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Original Research

Nirmatrelvir/ritonavir prescription: A chance for pharmaceutical care via telemedicine

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Abstract

Background: Nirmatrelvir/ritonavir was authorised for the treatment of COVID-19 patients, despite limited evidence regarding its effectiveness, adverse events or interactions. **Objectives:** Main objective is to assess the impact of pharmaceutical care interventions delivered via telemedicine in patients who started treatment with nirmatrelvir/ritonavir. Secondary objectives are to describe its effectiveness, to analyse its adverse effects, to describe the potential interactions and to analyse patients' adherence. **Method:** A cohort, prospective and multicentre study was conducted from April to November 2022. Adult patients who initiated nirmatrelvir/ritonavir were included. A descriptive study of the pharmacist interventions, adverse effects, clinical outcomes, interactions and treatment adherence was carried out. Pharmaceutical care was provided through a telephone call. **Results:** 281 patients were included and 100% of them received telephone information. A total of 349 interventions of pharmaceutical care were carried out. Sixty-four interventions were related to dose reduction. A total of 285 potential interactions were detected. Sixty-five pharmacist interventions were related to potential severe interaction, that led to discontinuation of the concomitant medication in 56 cases (86,2%) All the pharmacist interventions were accepted by the prescribers. A total of 112 (39.9%) patients experienced some adverse effects. Seventeen patients were hospitalised (6.0%) and five deaths were recorded (1.7%). The 95.3% of the patients reported a total adherence. **Conclusions:** Telepharmacy is a powerful tool for the safe management of the nirmatrelvir/ritonavir. Hospital pharmacists were able to prevent severe potential interactions. The percentages of hospitalised patients, deceased and adverse effects were higher than those reported in pivotal trials. Most patients reported total adherence to the treatment.

Keywords: nirmatrelvir/ritonavir; covid19; pharmaceutical care; adverse effects; interactions

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INTRODUCTION

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and illness with the associated coronavirus disease 2019 (COVID-19) continue to threaten global health. In 2022, COVID-19 led to a reported 394 million infections and 5.7 million deaths.[1] Therapeutic strategies aimed at disease prevention such as vaccines, monoclonal antibodies, and antivirals help prevent patients from developing severe or fatal COVID-19 disease were the most effective strategy. The role of pharmacists during the pandemic was also vital to help create new avenues of pharmaceutical healthcare provision and make medication delivery circuits a reality within record timeframes.[2]

Oral nirmatrelvir/ritonavir (Paxlovid®) is used in asymptomatic patients or those with mild symptoms to help avoid severe COVID-19, thereby decreasing related hospitalisations and deaths.[3]

Nirmatrelvir/ritonavir appeared to be generally well-tolerated in adult patients with symptomatic COVID-19. The most common adverse events of any causality reported for this drug combination were dysgeusia, diarrhoea, hypertension, and myalgia.[4] Nonetheless, these data are limited and so unexpected adverse events that have not been previously reported may emerge after greater clinical experience.[5]

At present, there is little evidence for adverse events resulting from interactions with nirmatrelvir/ritonavir. Moreover, some experiences of integrating hospital pharmacists into care teams have improved and allowed the use of nirmatrelvir/ritonavir in useful and efficient ways, especially in terms of preventing adverse effects.[6]

Main objective:

To describe the impact of pharmaceutical care delivered via telemedicine in patients who started treatment with nirmatrelvir/ritonavir.

Secondary objectives:

1. Describe the effectiveness of nirmatrelvir/ritonavir measured as mortality and hospitalisation 30 days after the initiation of treatment.

2. Analyse the adverse effects detected with the use of nirmatrelvir/ritonavir.

3. Describe the potential drug interactions detected with the use of nirmatrelvir/ritonavir.

4. Analyse patients' adherence to treatment with nirmatrelvir/ritonavir.

METHODS

Study context and setting

This was a prospective, multicentre cohort study conducted from April to November 2022. Patients were recruited from six hospitals within the Galician Health Service.

Patient eligibility, recruitment, and data collection

Patient eligibility and recruitment

Patients were eligible if they met all of the following criteria: 1) they had a current diagnosis of mild to moderate COVID-19; 2) were aged over 18 years; 3) had one or more risk factors for progression to severe COVID-19 according to the Spanish Medicines Agency (AEMPS) criteria [7]; 4) they had experienced the onset of symptoms within 5 days; 5) they did not require hospitalisation due to severe or critical COVID-19 when the treatment was initiated; 6) there was no known or suspected severe renal impairment (eGFR < 30 mL/min); 7) no known or

suspected severe hepatic impairment (Child–Pugh Class C); 8) no history of clinically significant hypersensitivity reactions to the active ingredients or other components of the product; and 9) a hospital pharmacist had authorised the treatment initiation.

Data collection

Two data sources were used to collect the variables of interest: electronic health records and structured telephone interviews with the patients.

Baseline variables (day 0, initiation of nirmatrelvir/ritonavir):

1) Sociodemographic characteristics: age, gender, weight and body mass index.

2) Number of days from the onset of symptoms to the initiation of nirmatrelvir/ritonavir.

3) Prescription indication according to the groups established by AEMPS.[7]

4) Prescription source (specialist care, emergency department, or primary care).

5) Comorbidities.

6) Renal and hepatic function.

7) Smoking status.

8) Concomitant treatments, medicinal herbs, and non-prescription drugs.

9) Potential clinical interactions with concomitant treatments. These interactions were classified based on the World Health Organization Anatomical, Therapeutic, and Chemical Classification; the severity of these were categorised following the University of Liverpool drug interaction database for COVID-19.[8] This database classifies interactions into three categories: 'red' (drugs that should not be co-administered); 'orange' (potentially clinically significant interactions likely to require additional monitoring or alteration of the drug dosage or administration timing); and 'yellow' (a potential interaction whose intensity is likely weak and where additional action, monitoring, or dosage adjustment is unlikely to be required).

Variables on day 30 after treatment initiation:

1) Adverse effects detected that may be related to the medication.

2) Death or hospitalisation of any cause.

3) Cause of death or hospital admission.

4) Visits to the emergency department or medical clinic related to COVID-19.

5) The percentage adherence calculated based on the number of tablets remaining on day 30.

Pharmacist clinical telemedicine intervention

We used the consensus document on telepharmacy positioning by the Spanish Society of Hospital Pharmacy (SEFH) as a reference for the pharmacist clinical interventions. By adhering to the recommendations and best practices outlined in the consensus document, the study aimed to ensure the delivery of high-quality telepharmacy services and maintain consistency with established standards in this field.[10]

The participating pharmacists were trained in the research objectives and protocol through virtual meetings. Once the pharmacists had received and analysed the patient's medical prescription, the patients were contacted by telephone twice on:

- Day 0: Patients were informed about the distribution circuit of nirmatrelvir/ritonavir. The patients were also counselled on the accurate use of nirmatrelvir/ritonavir. Additionally, the interview aimed to gather information about any concomitant medications the patients were taking including medical herbs, non-prescription drugs, and other drugs that did not appear in their electronic medical histories.
- Thirty days after starting the medication, the patient was contacted again to record any adverse effects, medication changes, and problems with treatment adherence not already noted in their electronic medical records.

The hospital pharmacist contacted the patient's medical team if any events or issues arose during the processes outlined above. By keeping the medical team informed, any adjustments or recommendations that were necessary could be implemented promptly, thereby ensuring patient well-being. Figure 1 shows the process taken from the time the medication was prescribed. After the pharmacist clinical telemedicine intervention, the medication was sent to the patient's home.

Data analysis

A descriptive analysis of the demographic and clinical data was performed. The statistical analysis was conducted using SPSS software for Windows® (version 20.0, IBM Corp., Armonk, NY). Continuous variables and those with a normal distribution were expressed as means and standard deviations. Non-parametric variables were presented as medians and interquartile ranges (25–75th percentiles). Categorical variables were reported as absolute frequencies and relative frequencies were provided as percentages.

Ethics approval

This study was approved by the Ethics Committee of Galicia on 27 October 2022, with reference code 2022/408. The research team complied with the standards of good clinical practice, Declaration of Helsinki, Oviedo Convention, and the current regulations on data protection (Organic Law 3/2018 of December 5 on the Protection of Personal Data and Guarantees of Digital rights) and the management of clinical histories while undertaking research.

RESULTS

Patient characteristics

A total of 281 patients were included in the study. Their

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characteristics and their hospital origin are detailed in table 1 and 2. Most of prescriptions originated from specialist care with the most frequent indication for the prescription of nirmatrelvir/ritonavir was patient immunosuppression.

Table 1. Demographic and clinical characteristics of the patients at baseline

Characteristics	**n(%)**
Gender	
Female	150 (53.4)
Male	131 (46.6)
Age (years)	
Median (IQR)	66.0 (51.5-81.0)
BMI (Body mass index)	
<18.5	9 (3.2)
18.5 – 24.9	110 (39.2)
25 – 29.9	101 (35.9)
>29,9	57 (20.3)
Unknown	4 (1.4)
Prescription source	
Primary care	93 (33.1)
Specialist care	153 (54.5)
Emergency Department	35 (12.4)
Prescription indication	
Unvaccinated >80 yo	18 (6.4)
Unvaccinated >65 yo and at least 1 risk factor	4 (1.4)
Inmunocompromised	207 (73.7)
Vaccinated > 6 months ago, >80 yo and at least 1 risk factor	52 (18.5)
Vaccinated	
Yes	252 (89.7)
No	29 (10.3)
Comorbidities	
At least 1 comorbidity	278 (98.9)
Number of comorbidities (median, IQR)	2 (1.0-3.0)
Cardiological disease	114 (40.6)
Onco-haematologic disease	150 (53.4)
Chronic respiratory disease	46 (16.4)
Inflammatory autoimmune disease	63 (22.4)
Diabetes	52 (18.5)
Neurological disease	28 (10.0)
HIV	2 (0.7)
Chronic hepatitis	2 (0.7)
Digestive disease	15 (5.3)
Chronic kidney disease	25 (8.9)
Other	126 (44.8)

Charlson comorbidity index	
0-3	102 (36.3)
4-9	154 (54.8)
>9	25 (8.9)
Renal clearance	
≥ 60 mL/min	215 (76.5)
30-59 mL/min	64 (22.8)
Unknown	5 (1.8)
Bilirubin	
≤ 1,2 mg/dL	268 (95.4)
> 1,2 mg/dL	8 (2.8)
Unknown	5 (1.8)
ALT (GPT)	
< 40 UI	240 (85.4)
40-80 UI (< 2 ULN)	32 (11.4)
81-120 UI (< 4 ULN)	4 (1.4)
121-160 UI and > 160 UI (>5 ULN)	3 (1.1)
Unknown	2 (0.7)
Smoking habit	
Smoker	15 (5.3)
Former smoker	69 (24.6)
Never smoker	113 (40.2)
Unknown	84 (29.9)

The means and standard distribution are shown for normally distributed values, while non-parametric variables are expressed as the median and interquartile range (IQR). Abbreviations: *n*, number of patients; %, percentage; GPT, glutamate pyruvate transaminase; ULN, upper limit of normal.

Table 2. Hospital origin

Hospital origin	**n(%)**
Vigo University Hospital (CHUVI)	88 (31.3)
Ourense University Hospital (CHOU)	63 (22.4)
Ferrol University Hospital (CHUF)	52 (18.5)
A Coruña University Hospital (CHUAC)	38 (13.5)
Lugo University Hospital (HULA)	31 (11.1)
Santiago University Hospitla (CHUS)	9 (3.2)

Abbreviations: *n*, number of patients; %, percentage

Pharmaceutical care interventions

All of the patients in the study received information by telephone about correctly taking the medication, possible adverse effects, and potential interactions. A total of 349 pharmaceutical care interventions were conducted though telephone interviews. Of these, 64 were related to a dose reduction because of decreased renal function and 285 were related to potential drug interactions. The intervention acceptance rate by the prescribers was 100%. Table 3 shows data on the potential interactions detected and the adjustments made accordingly. Most of the pharmaceutical interventions in relation to potential interactions were performed on patients receiving specialist care, in 154 (54.0%) cases. There were 96 patients (33.7%) in primary care and 35 (12.3%) in urgent care.

A total of 256 patients (73.3%) had a potential interaction of any type between their regular treatment and nirmatrelvir/ritonavir. The median number of drug interactions per patient was 1 (interquartile range 0–2). A description of the ATC groups

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Table 3. Farmaceutical care interventions about potential interactions				
	SEVERITY OF THE POTENTIAL INTERATION			Total
	RED n (%)	*ORANGE n (%)*	*YELLOW n (%)*	
Interactions detected	65 (16.4)	280 (70.7)	51 (12.9)	396 (100.0)
Pharmaceutical interventions	65 (100.0)	210 (75.0)	11 (21.6)	285 (72.0)
Dose change	5 (7.7)	61 (29.1)	2 (18.2)	68 (23.9)
Drug discontinuation	56 (86.2))	109 (51.9)	5 (45.5)	169 (59.3)
Other	4 (7.1)	40 (19.0)	4 (36.3)	48 (16.8)

Abbreviations: *n*, number of patients; %, percentage

involved in the potential interaction is presented in table 4. The C (cardiovascular system) and N (nervous system) ATC code groups had the highest number of interactions with statins in group C (84, 55.3%) and benzodiazepines in group N (46, 34.1%) standing out from among them.

Adverse effects

In this study, 112 (39.9%) patients treated with nirmatrelvir/ritonavir experienced some form of adverse effect. Treatment discontinuation because of an adverse effect was reported in only 1 case (as the result of diarrhoea). The most prevalent adverse reaction was dysgeusia (64, 22.8%), with the majority of these patients reporting a metallic taste. Additionally, the incidence of diarrhoea was 11.4% (32 patients). Headache was reported by 10 patients (3.6%). Nausea was also reported by 10 patients (3.6%), with hypotension in 4 patients (1.4%), and elevated transaminases in 6 individuals (3.2%). Other less frequent adverse reactions included fatigue (2 cases) and myalgias (2 patients). A summary of the adverse effects detected in this work is presented in table 5.

Clinical outcomes

Out of the 281 patients included in the study, seventeen patients were hospitalized (6.0%), with an average length of stay of six days (IQR 2.0–9.3). Of these, 8 patients (2.8%) were admitted for COVID-19-related infectious complications. Five deaths (1.7%) were recorded during the study. A total of 35 patients required medical visits within the first 30 days after initiating treatment. Among them, 18 visited the emergency department, 22 visited primary/specialist care physicians, and 5 patients visited both. A more detailed description is provided in table 6.

Treatment adherence

Of the 281 patients, 4 could not be reached, 1 could not recall, and another acknowledged not taking all the prescribed pills but could not provide specific information on the quantity remaining. A total of 262 patients (95.3%) reported full adherence, indicating that they had correctly taken the entire prescribed treatment and had no tablets remaining; 2 patients (0.7%) had decided not to start the treatment. Among the remaining 11 patients, the adherence was as follows: 2 patients had 10–20% adherence, 5 patients had 40–50% adherence, and 4 patients had 60–90% adherence. Non-adherence could not be correlated with other variables because of the small sample size.

Table 4. Interactions with nirmatelvir/ritonavir by ATC group					
RED		SEVERITY OF THE INTERACTION			Total
		ORANGE	***YELLOW***		
ATC group	A		2		2
	B	2	23	1	26
	C	16	125	11	152
	G	14	11	2	27
	H		4		4
	J		2		2
	L	8	23	6	37
	M		2	1	3
	N	23	85	27	135
	P		1	1	2
	R	1	2	2	5
	V	1			1

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Table 5. Adverse effects detected after treatment with nirmatrelvir/ritonavir

Variable	n (%)
Patients who suffered any type of adverse effect	112 (39.9)
Nervous system disorders	72 (25.6)
Gastrointestinal disorders	49 (17.4)
Liver disorders	8 (2.9)
Cardiovascular disorders	5 (1.8)
Renal disorders	1 (0.4)
Other disorders	13 (4.6)

Abbreviations: *n*, number of patients; %, percentage

Table 6. Clinical outcomes

Variable	n (%)
Medical visits 30 days after starting treatment	
Yes	22 (7.8)
No	254 (90.4)
Unknown	5 (1.8)
Emrgency Department visits 30 days after starting treatment	
Yes	18 (6.4)
No	261 (92.9)
Unknown	2 (0.7)
Hospitalisation within 30 days after starting treatment	
Yes	17 (6.1)
No	264 (93.9)
Hospitalisation causes	
Infectious complication related to COVID19	8 (2.8)
Other	9 (3,2)
Hospitalisation length (days)	
Median (IQR)	6,0 (2,0-9,2)
Exitus	
Yes	5 (1.8)
No	273 (97.1)
Unknown	3 (1.1)

The means and standard distribution are shown for normally distributed values, while non-parametric variables are expressed as the median and interquartile range (IQR)

DISCUSSION

Pharmacists played a vital role in public healthcare during the SARS-CoV-2 pandemic by safekeeping and storing different drugs and in the development of COVID-19 treatment protocols. Above all, pharmacists participated in multidisciplinary teams during this period to ensure the efficient and safe use of medicines. This current work demonstrated that, by following the same work protocol in several hospitals in the same health service, a rapid and effective healthcare provision circuit was created that guaranteed patients with COVID-19 access to nirmatrelvir/ritonavir in an effective and safe manner. This study highlighted the importance of pharmacist interventions through telepharmacy in ensuring the safe and effective use of nirmatrelvir/ritonavir in patients with COVID-19.

The number of pharmaceutical care interventions we recorded per patient was very high. Integration of pharmacists into multidisciplinary teams facilitated rapid interventions and dispensing/refusal of treatment in patients infected with SARS-CoV-2. Moreover, having a single electronic record for every level of care was also a useful tool which facilitated contact with prescribers, especially primary physicians. The studies published by Margusino-Framiñan et al.[2] or the review by Unni et al,[11] highlighted new forms of pharmaceutical care or medication delivery with the objective of patient safety and system efficiency. However, we were unable to identify any interventions conducted directly by hospital pharmacists.

Regarding drug interactions, of those that did not contraindicate starting treatment, most were related to the discontinuation or dose adjustment of one of the patient's usual treatments and very few patients had no interactions. The most common drug classes involved in interactions were cardiovascular and nervous system medications, which was to be expected, given that these drugs are prescribed to a high percentage of patients. Thus, nirmatrelvir/ritonavir, even as a short treatment course, has a high potential to cause harm from drug–drug interactions with other drugs metabolised through the same pathway.

This effect was described in detail in a recent review that identified 371 different drugs that interact with nirmatrelvir/ritonavir, with particular relevance to antiarrhythmics, antiplatelet agents, antihypertensives, statins, antipsychotics, and anticancer drugs. This coincides with the results obtained in our study and may be because the target population that received the most treatment were patients with chronic diseases and a mean age of 66 years.[12]

This is the first study to date to present results showing the avoidance of potential interactions in real clinical practice. Indeed, this work verifies the conclusions of research such as that by Igho-Osagie et al.[13] which estimated that approximately one-third of the US population would be at risk for a major or contraindicated potential drug–drug interaction should they receive a ritonavir-containing regimen. These authors showed that this risk increases significantly among individuals aged 60 years or more with comorbidities such as serious heart conditions, diabetes, or HIV.[13] Thus, the interventions by pharmacists in this current work may have prevented hospital admissions as the result of failure to appropriately suspend treatments or reduce or adjust nirmatrelvir/ritonavir doses based on the patients' baseline characteristics.

Our study also revealed a higher global incidence of adverse effects associated with nirmatrelvir/ritonavir treatment in a real-life setting (39.9%) compared to the 23.1% reported in the clinical trial that led to its initial commercialisation.[14] The most prevalent adverse reaction in our study was dysgeusia at a real-life value nearly four times higher than that observed in the original trial (22.8% vs. 5.6%). The incidence of diarrhoea was also significantly higher in our cohort compared to the clinical trial (11.39% vs. 3.1%).

Of note, a recent pharmacovigilance study conducted in 2022 revealed that from the second quarter of 2020, over 70,000 cases of adverse events associated with COVID-19 had been reported to the US Food and Drug Administration's database of post-marketing surveillance.[15] Specifically, more than 9,500 of these cases had been related to nirmatrelvir/ritonavir treatment and, as in our work, these authors also identified dysgeusia as one of the most common adverse events. This finding also coincides with those from a recently published meta-analysis in which dysgeusia and diarrhoea were the most frequent side effects although, as in our study, this did not lead to treatment discontinuation.[16] Therefore, our findings agree with other studies regarding the need for comprehensive pharmacovigilance monitoring in clinical practice to prevent and inform patients of potential side effects and to ensure compliance.

All of the above justifies the presence of pharmacists in multidisciplinary teams to evaluate, validate, and dispense nirmatrelvir/ritonavir. Indeed, approximately 6% of patients receiving nirmatrelvir/ritonavir treatment were hospitalised within the first 30 days of starting treatment. This percentage was higher than that published in the pivotal trials (0.7% of patients in the nirmatrelvir/ritonavir group) or by Hammond et al.[14] (0.77%). No patient deaths were reported by Hammond et al.[14] while in our work 6 patients (1.7%) died. Interestingly, although our work was an uncontrolled, observational study, almost 90% of the patients included had been vaccinated, which should lead us to expect better results than in clinical trials.

In this sense, a retrospective study carried out in Israel showed that nirmatrelvir/ritonavir and adequate COVID-19 vaccination status were associated with a significant decrease in the rate of severe COVID-19 or mortality, with adjusted HRs of 0.54 (95% confidence interval [0.39, 0.75]) and 0.20 (95% confidence interval, [0.17, 0.22]), respectively.[17] They assessed all adults aged 18 years or older with a first-ever positive test result for SARS-CoV-2 performed between 1 January and 28 February 2022. Patients were followed from the start dates until the first occurrence of severe COVID-19 or death, with a follow-up period of 28 days or up until 10 March 2022, whichever came first. Multivariable Cox proportional-hazards regression models were used to assess the association between drug use and the composite of severe COVID-19 or mortality.

However, although this study included vaccinated patients, their results cannot be compared with ours because of methodological differences.[17] Another potential difference may have been the high number of patients with comorbidities because of prescription restrictions for hospitalised patients. Above all, it stood out that more than 50% of the participants in our cohort were oncological patients. Therefore, although no conclusions can be drawn regarding vaccination status, it does highlight the need for more controlled real-life studies. Such work could explore the impact of patient characteristics and comorbidities on treatment outcomes and would be valuable for tailoring therapies to individual patient needs.[16]

The strengths of this present study were its multicentric and prospective nature, the fact there was a single electronic medical record for the entire health system, and the value of obtaining real-life results. There were also limitations to this study including: (1) the absence of a comparison group that could provide more data about the effectiveness of the drug; (2) the fact that the adverse effects were recorded via a telephone interview with the patients on day 30 and so there may have been memory bias; and (3) there may have been a selection bias given that certain pathologies (i.e. transplant patients using immunosuppressants) were excluded from the study because of a contraindication for ritonavir with their medication.

CONCLUSIONS

The use of telepharmacy with patients with COVID-19 who were candidates for treatment with nirmatrelvir/ritonavir was a powerful tool for the safe administration management of this drug combination. This study also demonstrated the importance of hospital pharmacists in avoiding potential interactions that could have otherwise caused serious adverse effects or treatment discontinuations. A total of 396 potential interactions were detected, with medications for the cardiovascular and nervous system being the most commonly involved. In addition, almost all patients reported complete adherence to treatment with nirmatrelvir/ritonavir. Importantly, the percentage of patients hospitalised within the first 30 days of starting treatment, as well as the number of patients who died, was higher than that published in pivotal clinical trials. Finally, our results also showed a higher percentage of adverse effects than those described in the pivotal clinical trial, although they were all mild and did not lead to treatment discontinuation.

AUTHORS ROLES

APL, EYRV, APC and NMLC have contributed substantially to the conceptualization, methodology, software, supervision and validation of this study; SCL, AMRA, MGR, MAP, CAC, MCF, DFM, CG, MBLE, PPM, DRT, JPVB and MMLGO collaborated in the formal analysis, investigation, data curation and resources; ARV, NVP, DBN, MDG, JGD, ALVC and HEC contributed to the collection of data from external centers. Project administration, APL, APC and NMLC. SGC, MSU, APL, EYRV and NMLC writing-original draft preparation. APL, EYRV and NMLC had writing, reviewing & editing. All authors have read, visualization and agreed to the published version of the manuscript.

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