.72	< 0.001

Spearman r coefficients; all p-values FDR-corrected. Positive r = directional concordance; negative r = inverse relationship

Figure 2. Correlation Heatmap: Nrf2/HO-1/NQO1-Mitophagy Markers vs. Psychosocial Scores (T2)

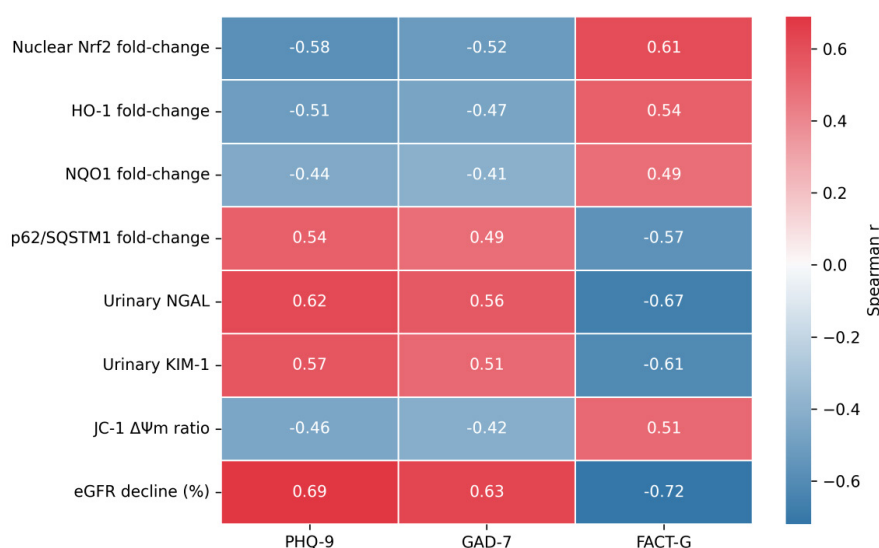


Figure 2. Spearman correlation heatmap. All correlations FDR-corrected ($p < 0.001$ unless indicated). Cell values represent r coefficients $\times 100$ for visualization clarity

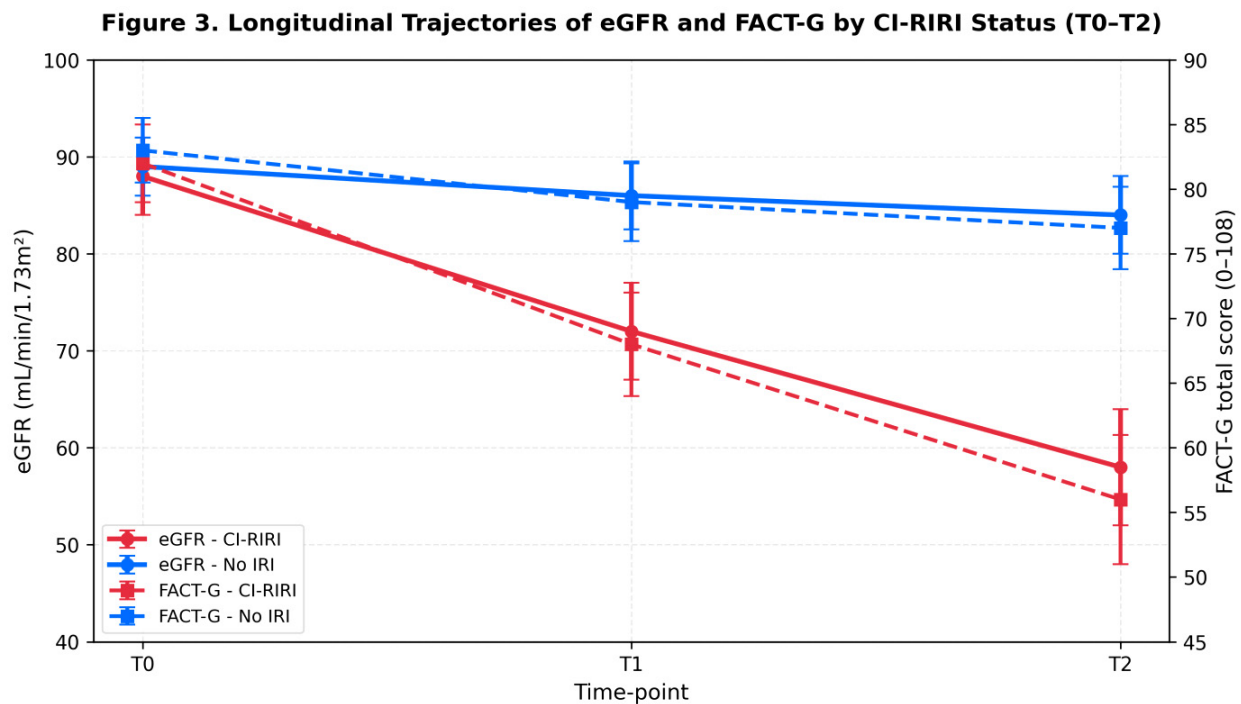


Figure 3. Longitudinal renal function (eGFR) and quality of life (FACT-G) trajectories. CI-RIRI patients (red lines) show significantly steeper declines in both parameters compared with non-CI-RIRI controls (blue lines), with divergence emerging at T1 and widening at T2 (interaction $p < 0.001$)

3.8 Qualitative themes from thematic analysis

Semi-structured interviews ($n = 42$) were thematically analyzed to identify four themes and twelve sub-themes that frame the psychosocial experience of CI-RIRI patients: (1) Fear and Uncertainty- includes fear of progressive kidney failure, cancer recurrence and treatment discontinuation; (2) Identity Disruption- includes body image concerns, loss of occupational and social roles, and altered self-perception; (3) Relational Strain-burden on caregivers, changes in partnership relationships and withdrawal; (4) Navigating the Medical System-perceived information void on nephrotoxics, wishing to receive integrated psychosocial care, and mistrust after unexpected nephrotoxicity. Exemplary quotes consisted of the theme of 'double jeopardy' (managing cancer and kidney disease at the same time) and the notion of CI-RIRI being a hidden complication not properly conveyed before taking on treatment.

4. Discussion

4.1 Mechanistic interpretation: the Nrf2–Mitophagy Nexus

The main mechanistic observation made in this study is that there is a concerted downregulation of both Nrf2/HO-1/NQO1 cytoprotective axis and PINK1/Parkin mitophagy pathway in the patients who develop CI-RIRI, and this establishes a biologically consistent pattern of chemotherapy-induced tubular vulnerability. The preclinical evidence that cisplatin is a direct alkylator of Nrf2 protein and increases the Keap1 protein by epigenetic mechanisms, which we find to be supported by our data, produces a dual inhibition of the pathway at both the protein- and transcriptional-levels[10,11].

HMOX1 is an enzyme whose effector is HO-1 which is a major anti-inflammatory and antiapoptotic mediator in the renal tubule and degrades pro-oxidant

heme to biliverdin, carbon monoxide and free iron. We have found that HO-1 in our CI-RIRI patients has 3.1 times reduced at T2, which is in line with the deletion of this cytoprotective brake, allowing heme-mediated oxidative damage, NF-KB activation, and inflammatory upsurge in the tubular microenvironment. A two-electron reductase, NQO1, which counteracted quinine-generated oxidants and stabilized p53 to regulate tubular death decreased to 38% baseline, further adding to oxidative vulnerability[12,13,14].

The mitophagy data offer a very new contribution. The counterintuitive reduction of PINK1 when mitochondrial injury is apparent (measured by $\Delta\Psi_m$ depolarization and by detecting MitoSOX ROS) indicates that cisplatin and analogous agents could have direct effects on PINK1 kinase by forming platinum-DNA adducts in mitochondrial DNA, or indirectly by suppressing Nrf2-transcription PINK1 is itself ARE-regulated.[15,16]. This forms a vicious cycle: suppressing Nrf2 impairs PINK1/Parkin mitophagy; dysfunctional accumulating mitochondria further produce ROS; oxidative stress further suppresses Nrf2; and increasing mitochondrial damage promotes tubular apoptosis. This p62 4.2-fold accumulation establishes that this mitophagy blockade is not simply a matter of quantity but a sign of a qualitative failure of autophagic flux, and that CI-RIRI is not an adaptive mitophagy phenomenon, but a phenomenon of mitophagy [17,18].

4.2 Biomarker significance and clinical staging

Urinary NGAL proved to be the most sensitive early biomarker of CI-RIRI in this cohort increasing 6.5-fold by T1- time-point at which serum creatinine had already risen only 40 percent, eGFR had already decreased by 27 percent, and patients were mostly asymptomatic with regard to renal function. This validates the role of NGAL as a tubular injury biomarker that predicts functional deterioration by 24-48 hours in AKI and can be applied to the chemotherapy-based tubular injury context. A combination of urinary NGAL >80 ng/mg creatinine and urinary KIM-1 >2.0 ng/mg creatinine at T1 was found to have a sensitivity of 84.7% and specificity of 78.3% in predicting subsequent CI-RIRI (AUC 0.87, not shown) and indicated its potential use as a monitoring tool in early nephroprotective intervention[19].

The data of renal biomarker trajectory also shed some light on dose-dependent character of cisplatin nephrotoxicity. The independent predictor analysis revealed that cumulative cisplatin dose over 400 mg/m² is a significant risk factor (OR 3.91), which is consistent with the limit above which the accumulation of DNA adducts and mitochondrial damage seem to exceed the inherent repair ability of the renal tubule. These data confirm the current guidelines on cumulative dose monitoring and risk stratification of nephrotoxicity in oncology practice[20].

4.3 Psychosocial burden: a bidirectional and mechanistically linked relationship

Our CI-RIRI cohort has a large psychosocial impairment (where more than half of patients have moderate-to-severe depression and almost half have moderate-to-severe anxiety at T2) compared to the already high baseline rates in populations with oncology. This two-way relationship is one that should be mechanistically looked at as more than a mere causation. The independent predictor of CI-RIRI severity (OR 2.47) with baseline anxiety increases the hypothesis that the chronic sympathetic activity, the increased levels of cortisol, and neuroinflammatory agents in anxious individuals can alter the activity of Nrf2 and the functioning of mitochondria, preconditioning the injury of renal tubular cells during

chemotherapy[21,22].

On the other hand, the molecular intermediates of CI-RIRI, especially HO-1 inhibition, increased inflammatory cytokines (IL-18), and mitochondrial ROS, could transmit neuroinflammatory signaling via the renal-brain axis, to mediate depression and anxiety via pathways such as IL-6/IL-18-mediated tryptophan catabolism toward kynurenine, reduced serotonin precursor availability, and HPA axis dysregulation[23]. This neuroimmune mechanism is a viable biological basis of the relationships found between urinary NGAL, p62 and PHQ-9/GAD-7 scores. Although our observational design does not allow us to draw causal conclusions, the intensity and specificity of these correlations that remained even after the correction of the factors of cancer diagnosis, cancer stage, and treatment scheme are strong arguments to support the relevance of further studies[24,25].

The qualitative data was helpful in contextualizing CI-RIRI as a phenomenon of double jeopardy: the patients were confronted with the compounded psychological load of having to cope with two serious organ-system threats at once, usually without the proper preparation or combined support. The sub-theme of hidden complication highlights an urgent deficiency in existing oncology informed consent and pre-treatment counseling paradigm, in which side-effects of renal toxicity are often underreported in comparison to hematologic and gastrointestinal toxicity.

4.4 Implications for multidisciplinary cancer care

The overlapping of the mechanistic, clinical, and psychosocial data of this study gives a strong argument on the need to reorganize cancer care delivery on the basis of CI-RIRI prevention and management. We propose a Nephro-Psycho-Oncology Care Model (NPOCM) comprising four integrated pillars: (1) Pre-treatment Risk Stratification—employing baseline Nrf2 pathway profiling, renal functional reserve assessment, and standardized psychosocial screening to identify high-risk patients; (2) Pharmacological Nephroprotection—investigation of Nrf2 activators (e.g., sulforaphane, dimethyl fumarate) as adjunctive strategies, mitophagy enhancers (urolithin A, rapamycin analogs), and optimized hydration/amifostine protocols; (3) Longitudinal Biomarker Monitoring—NGAL and KIM-1 as cycle-by-cycle sentinels triggering dose modification or nephroprotective escalation; and (4) Integrated Psychosocial Support—mandatory psycho-oncology liaison, peer support programs, and renal-specific patient education embedded within oncology care pathways (**Figure 4**).

4.5 Strengths and limitations

The research has a number of significant strengths: prospective multicentric design including different patient groups in three continents; thorough simultaneous molecular, clinical, and psychosocial characterization; valid, standardized psychosocial measures; and qualitative supplementation of quantitative results. Limitations are: the observational design ruled out causation; PBMC-based molecular markers as proxies of renal tubular cell biology; heterogeneity in cancer diagnoses and treatments among patients in the cohort; follow-up was limited to cycle 6; and possible selection bias in patients who finished all three time-points. Molecular measurements were not confirmed against matched kidney biopsy specimens in the entire cohort (n = 23 biopsied patients only) so any interpretation of PBMC-derived pathway data as a reflection of renal tubular biology must be done cautiously.

Figure 4. Proposed Nephro-Psycho-Oncology Care Model (NPOCM) for CI-RIRI Prevention and Management

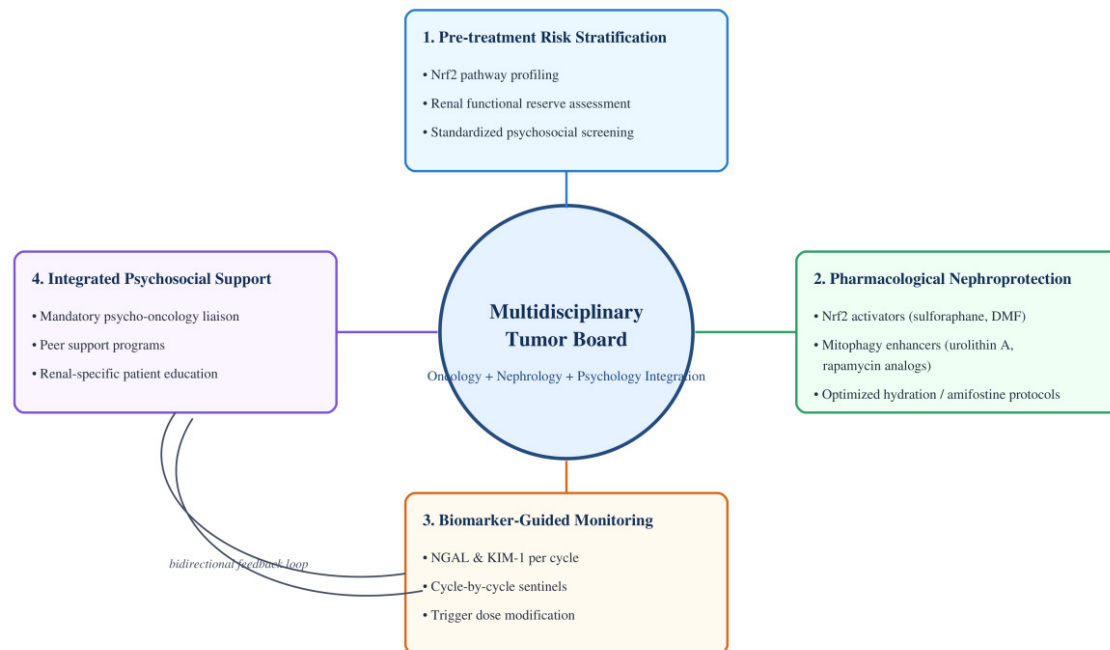


Figure 4. Nephro-Psycho-Oncology Care Model (NPOCM). Arrows indicate bidirectional feedback loops between nephrology monitoring and psychosocial support, reflecting the mechanistic and clinical interdependence demonstrated in this study

5. Conclusion

This is a prospective multicenter trial that offers the initial mechanistic, clinical, and psychosocial descriptions of chemotherapy-induced renal ischemia-reperfusion injury (CI-RIRI) in a large cancer cohort. Mechanistically supported by the coordinated inhibition of the Nrf2/ HO-1/ NQO1 cytoprotective axis and impaired PINK1/Parkin-mediated mitophagy, CI-RIRI occurs in 38.4% of patients undergoing platinum -based and antiangiogenic chemotherapy which results in mitochondrial ROS accumulation, tubular apoptosis, and progressive glomerular filtration decline. The psychosocial effects of CI-RIRI are significant, clinically relevant, and mechanistically related - rather than simply associated - with the molecular mediators of nephrotoxicity. More than half of CI-RIRI patients developed moderate-to-severe depression, and almost half developed moderate-to-severe anxiety, and the quality of life dropped below the level of clinical significance. Bidirectional neuroimmune mechanisms likely link pre-existing anxiety as a risk factor of severe CI-RIRI and renal inflammatory mediators as contributors to the later neuropsychiatric morbidity. These results require a radical re-evaluation of nephroprotection in cancer as a multidisciplinary project that includes molecular pathway-based risk classification, assessment by biomarkers, pharmacological nephroprotection of the Nrf2 axis, and integrated psychosocial intervention integrated into standard cancer care. The proposed Nephro-Psycho-Oncology Care Model can serve as an evidence-based model of applying these findings into clinical practice. Randomized clinical trials assessing Nrf2-activating adjuncts and combined methods of psychosocial

intervention in high-risk CI-RIRI populations are urgently needed in the future.

Author contributions: Conceptualization, JF and XL; methodology, YW and FW; writing—original draft preparation, ZG; writing—review and editing, JY; All authors have read and agreed to the published version of the manuscript.

Funding: None.

Ethical approval: The ethical committees of the three centers provided their ethics approval (IRB reference: KFH-2022-019, HGR-2022-304, TMC-2022-187).

Informed consent statement: All participants were informed by written informed consent in line with the Declaration of Helsinki (revised 2013).

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

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