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REVIEW

Long-term nephrotoxicity in irradiated pediatric kidney tumor survivors: A systematic review

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Abstract

Objective: Nephrotoxicity can occur as a side effect after treatment for kidney tumor in childhood. The use of radiotherapy (RT) has a potential additional effect.

Methods: A systematic electronic literature search that combined childhood kidney cancer with different treatments and nephrotoxicity terms was performed in EMBASE. Studies were included based on the reporting of nephrotoxicity occurrence after treatment for kidney tumor during pediatric age, with 75% of participants being under the age of 25 years at the time of diagnosis, and having been treated with any type of kidney surgery, chemotherapy, and/or RT.

Results: A pooled analysis did not show significant difference in estimated glomerular filtration rate between the group of patients who received RT compared with the group treated without RT (SMD −0.11 [95% CI −1.07–0.84] $p = .733$).

Conclusion: The current literature suggests that the use of RT does not have a significant impact on the decline of kidney function as independent factor.

KEYWORDS
childhood, kidney failure, kidney tumor, nephrotoxicity, radiotherapy

1 | INTRODUCTION

Childhood kidney tumors represent around 7% of all pediatric cancers.[1–3] The majority of the kidney tumor cases (~90%) consists of Wilms tumor (WT or nephroblastoma).[4] Major improvements in treatment strategies for kidney tumors in childhood led to an increased survival over the past few decades. At present, long-term overall survival of WT patients exceeds 90% in localized disease and 80% in metastatic patients.[5–9] Overall, non-WT have a poorer outcome than WT.[10–13] In parallel to this improvement in survival rates, an increased alertness for the late adverse events as a consequence of the treatment effects has occurred.[14–16] Kidney injury is one of the complications of cancer treatment in children.[17] Treatment-related factors such as the use of systemic therapy containing platinum agents and ifosfamide, nephrectomy, and abdominal radiotherapy (RT) are perceived as potential risk factors for the onset of kidney injury.[17–19] The exact incidence of kidney failure (KF) developed after treatment for kidney tumors differs between series and has been reported up to 20% of the cases in bilateral WT.[20] Reports have suggested that the risk of chronic kidney disease (CKD) may be significant after unilateral

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; I2, inconsistency index; KF, kidney failure; RT, radiotherapy; SMD, standardize mean difference; WT, Wilms tumor.

nephrectomy and RT for WT.[21,22] However, the exact contribution of RT as independent determinant has not been established yet. So far, no systematic review with the objective to answer this question was performed. The aim of the current literature review is to gain insight into the specific contribution of RT to the development of kidney disease after treatment for childhood kidney tumor by identifying all studies reporting on adverse kidney effects in this survivors population, contributing to fill in the existing knowledge gap.

2 | METHODS

2.1 | Literature search strategy

A systematic electronic literature search was performed in the EMBASE database up to 28th January 2021. Medical Subject Heading and Title/Abstract terms were applied in our search strategy to detect references that combined pediatric kidney cancer treatment and nephrotoxicity. The reporting guideline for systematic review protocols, Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols, was used (Table S1). All terms used in the search are listed in Table S2. Cross-reference checks were performed to identify potential relevant additional articles. In order to expedite the systematic review process, the Rayyan tool, developed through the Qatar Computing Research Institute, funded by the nonprofit Qatar Foundation, was employed.

2.2 | Inclusion and exclusion criteria

Studies were included based on the reporting of nephrotoxicity occurrence after treatment for kidney tumor at pediatric age. The search was not limited to the English language. Any type of kidney tumor and treatment with any type of chemotherapy, RT, and/or surgery was included. Age below 25 years at the time of diagnosis in ≥75% of the study population individuals was required. Book chapters, articles not in full text, systematic reviews, and case reports were excluded. Duplicate publications were removed.

2.3 | Data extraction

Titles and abstracts of the available publications were screened by R.D.F. Selected abstracts for full text inspection were checked based on the inclusion criteria. P. R. J., M. v. H., G. J., and M. v. G. reviewed the identified papers. From the selected papers, the following data were extracted: sample size, patients' characteristics (age at diagnosis and age at follow-up), kidney tumor type, antitumor treatment (type of chemotherapy, and/or RT site and dose, and/or surgery), follow-up time and determinants of developing nephrotoxicity. Data on CKD and KF were collected based on the different outcomes shown in the different studies. Risk of CKD compared with healthy controls was reported as odds ratio.

2.4 | Assessment of study quality

A risk of bias assessment was performed to define the quality of the included publications per study question. The Strengthening the Reporting of Observational Studies in Epidemiology statement checklist was used to determine the appropriateness of the research reporting while the Downs and Black tool was used to evaluate the methodological quality.[23,24] The Downs and Black tool was designed to evaluate the methodological quality of both randomized and non-randomized comparative studies and consist of a checklist with 27 items that refer to different methodological components distributed between five sub-scales: reporting, external validity, internal validity (bias and confounding) and power.[23] Scores ˂12 were considered to reflect low quality, scores between 12 and 13 moderate quality, and scores ≥14 high quality.

2.5 | Statistical analysis

The study characteristics are summarized as frequencies and percentages. To analyze our primary outcome regarding the role of RT as independent risk factor for nephrotoxicity, we performed a meta-analysis using DerSimonian-Laird random effects models in order to obtain overall pooled weighted estimated glomerular filtration rate (eGFR), with or without RT, and their 95% confidence interval (CIs). Because of the different outcome measures evaluated per study on long-term kidney damage, it was not feasible to pool every outcome, instead we summarized them. The heterogeneity among studies was tested using the inconsistency index (I2). Heterogeneity was categorized as low (I2 = 25–50%), moderate (I2 = 50–75%) or high (I2 > 75%).[25] A p value of less than .05 was considered significant. All statistical analyses were performed using OpenMeta[analyst] (cebm.brown.edu/open-meta) and IBM SPSS 22.0.

3 | RESULTS

In total, 2573 publications were identified through database searches, of which 70 duplicate articles were removed. Based on the title and abstract screening, 2472 manuscripts were excluded. After assessing the full-text of the remaining 33 articles, 12 studies fulfilled the selection criteria and were included for this review. All 12 papers included kidney damage as outcome after treatment for kidney tumor in childhood and were retrospective cohort, single-center studies. The selection process is shown in Figure 1. All included studies were of good methodological quality. The Downs and Black score ranged from 18 to 26, with a median of 21 (interquartile range, 19.0–23.0) (Table S3).

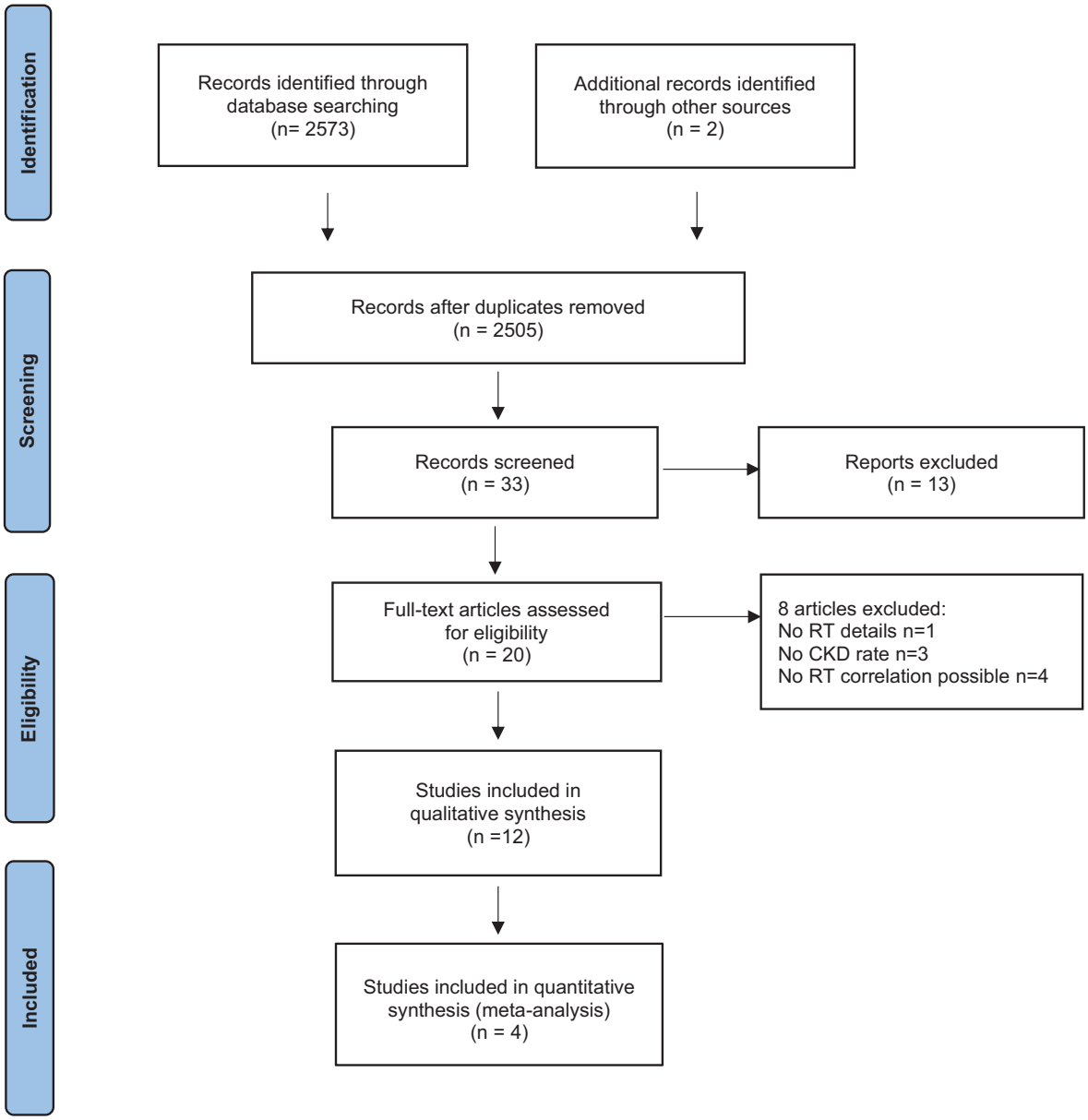


FIGURE 1 Flow-diagram—inclusion and exclusion study selection process.

3.1 | Characteristics of the included studies

Of the 12 studies, 11 utilized the eGFR to assess the CKD stage either using serum creatine- or cystatin *C*-values; creatinine clearance test or renography methods were also used to measure clearance. A detailed summary of the studies and patient characteristics, as well as the outcome measures evaluated per study can be found in Tables S4 and S5. The studies were carried out between 1991 and 2020. Overall, the majority of the patients had unilateral WT. In four studies,[20,26–28] a total of 34 patients with bilateral WT were included. Six patients underwent treatment for unilateral non-WT.[29] All studies reported on the performed surgery (total nephrectomy, nephron-sparing surgery, or combination), and the use of RT. Administered chemotherapy type varied across the studies; seven studies[22,26–31] reported on the use of nephrotoxic chemotherapy. Most patients were under the age of 10 years at the time of diagnosis. All 12 studies had a median follow-up time longer than 5 years.

3.2 | Nephrotoxicity occurrence and contribution of RT to the risk of nephrotoxicity after treatment for pediatric kidney cancer

Table 1 shows a summary of the studies on CKD in irradiated kidney tumor survivors.[20,22,26–35] Ten studies reported on the occurrence of KF. The incidence rates of KF varied between 0 and 12%. Multivariate

TABLE 1 Summary of studies on chronic kidney disease in irradiated kidney tumor survivors.

					Methods			Outcomes			MVA	Risk of bias	
Paper no.	Authors (year)	*N* (RT/total renal tumor cohort)	eGFR	CKD stage	CKD specified	Proteinuria	RT dose remaining kidney (Gy)	KF	KF (%)	RT impact on CKD		Total score	Quality
1	Aronson (2011)	5/25	NA	NA	NA	NA	NA	Y	12	NS	Y	18	High
2	Bailey (2002)	19/40	Y	Y	CKD > 1	Y	D_{mean} 3.3	Y	0	NS	N	23	High
3	Bal (2016)	20/50	Y	Y	CKD > 1	Y	NA	Y	0	NS	Y	23	High
4	Daw (2009)	11/11	Y	Y	CKD > 1	Y	10.5–12 ($n = 5$)	Y	8	NS	N	22	High
5	Dekkers (2013)	29/85	Y	Y	CKD 1–5	Y	NA	Y	3.5	S	Y	25	High
6	Green (2020)	20/40	Y	Y	CKD 1–3	NA	Median (STD)D100% =11 (range 10.0–11.5)D50% =11 (range 10.5–12.0)	Y	0	NS	Y	26	High
7	Kern (2014)	27/55	Y	Y	CKD > 2	NA	NA	NA	NA	NS	Y	19	High
8	Mavinkurve (2016)	19/79	Y	Y	CKD 1–2	Y	NA	Y	0	NS	Y	20	High
9	Makipernaa (1991)	27/30	Y	Y	CKD > 2	NA	NA	NA	NA	NS	N	19	High
10	Neu (2017)	22/37	Y	Y	CKD 1–3	Y	NA	Y	0	S	N	22	High
11	Sánchez (2019)	12/39	Y	Y	CKD 1–3	NA	NA	Y	0	NS	Y	20	High
12	Schiavetti (2015)	8/35	Y	Y	CKD 1–2	Y	NA	Y	0	NS	N	19	High

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KF, kidney failure; MVA, multivariate analysis; NA, not available; NS, not significant; S, significant; STD, standard deviation; Y, yes.

analysis was performed in seven studies. The dose received by the remaining kidney was reported in three studies[26,30,33] and ranged between 3.3 and 12 Gy. Only one study[27] reported a significant higher risk for development of CKD in patients receiving flank/abdominal RT above 25 Gy based on univariate analysis ($p = .021$); the remaining kidney dose received by these patients was not reported.

3.3 | Pooled data analysis

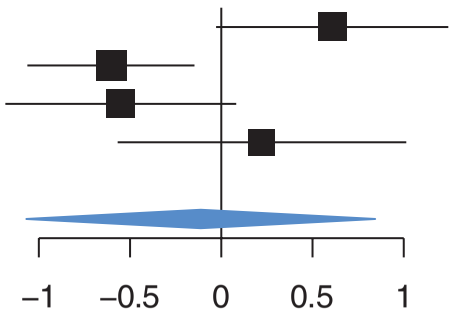
In four studies, the raw eGFR data were reported.[22,26,29,33] These four studies were included in a meta-analysis. Table 2 shows the details of the performed pooled analysis where the relation between eGFR and the impact of the use of RT is gathered. Figure 2 shows the pooled estimate for the primary outcome. The subset of pediatric kidney tumor patients treated with RT has no significant difference in eGFR compared with the group not receiving RT (SMD −0.11 (95% CI −1.07–0.84) $p = .733$) (Figure 2).

4 | DISCUSSION

CKD can occur as an adverse event after kidney tumor treatment in childhood.[17,36] The use of RT has recurrently been appointed as a potential contributing factor although no strong supporting data are available. Through this systematic review, we aimed to provide insight as to the actual contribution of RT to the development of kidney injury as independent factor in this patient population. From the available data, there is no strong evidence that the kidney RT volumes impact the development of CKD in pediatric patients treated for a kidney tumor.

The reported incidence of chronic kidney damage varies across the different cohorts, most often single-center experiences. Although a significant number of WT survivors can develop a glomerular and tubular damage during the treatment (acute kidney injury), that often spontaneously recovers, the risk of KF is remarkably low for patients with nonsyndromic, unilateral WT (0.6%); in the context of bilateral disease the risk is known to be higher (12%), as well as in syndromic WT cases (36–74%).[37,38]

Study, year	RT (eGFR)			No RT (eGFR)				SMD
	Mean	SD	N	Mean	SD	N	Weight	Random, 95% CI
Bailey, 2002	109.50	28.84	19	95.52	14.80	21	24.8%	0.61 [−0.03; 1.24]
Dekkers, 2013	86.00	25.10	29	101.00	24.30	56	28.7%	−0.60 [−1.06; −0.15]
Green, 2020	94.90	14.70	20	103.90	17.20	20	24.9%	−0.55 [−1.18; 0.08]
Schiavetti, 2015	102.30	12.99	8	98.92	15.30	27	21.5%	0.22 [−0.57; 1.01]
Total (95% CI)			**76**			**124**	**100.0%**	**−0.11 [−1.07; 0.84]**



Heterogeneity: $Tau^2 = 0.2671$; $Chi^2 = 11.46$, df = 3 ($P < 0.01$); $I^2 = 74\%$
Overall effect: p= 0.7326

* The provided eGFR SD in the paper of Dekkers applies to the total patient cohort having received abdominal radiotherapy included in the publication (n=763). Only the adjusted mean eGFR could be retrieved for renal kidney tumour survivors (n=85)

Abbreviations: RT: radiotherapy; eGFR: estimated glomerular filtration rate; SD: standard deviation; SMD: standardized mean difference; CI: confidence interval.

FIGURE 2 Pooled analysis.

TABLE 2 Relation between eGFR and radiotherapy dose in kidney tumors.

Paper no.	Reference	Patients *n*		eGFR (mean)/STD		RT prescribed dose (Gy)	RT dose remaining kidney (Gy)	RT impact
		No RT	RT	No RT	RT			
2	Bailey	21	19	95.52/14.81	109.52/28.48	Median 30 (range 19.8–34)	D_{mean} 3.3	NS
5	Dekkers[a]	56	29	101[a]/24.3	86[a]/25.1	21 (15–30) TCD	NA	S
6	Green	20	20	103.9/17.2	94.9/14.7	D_{mean} 16.5 (range 12.0–29.0)	Median (STD)$D_{100\%}$ =11 (range 10.0–11.5)$D_{50\%}$ =11 (range 10.5–12.0)	NS
12	Schiavetti	27	8	98.92/15.29	102.3/12.99	Median 20 (range 15–34)	NA	NS

Abbreviations: D, dose; eGFR, estimated glomerular filtration rate; Gy, Gray; NA, not available; NS, not significant; RT, radiotherapy; S, significant; STD, standard deviation; TCD, total cumulative dose.

[a]The provided *eGFR STD* in the paper applies to the total patient cohort having received abdominal radiotherapy included in the publication ($n = 763$). Only the *adjusted mean eGFR* could be retrieved for renal tumor survivors ($n = 85$).

RT is a well-recognized factor for the development of CKD in adults.[39,40] Radiation nephropathy has been reproduced in many animal models.[40–42] Long-term follow-up of the patients at risk is required since radiation kidney damage can occur as a late event, usually presenting months or years after the radiation exposure. Low mitotic rates of normal kidney tissue associates with delayed expression of kidney injury after RT.[40,43] Early changes of microvascular injury are followed by parenchymal damage leading to kidney mass reduction and finally fibrosis.[44,45] Whether the radiosensitivity of the kidneys in children is comparable to adults, and/or the radiation constraints can be extrapolated to the still growing pediatric population is not well known, although it is conceivable since the number of nephrons we are born with is fixed and does not increase during the infancy period.[46,47] Nevertheless, the need for removal of kidney tissue in children with WT, and the use of potentially nephrotoxic chemotherapeutic agents and/or RT, may imply that the kidney constraint dose might be lower due to the increased risk for impaired kidney function in this patient population.

The kidneys are dose-limiting organs for RT involving the upper abdomen.[48] A mean dose below 18 Gy is mostly recommended as dose–volume constraint, accepting an estimated risk below 5% of developing RT-induced kidney damage in solid tumors. In the context of total body irradiation a mean dose to the kidneys below 10 Gy is recommended.[48–50] In the treatment of pediatric kidney tumors prescribed radiation doses >25 Gy have been associated with a decrease in kidney function[27] while others fail to prove any relation between irradiation of the contralateral kidney and the use of RT for developing KF.[51] A kidney dose constraint <12 Gy, whenever feasible, has traditionally been used when irradiating pediatric kidney tumors.[2,52] The majority of the studies that report on nephrotoxicity and the use of RT only mention the prescribed dose to the target volume, while the remaining in situ kidney is located at the contralateral side, and efforts are made to limit the dose that this organ receives. Therefore, a more meaningful parameter is the dose received by the remaining kidney. Three of the studies included in this review[26,30,33] describe this parameter. In all three studies, the dose on the contralateral kidney was lower than 12 Gy. In none of these studies, RT appeared to influence the development of CKD. In case of whole-abdomen RT, the remaining kidney traditionally received a mean dose of around 12 Gy by shielding the organ, and, thereby, often partly the target volume. With contemporaneous RT approaches, such as intensity-modulated RT or volumetric-modulated arc therapy a better dose reduction to the organ can be achieved while respecting the coverage of the surrounding target volume.[53,54]

More recently, after the current systematic electronic literature search was performed, a report of the Childhood Cancer Survivor Study on the self-reported late-onset of KF in survivors of childhood cancer was published. KF was defined as either dialysis or kidney transplantation (grade 4), or death attributable to kidney disease (grade 5), based on the Common Terminology Criteria for Adverse Events. A radiation kidney dose above 15 Gy, together with the use of high-dose anthracycline, any ifosfamide, and nephrectomy were factors associated with increased risk. Since the duration of dialysis was not taken into account, any episode of kidney injury that required short term dialysis qualified as grade 4, which can eventually lead to an overestimation of the percentage of the reported KF.[55] Another study on the kidney function of childhood cancer survivors demonstrated an association between the development of stage 3–5 CKD and the radiation dose received by a certain percentage of the total kidney volume [≥5 Gy (V5), ≥10 Gy (V10), ≥15 Gy (V15), and ≥20 Gy (V20)] in a multivariate analysis, based on the reconstructed radiation treatment plans of 86% of the irradiated patients whose kidney dosimetry could be quantified; 6.5% of the patient population had been treated for a kidney tumour.[56]

Our systematic review and meta-analysis, which specifically looked into the role of RT as part of the treatment of pediatric patients with a kidney tumor, suggests that RT does not have an independent effect on the decline of kidney function in this patients population.

4.1 | Strengths and limitations

This systematic review facilitates the interpretation of the summarized literature by offering an inclusive overview of relevant publications. The development of nephrotoxicity after treatment for a kidney tumor in childhood is an impactful side effect with multifactorial origin. To be able to extract the exact contribution of RT as an independent factor remains challenging since the available studies are underpowered to answer this question which can lead to an underestimation of the real problem. The retrospective character of the studies, the differences in patient population and follow-up duration, the variety of outcome measures and criteria definitions, the lack of data regarding the exact kidney volume exposed to RT dose, the small patient numbers, and the single-center cohorts hamper a deeper understanding. Moreover, the use of eGFR based on serum creatinine as marker in this specific patient population may be debatable since the serum creatinine levels of these patients could already be low due to loss of muscular cell mass, low protein intake, cachexia and inflammation.[57,58] The future conduct of randomized clinical trials by the international collaborative groups that not only focus on questions regarding efficacy of the treatments but also involve toxicity outcomes are encouraged to appropriately interpret the issue of RT-induced nephropathy.

5 | CONCLUSION

Nephrotoxicity is a recognized adverse event after treatment for a kidney tumor in childhood. Based on the existing literature, there is no strong evidence that the use of RT has an impact on the development of CKD as independent factor. Limiting the radiation dose under 12−15 Gy to the remaining kidney seems to be safe. Further research that incorporates radiation dosimetry and is specifically designed to address nephrotoxicity in the context of a clinical trial will be relevant to obtain growing evidence for the safety and efficacy of currently used RT modalities.

AUTHOR CONTRIBUTION

Conceptualization: R. D. F., P. R. J., M. v. H., G. O. J., and M. v. G. *Methodology*: R. D. F., P. R. J., M. v. H., M. L., G. O. J., and M. v. G. *Software*: R. D. F. and P. R. J. *Validation*: R. D. F., P. R. J., M. v. H., M. L., G. O. J., and M. v. G. *Formal analysis*: R. D. F. and P. R. J. *Investigation*: R. D. F., P. R. J., M. v. H., M. L., G. O. J., and M. v. G. *Resources*: R. D. F., P. R. J., M. v. H., M. L., G. O. J., and M. v. G. *Data curation*: R. D. F., P. R. J., M. v. H., M. L., G. O. J., and M. v. G. *Writing—original draft preparation*: R. D. F., P. R. J., M. v. H., M. L., G. O. J., and M. v. G. *Writing—review and editing*: R. D. F., P. R. J., M. v. H., M. L., G. O. J., M. v. G., C. H. T., and R. M. v. A. *Supervision*: R. D. F., P. R. J., M. v. H., G. O. J., and M. v. G. *Funding acquisition*: not applicable. *Project administration*: R. D. F., P. R. J., M. v. H., G. O. J., and M. v. G. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have declared no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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