


RESEARCH ARTICLE

The influence of acute kidney disease on the clinical outcomes of patients who received cisplatin, carboplatin, and oxaliplatin

Alexandre Ricardo Da Silva Fernandes¹ | Germana Alves de Brito² |
Aline Lourenço Baptista² | Luis André Silvestre Andrade² |
Marina Harume Imanishe² | Benedito Jorge Pereira² 

¹Department of Intensive Care, A.C. Camargo Cancer Center, São Paulo, Brazil

²Department of Nephrology, A.C. Camargo Cancer Center, São Paulo, Brazil

Correspondence

Benedito Jorge Pereira, AC Camargo Cancer Center, Professor Antônio Prudente Street, 211, Liberdade. CEP: 01509-010, São Paulo, SP, Brazil.
Email: benedito.pereira@accamargo.org.br

Abstract

Background and Aims: Cisplatin (CDDP) is used as the first line of treatment for some tumors, but its use may be restricted due to its nephrotoxicity. Carboplatin (CARBO) and oxaliplatin (OXA) are less nephrotoxic alternatives to CDDP. This study has the objective to determine the incidence of acute kidney disease after chemotherapy with CDDP, CARBO, or OXA.

Methods: A clinical study of a retrospective cohort of patients who underwent treatment with CDDP, CARBO, or OXA from January–December 2016. Acute kidney disease (AKD) was defined as elevated serum creatinine (sCR) levels before and up to 3 months after chemotherapy. Morbidities, type of tumor, and treatment data were recorded.

Results: A total of 212 patients aged 55.5 ± 14.0 years were evaluated. Among the comorbidities, 30% had arterial hypertension (AH) and 11% had diabetes, and 18% were treated with CDDP, 41% with CARBO, and 41% with OXA. There was no difference in sCR levels before and after chemotherapy regardless of the chemotherapy used. The prevalence of eGFRs <60 mL/min after chemotherapy was higher in patients with AH and cardiovascular disease (CVD). The incidence of post-chemotherapy AKD was 7.0% ($n = 13$) and the mortality rate was 38.2%. Survival was lower in patients with AKD ($P = .012$).

Conclusions: There was a low incidence of AKD among the patients regardless of the chemotherapy used, but the patients with AKD had shorter survival. In addition, the reduction in eGFR after chemotherapy was greater in patients with AH and CVD.

KEYWORDS

cancer, carboplatin, chemotherapy, cisplatin, nephrotoxicity, oxaliplatin

1 | INTRODUCTION

In 2020, 309 750 cases are expected among men and 316 280 cases among women in Brazil. Most of the cases were nonmelanoma skin

cancers.^{1–3} Of the chemotherapeutic drugs used in the clinical treatment of cancer, cisplatin (CDDP) was one of the first platinum-derived drugs discovered and was approved by the U.S. Food and Drug Administration (FDA) in 1979.^{3–6}

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Since its approval by the FDA, CDDP has been used as the first line of treatment for breast, lung, head and neck, and ovary and testis cancers, but its use has been limited due to neurotoxicity, ototoxicity, and nephrotoxicity.³⁻⁵ The main excretion route of CDDP is through the kidneys, thus nephrotoxicity occurs in ~20% of outpatients and hospitalized patients.³

It is important to note that CDDP nephrotoxicity is dose-dependent and that trials have shown that low doses of CDDP cause late kidney damage differently than high doses of CDDP.⁴⁻⁶ Changes in glomerular filtration were found in 20% to 40% of patients 7 to 10 days after the first dose of CDDP was administered.⁶

The main mechanisms of CDDP-induced damage in the renal tubular cell include DNA damage, changes in cell transport, loss of cell polarity/cytoskeleton, mitochondrial dysfunction, inhibition of fatty acid oxidation, oxidative stress, inflammatory response, activation of apoptotic pathways, activates p53, and apoptosis in renal tubules.^{5,6}

After discovery of CDDP and identification of its side effects, second and third generation drugs derived from CDDP, such as carboplatin (CARBO) and oxaliplatin (OXA) were synthesized to reduce unwanted side effects, including nephrotoxicity.⁷⁻¹¹ CARBO has the same effect as CDDP on cell proliferation, but CARBO does not reduce the cell detoxification mechanisms that remove free radicals.^{10,11}

OXA induces DNA damage, but to a lesser extent, and more effectively inhibits DNA replication and induces apoptosis in normal and mutant cells than CDDP and CARBO.

It is unclear whether nephrotoxicity remains a risk after switching to CARBO or OXA after a previous cycle of CDDP treatment, studies that evaluate CARBO or OXA nephrotoxicity after a CDDP treatment are needed.¹⁰⁻¹⁶

The methods that can assess renal function after long-term treatment with CDDP or CDDP analogs include the serum creatinine (sCR), urea, and fractional sodium excretion.¹⁷ Although sCR is a standard serological marker, its serum levels are variable and should be evaluated with caution and several variables, including age, sex, muscle mass, and hydration must be considered.¹⁷

Therefore, this study aimed to survey the incidence of acute kidney disease in outpatient chemotherapy patients treated with CDDP, CARBO, or OXA and to analyze the clinical factors associated with renal dysfunction occurrences in the chemotherapy patients.

2 | METHODS

A clinical, retrospective cohort study of 212 patients >18 years of age who underwent treatment with CDDP, CARBO, or OXA at AC Camargo Hospital, a Cancer Center in Sao Paulo, Brazil, with assistance, teaching, and research programs was performed to evaluate changes in creatinine levels before and after the start of chemotherapy from January to December 2016. Patients with estimated glomerular filtration rates (eGFRs) >60 mL/min at the beginning of treatment were included in the study and patients with eGFRs <60 mL/min, or who developed AKD due to causes other than chemotherapy were excluded from the study.

Demographic data, including age, sex, comorbidities, oncological disease data, such as date of confirmed diagnosis, tumor staging, and classification of performance status assessed by the Zubrod Scale-ECOG description were collected.

Renal function data (creatinine) were collected before the start of chemotherapy (baseline sCR), at the start of chemotherapy (initial

TABLE 1 Demographic and clinical characteristics of patients undergoing treatment with platinum derivatives at the AC Camargo Cancer Center (n = 212)

	N	%
Age years	55.5 ± 14.0	
Sex	n	%
Male	109	51
Feminine	103	49
Type of health insurance		
Private	151	71
SUS	48	23
Particular	4	1.9
Comorbidities	84	39.6
AH	64	30
DM	24	11
Dyslipidemia	20	9.4
Hypothyroidismo	10	4.7
CVD	8	3.8
Smoking	79	37
Alcoholism	38	18
Tumor location		
Pelvis	68	32
Chest	64	30
Abdomen	52	25
Head and neck	23	11
Hematological	2	0.9
Undefined	3	1.4
Performance scale		
ECOG 0	80	45
ECOG 1	68	38
ECOG 2	17	9.6
ECOG 3	11	6.2
ECOG 4	2	1.1
Chemotherapy		
Cisplatin	38	18
Carboplatin	87	41
Oxaliplatin	87	41
Surgery	102	48
Radiotherapy	94	44

Abbreviations: AH, arterial hypertension; CVD, cardiovascular disease; DM, diabetes; ECOG, Eastern Cooperative Oncology Group; SUS, single health service.

sCR), and up to 3 months after the end of treatment (sCR after chemotherapy). eGFRs were calculated using the formula established by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). Mortality and AKD outcomes were analyzed. To identify the presence of Acute kidney diseases (AKD), we used the KDIGO definition, that is: AKI (an sCR increase >0.3 mg/dL compared to the baseline sCR), or GFR <60 mL/min per 1.73 m² for <= 3 mo.¹⁸

The characteristics of the study population were described in absolute and relative frequencies in addition to measures of central tendency and dispersion when the variables were continuous. The relative frequencies and 95% confidence intervals (CI) were determined according to the Clopper-Pearson method. The Kaplan-Meier method was used to estimate population survival and the log-rank test was used to evaluate differences between groups.

To identify factors associated with outcomes, simple or multiple logistic regression analysis was performed. Pearson's Chi-Square test

or Fisher's exact test (when indicated) was used to identify variables associated with the outcome. The distribution of the values of the renal function markers according to groups was evaluated using the Mann-Whitney test. The prevalence of outcomes at two different patient follow-ups was compared using the McNemar test. The analyses were performed using the IBM SPSS version 20.0 statistical package. Results with a type I error probability of <5% were considered statistically significant.

2.1 | ETHICS STATEMENT

This study was approved by AC Camargo Cancer Center Ethics Committee (approval no. 466/12). All ethical measures were taken, and the collection of the data presented was initiated only after approval by the Research Ethics Committee of this institution.

TABLE 2 Values of serum creatinine levels before and after chemotherapy with patients undergoing treatment with platinum derivatives at the AC Camargo Cancer Center (n = 199)

Chemotherapy	sCR (mg/dL)	Median sCR (mg/dL)	P
Before-CT			
All (n = 197)	0.87 ± 0.32	0.80 (0.47-3.05)	.530
Cisplatin (n = 33)	0.83 ± 0.16	0.83 (0.83-1.20)	
Carboplatin (n = 83)	0.86 ± 0.35	0.86 (0.77-2.43)	
Oxaliplatin (n = 83)	0.90 ± 0.33	0.90 (0.85-3.05)	
Post-CT			
All (n = 189)	0.86 ± 0.31	0.77 (0.40-2.46)	.899
Cisplatin (n = 31)	0.85 ± 0.23	0.90 (0.91-1.28)	
Carboplatin (n = 80)	0.85 ± 0.31	0.74 (0.74-2.26)	
Oxaliplatin (n = 83)	0.87 ± 0.33	0.80 (0.80-2.46)	

Abbreviations: CT, chemotherapy; sCR, serum creatinine; SD, standard deviation.

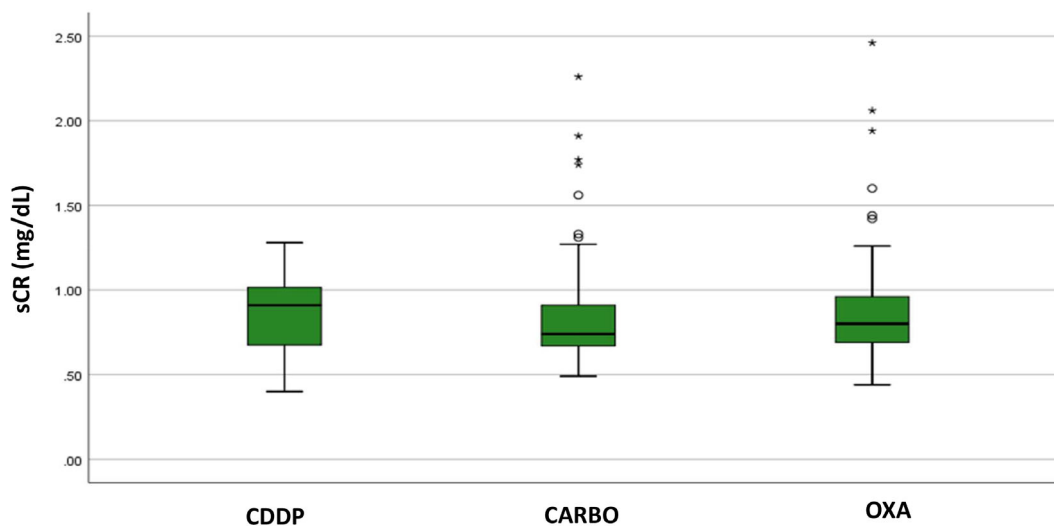


FIGURE 1 Comparison of sCR values after chemotherapy with CDDP vs CARBO vs OXA (n = 19; P = .899)

3 | RESULTS

We evaluated 212 patients treated with CDDP, CARBO, or OXA from January to December 2016 with 51% male and an average age of 55.5 ± 14.0 years. Demographic and clinical characteristics of the patients, including distribution of the chemotherapeutic drugs used and location of the disease are shown (Table 1).

The average pre- and post-chemotherapy sCR levels in patients were 0.87 ± 0.32 and 0.86 ± 0.31 mg/dL, respectively, thus there was no difference in sCR levels before and after chemotherapy. There were also no statistical differences pre- and post-chemotherapy when comparing sCR values between treatment groups (Table 2). The sCR

levels before and after chemotherapy with platinum derivatives ($n = 199$) are shown (Table 2).

The pre-chemotherapy eGFR was 86.7 ± 21.0 mL/min with a median of 88.0 mL/min (18.6-130.4 mL/min). After chemotherapy, the eGFR was 87.16 ± 21.9 mL/min with a median of 90.7 mL/min (24.2-135.6 mL/min). The sCR values for the various treatment groups are shown in Figure 1. Comparisons of sCR values from the CDDP, CARBO, and OXA treatment groups are shown in Figure 2.

The clinical characteristics related to renal dysfunction based on an eGFR <60 mL/min before and after chemotherapy are described in Table 3.

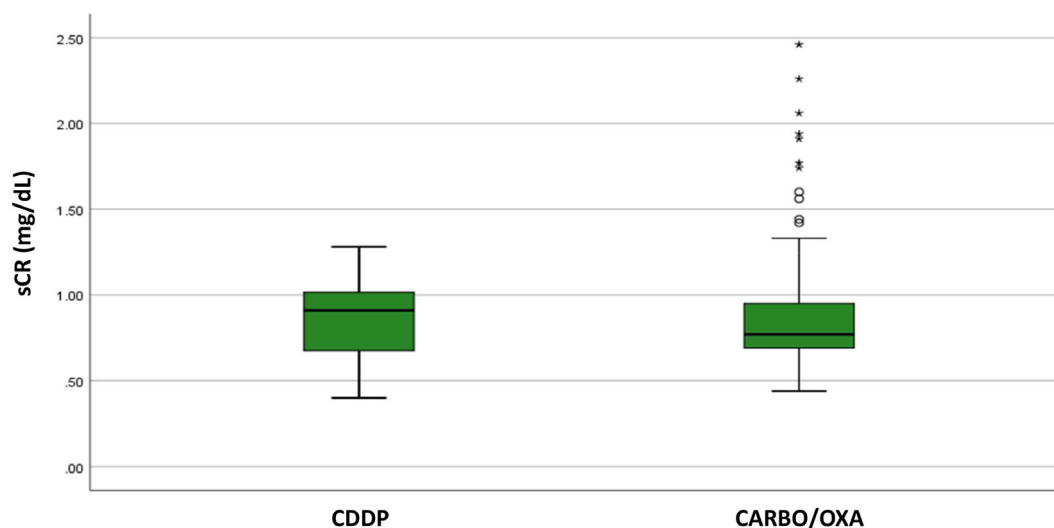


FIGURE 2 sCR levels in patients after chemotherapy with CDDP, CARBO, or OXA at the AC Camargo Cancer Center ($n = 199$; $P = .871$)

Characteristics	All N (%)	eGFR < 60 mL/min N (%)	eGFR > 60 mL/min N (%)	P
Tumor type				
Solid	186 (98.9)	24 (100)	162 (98.8)	1.000
Hematological	2 (1.1)	0 (0)	2 (1.2)	
Chemotherapy				
Cisplatin	31 (16.4)	3 (12.5)	28 (17)	.878
Carboplatin	78 (41.3)	11 (45.8)	67 (40.6)	
Oxaliplatin	80 (42.3)	10 (41.7)	70 (42.4)	
Comorbidities				
AH	78 (42.2)	15 (62.5)	63 (39.1)	.052
DM	58 (30.7)	12 (50)	46 (27.9)	.050*
CVD	21 (11.1)	5 (20.8)	16 (9.7)	.203
Hypothyroidism	6 (3.2)	3 (12.5)	3 (1.8)	.030*
Dyslipidemia	9 (4.8)	0 (0)	9 (5.5)	.510
Dialysis	19 (10.1)	2 (8.3)	17 (10.3)	1.000
Obesity	7 (3.7)	6 (25)	1 (0.6)	.000
	6 (3.2)	1 (4.2)	5 (3.0)	1.000

TABLE 3 Evaluation of clinical features in relation to renal dysfunction after chemotherapy with platinum derivatives in patients at the AC Camargo Cancer Center ($n = 188$)

Abbreviations: AH, systemic arterial hypertension; CVD, cardiovascular disease; DM, diabetes mellitus.

* $P < .05$.

The significant variables in Table 3 were submitted to simple logistic regression analysis and with this we observed that the presence of preexisting disease was significant $P = .035$, $OR = 2.59$ (95% CI 1.07-6.28), and among these comorbidities, hypertension $P = .032$, $OR = 2.58$ (CI 95% 1.08-6.17) and CVD $P = .016$, $OR = 7.71$ (95% CI 1.46-40.71). Before multiple analysis, hypertension (AH) was not considered a significant factor 0.080, $OR = 2.22$ (95% CI 0.90-5.43) and CVD was significant with 0.041, $OR = 5.91$ (95% CI 1.07-32.54).

Table 3 shows that the presence of morbidities, such as AH and cardiovascular disease (CVD), were significantly more prevalent in patients with eGFRs <60 mL/min after chemotherapy.

Survival curves of patients based on eRFG are compared in Figure 3.

Among patients with valid data, 13 patients (7.02%) presented with AKD (according to KDIGO criteria) after chemotherapy. The characteristics of these patients are shown in Table 4 and clinical evolution of their disease is shown in Figure 4.

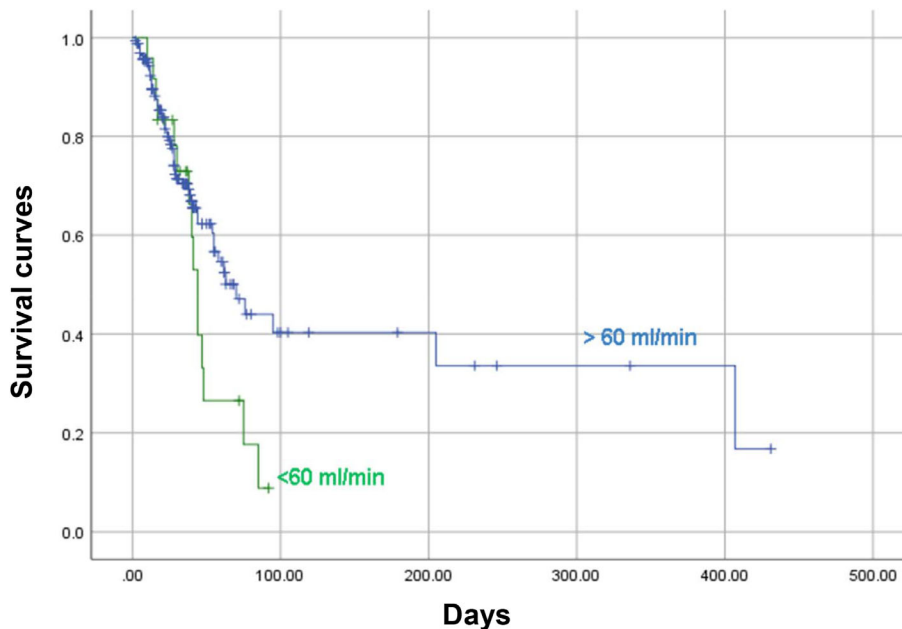


FIGURE 3 Survival curves based on eGFR after chemotherapy at A.C. Camargo Cancer Center (n = 187; log rank = 0.083)

TABLE 4 Presence of renal dysfunction after QT with platinum derivatives at the AC Camargo Cancer Center (n = 185)

	All N (%)	Without AKD N (%)	With AKD N (%)	P
Chemotherapy				
Cisplatin	28 (15.1)	27 (15.7)	1 (7.7)	.738
Carboplatin	77 (41.6)	71 (41.3)	6 (46.2)	
Oxaliplatin	80 (43.2)	74 (43)	6 (46.2)	
CDDP VS Carbo/Oxa	28 (15.1)	27 (15.7)	1 (7.7)	.707
Tumor type				
Solid	182 (98.9)	169 (98.8)	13 (100)	1.000
Hematological	2 (1.1)	2 (1,2)	0 (0.0)	
Comorbidities				
AH	75 (41.4)	69 (40.8)	6 (50.0)	.749
DM	55 (29.7)	49 (28.5)	6 (46.2)	.303
CVD	21 (11.4)	19 (11)	2 (15.4)	.982
Hypothyroidism	6 (3.2)	6 (3.5)	0 (0.0)	1.000
Dyslipidemia	9 (4.9)	9 (5.2)	0 (0.0)	.859
Dialysis	18 (9.7)	18 (10.5)	0 (0.0)	.458
Obesity	7 (3.8)	7 (4.1)	0 (0.0)	1.000
	6 (3.2)	6 (3.5)	0 (0.0)	1.000

Abbreviations: AH, arterial hypertension; AKD, Acute Kidney Disease; Carbo, carboplatin; CDDP, cisplatin; CVD: cardiovascular disease; DM, diabetes; Oxa, oxaliplatin.

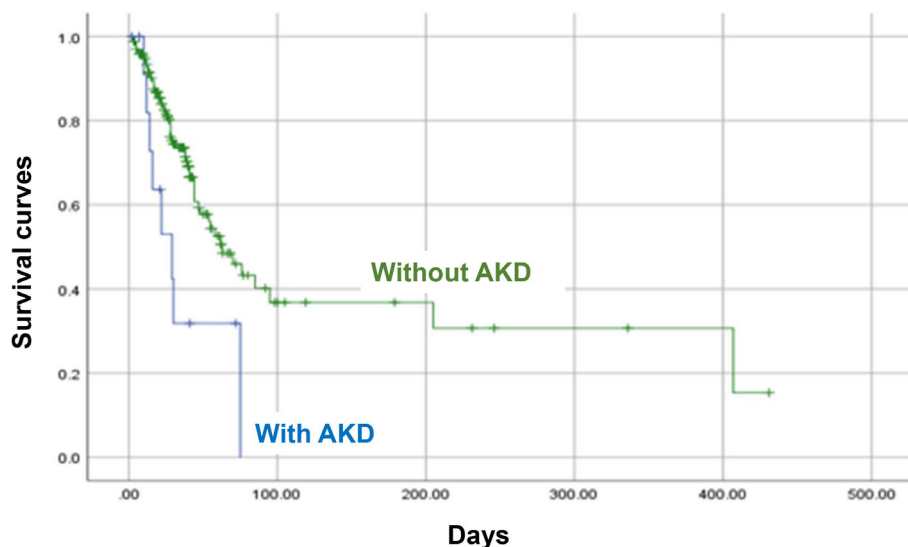


FIGURE 4 Survival curves of patients with AKD after chemotherapy at the AC Camargo Cancer Center (n = 183; log rank = 0.012)

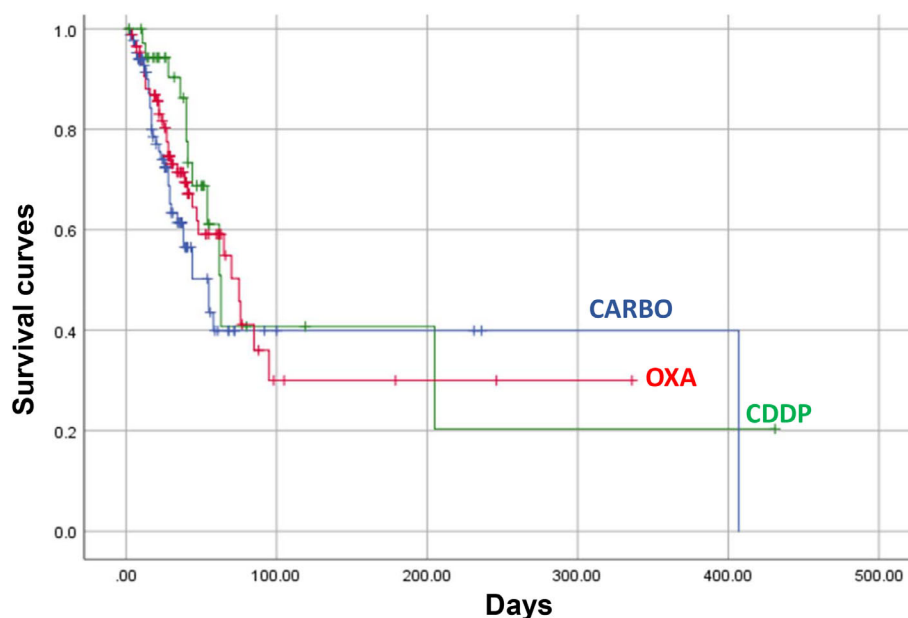


FIGURE 5 Survival curves of patients treated with CDDP, CARBO, or OXA at A.C. Camargo Cancer Center (n = 210; log rank = 0.246)

The significant variables in Table 4 were submitted to simple logistic regression analysis and with this we observed that the presence of pre-existing diseases was not considered significant $P = .535$ OR = 1.44 (CI 95%, 0.449-4.681), even though AH $P = .188$ and CVD $P = .999$.

In general, patients treated with platinum derivatives had a mortality rate of 38%, and there were no survival differences among the chemotherapy treatment groups (Figure 5).

In Cox regression, the presence of AKD was related to higher mortality $P = .015$ with RR = 2.50 (95% CI 1.19-5.26).

4 | DISCUSSION

Among the demographic characteristics of the patients in this study, there was a slight predominance of males over females, and this is consistent with estimates of new cancer cases in Brazil.

Among the associated morbidities, we observed incidences of hypertension in 30% of cases, diabetes in 11% of cases, and CVD in 8% of cases, which is compatible with cancer risk factors, such as obesity, smoking, alcoholism, and physical inactivity observed in other study.¹²

In our study, a predominance of cases had an ECOG of 0 and 1, which are cases with higher performance of clinical conditions, early treatment initiation, and better prognosis than the late onset cases described in other studies.^{19,20}

In our study, we found no significant difference in sCR levels pre- and post-infusion (Table 2 and Figure 2). In our study, there were more cases of patients treated with less nephrotoxic drugs, such as CARBO and OXA, and this may reflect careful selection of appropriate chemotherapy for patients with previous renal dysfunction and effective nephroprotection strategies by the oncology team based on previous studies.^{11-15,21,22}

However, when assessing renal dysfunction after chemotherapy, the presence of dyslipidemia was no longer significant. Some authors showed that AH and CVD morbidities correlated significantly with renal dysfunction that worsened after treatment with CDDP.^{11,12,21,23-25}

The presence of renal dysfunction did not correlate significantly with lower survival (Figure 4); a non-significant trend of lower survival was seen in patients with eGFRs <60 mL/min than in patients with eGFRs >60 mL/min. Perhaps with a larger sample, a significant survival difference may have been observed. The adequacy of treatment could also affect survival as noted other studies.^{3,21,23}

We were also unable to verify an association between AKD and platinum-derived chemotherapeutics (Table 4), perhaps due to the method used for infusion, or due to the predominance of patients treated with CARBO and OXA, which are less or non-nephrotoxic drugs.^{16,22} However, upon analysis of survival curves of patients who presented with AKD after the start of chemotherapy we found that patients with AKD during treatment had the lowest survival (Figure 4), which is compatible with previous studies.^{11,21,26-30}

In this study, analysis of survival curves based on the chemotherapy agent used showed no differences (Figure 5). In the literature, the use of CDDP associated with the presence of complications due to its recognized toxicity and side effects, and the use of new platinum derivatives associated with adverse events less.^{3,10,16,19,20} This study demonstrated that, regardless of the type of chemotherapy, the presence of AKD or other morbidities may be responsible for a patient's poorest performance and that multi-disciplinary care during platinum-derived chemotherapy should be provided to these patients.

5 | CONCLUSIONS

In this study, we observed a low incidence of nephrotoxicity regardless of whether the treatment scheme included CDDP, CARBO, or OXA. Hypertension and CVD associated with lower eGFR in patients, especially after chemotherapy.

Survival curves of patients based on the type of chemotherapy used did not differ even when CARBO and OXA were used in combination with CDDP. In this study, despite a low incidence of AKD among patients, the presence of AKD associated with the risk of death by more than two times compared to those who did not have AKD.

Future studies may use new techniques to assess kidney function after the use of chemotherapeutics in prospective clinical studies, such as Cystatin C and/or Lipocalin Associated with Neutrophilic Gelatin for a careful assessment of kidney function.

ACKNOWLEDGMENTS

Acknowledgments to the Graduate Committee of the AC Camargo Cancer Center.

FUNDING

We did not receive any specific grant from any funding agency.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Conceptualization: Benedito Jorge Pereira.

Data Curation: Marina Harume Imanishe.

Investigation: Alexandre Ricardo Da Silva Fernandes.

Project Administration: Benedito Jorge Pereira.

Visualization: Germana Alves de Brito, Aline Lourenço Baptista.

Writing – Original Draft Preparation: Germana Alves de Brito, Luis André Silvestre Andrade, Marina Harume Imanishe.

Writing-Review & Editing: Benedito Jorge Pereira.

All authors have reviewed, discussed, and agreed to their individual contributions.

The corresponding author confirms that he has full access to all study data and assumes full responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by AC Camargo Cancer Center Ethics Committee (approval no. 466/12). All ethical measures were taken, and the collection of the data presented was initiated only after approval by the Research Ethics Committee of this institution.

ORCID

Benedito Jorge Pereira  <https://orcid.org/0000-0002-7020-4573>

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How to cite this article: Fernandes ARDS, de Brito GA, Baptista AL, Andrade LAS, Imanishe MH, Pereira BJ. The influence of acute kidney disease on the clinical outcomes of patients who received cisplatin, carboplatin, and oxaliplatin. *Health Sci Rep.* 2022;5:e479. doi:10.1002/hsr2.479