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Serum cytokine profiles in patients with pancreatic cancer and chronic pancreatitis

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ABSTRACT

Background: Chronic pancreatitis (CP) may cause tumor-like lesions, creating a challenge in distinguishing between CP and pancreatic ductal adenocarcinoma (PDAC) in a patient. Given that invasive surgery is a standard cancer treatment, we aimed to examine whether a noninvasive diagnostic tool utilizing serum cytokines could safely differentiate between PDAC and CP.
Methods: A pre-operative serum panel comprising 48 inflammatory cytokines, CA19-9, and C-reactive protein (CRP) was analyzed, consisting of 231 patients, 186 with stage I–III PDAC and 45 with CP. We excluded PDAC patients who underwent neoadjuvant therapy and those CP patients with other active malignancies. The laboratory variables most associated with PDAC diagnosis were assessed using logistic regression and selected using the lasso method.
Results: The cytokines CTACK, GRO-α, and β-NGF were selected alongside CA19-9 and CRP for our differential diagnostic model. The area under the curve (AUC) for our differential diagnostic model was 0.809 (95% confidence interval [CI] 0.738–0.880), compared with 0.791 (95% CI 0.728–0.854) for CA19-9 alone (not significant).
Conclusions: We found that inflammatory cytokines CTACK, GRO-α, and β-NGF alongside CA19-9 and CRP may help distinguish PDAC from CP.

1. Introduction

Pancreatic cancer is a well-known disease with relatively poor survival rates. Despite its rarity, pancreatic cancer is the fourth leading cause of cancer death in developed countries, with estimates expected to surpass breast cancer in the future [1]. Thus, it is paramount that we further explore this type of cancer and develop more effective diagnostic and treatment strategies.

Chronic pancreatitis (CP) is a notable risk factor for pancreatic cancer [2,3]. Clinically, it may be challenging to differentiate between the two diseases since CP may cause lesions that appear tumor-like in medical imaging [4]. This presents a well-acknowledged problem during differential diagnosis [5,6].

The pancreas is located behind other internal organs, making it difficult to obtain a reliable biopsy to rule out cancer. Sometimes diagnostic procedures do not result in a clear outcome, and the diagnosis of cancer is uncertain. Patients with unclear diagnosis often go through heavy surgery to make sure no cancer is left untreated. The proportion of patients with suspected malignancy whose diagnosis was confirmed benign after pancreaticoduodenectomy has been reported at 8–13% [7,8]. This kind of procedures pose unnecessary health risks for those treated in vain and constitute a high economic cost.

Inflammation may be either protumorigenic or antitumorigenic. Cancer occurrence and progression depend on which type of inflammation dominates in the tumor microenvironment [9,10]. This leads to the assumption that the inflammation profiles present in PDAC and CP microenvironments differ. We hypothesize that this difference is also detectable in the sera of patients, via different

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concentrations of circulating cytokines.

Cytokines are small proteins that operate in cell signaling and immune modulation and are the primary operators in defining the inflammation state of the tumor microenvironment. Different combinations of tumor markers and cytokines have previously appeared to help differentiate between PDAC and CP [11–15]. However, the results are inconsistent and mixed: for example, higher IL-8 levels have been associated with PDAC and CP [12,15]. In addition, serum interleukin-17 levels have been speculated to help discriminate between PDAC and CP [16]. In addition, the cytokine levels of IFNβ IL-17F, and PDGFB have been shown to differ in PDAC and CP [17]. In addition to cytokines, many other biomarkers have been recently investigated to help differentiate between PDAC and CP. Increased levels of the biomarkers P-suPAR (plasma soluble urokinase-type plasminogen activor receptor) and AXL have been detected in PDAC but not CP [18,19]. In addition, serum miRNA (miR-210-3p) may help with diagnosis [20]. A promising metabolite panel has also been proposed [21]. Exploring such a vast pool of biomarkers requires meticulous statistical analysis and planning.

Thus, here, we aimed to examine how serum cytokines differ in patients undergoing surgery for PDAC and CP using sophisticated statistical methods and whether we could use that information to build a noninvasive diagnostic tool to help differentiate between the two diseases.

2. Materials and methods

We analyzed data from 231 patients—186 with PDAC and 45 with CP—surgically treated in the Department of Surgery at Helsinki University Hospital between 2000 and 2014. We excluded PDAC patients with pre-operative neoadjuvant therapy or stage IV disease and CP patients with other concurrent malignancies or autoimmune pancreatitis. The purpose for exclusion was our presumption that neoadjuvant therapy, unrelated active malignancies, or a metastatic PDAC cancer stage may affect the patients' systemic inflammation response and thus skew our cytokines analyses. Preoperative sera from study patients were frozen promptly after collection, stored at −80 °C, and thawed for the first time for this study. The cytokine analyses are known to remain reliable for comparison even despite freezing and thawing the sera [22].

Serum analysis comprised 48 different cytokines in the Bio-Plex Pro Human Cytokine 27-plex Assay (#M500KCAF0Y) and the 21-plex Assay (#MF0005KMII; Bio-rad, Hercules, CA, USA). Manufacturer's instructions were followed, with the exception of the number of beads, detection antibodies, and the streptavidin-phycoerythrin conjugate, which were used at 50% of their recommended concentration. This was confirmed to be sufficient in earlier preliminary tests and this method has been applied elsewhere [23–25]. We also used previously determined serum CA19-9 levels for comparative purposes [26].

Using logistic regression, we assessed those laboratory variables associated with a PDAC diagnosis by calculating the odds ratios (ORs) with the 95% confidence intervals (CIs). The

Table 1
Patient characteristics.

Patient characteristics		
	PDAC n = 186	**CP** n = 45
Age, in years		
mean	65	56
median	66	55
range	40–81	29–76
Gender		
male	107 (58%)	20 (44%)
female	79 (42%)	25 (56%)
Stage		
IA	10 (5.4%)	
IB	16 (8.6%)	
IIA	33 (18%)	
IIB	113 (61%)	
III	6 (3.2%)	
Presence of Diabetes		
Yes	46 (25%)	11 (24%)
No	138 (74%)	34 (76%)
Missing Data	2 (1.1%)	0 (0%)

Tablee 2
Univariate logistic regression analysis.

	p value	FDR-adjusted *p* value	OR	95% CI	
				lower	upper
Logarithmic					
Chemokines					
IL-8	0.073	0.186	1.44	0.97	2.13
Eotaxin	0.894	0.946	1.02	0.76	1.37
IP-10	**0.009**	**0.031**	1.63	1.13	2.35
MCP-1	0.156	0.332	1.25	0.92	1.70
MIP-1α	0.968	0.968	1.01	0.73	1.39
MIP-1β	**0.03**	0.096	1.45	1.04	2.01
RANTES	0.084	0.204	0.73	0.50	1.04
CTACK	**<0.001**	**<0.001**	1.97	1.39	2.79
GRO-α	**0.001**	**0.005**	1.93	1.33	2.82
MCP-3	0.128	0.297	1.35	0.92	1.99
MIG	**0.001**	**0.005**	1.89	1.30	2.73
SDF-1α	**0.042**	0.126	1.44	1.01	2.04
Growth factors					
IL-7	0.052	0.147	1.41	1.00	1.99
Basic FGF	0.776	0.899	1.05	0.76	1.44
G-CSF	0.264	0.481	0.83	0.60	1.15
PDGF-BB	0.181	0.355	0.78	0.54	1.13
VEGF	0.684	0.812	0.93	0.68	1.29
HGF	0.304	0.505	1.19	0.85	1.65
LIF	0.056	0.150	1.40	0.99	1.97
M-CSF	**<0.001**	**<0.001**	1.96	1.37	2.81
β-NGF	**<0.001**	**<0.001**	2.28	1.59	3.27
SCF	**<0.001**	**<0.001**	2.23	1.43	3.46
SCGF-β	0.529	0.722	1.08	0.84	1.39
Other cytokines					
IL-1β	0.581	0.760	0.92	0.67	1.25
IL-1ra	0.859	0.932	1.03	0.77	1.38
IL-2	0.909	0.946	1.02	0.73	1.42
IL-4	0.318	0.507	0.82	0.56	1.21
IL-5	0.685	0.812	1.08	0.75	1.55
IL-6	0.286	0.503	1.21	0.85	1.71
IL-9	0.813	0.911	1.04	0.75	1.44
IL-10	0.943	0.962	1.01	0.74	1.39
IL-12 p70	0.615	0.765	0.92	0.65	1.29
IL-13	0.388	0.565	1.14	0.84	1.55
IL-15	0.538	0.722	0.91	0.66	1.24
IL-17	0.170	0.347	0.78	0.54	1.11
GM-CSF	0.599	0.764	1.10	0.78	1.55
IFN-γ	0.419	0.594	0.88	0.64	1.21
TNF-α	0.346	0.519	0.87	0.65	1.16
IL-1α	0.143	0.317	1.31	0.91	1.89
IL-2Rα	**<0.001**	**<0.001**	2.04	1.37	3.03
IL-3	**<0.001**	**<0.001**	2.11	1.42	3.13
IL-12 p40	0.343	0.519	1.22	0.81	1.83
IL-16	**0.007**	**0.026**	1.53	1.12	2.08
IL-18	**0.003**	**0.012**	1.70	1.20	2.42
IFN-α2	**0.003**	**0.012**	1.95	1.26	3.02
MIF	0.307	0.505	1.19	0.85	1.65
TNF-β	**0.002**	**0.009**	1.80	1.24	2.61
TRAIL	0.256	0.481	1.19	0.88	1.62
Markers					
CEA	0.822	0.911	1.05	0.68	1.63
CA19-9	**<0.001**	**<0.001**	3.47	2.07	5.83
Other					
CRP	**0.001**	**0.005**	1.77	1.25	2.51

Abbreviations: CI, confidence interval; OR, odds ratio.
Standardized logarithmic (base 10) values were used. Statistically significant values appear in bold.

Benjamini–Hochberg procedure allowed us to calculate the adjusted *p* values in the univariate analysis (false-discovery rate (FDR) set to 5%, p.adjust function in R). To improve the prediction accuracy and interpretability of the regression model, we used the lasso method (least absolute shrinkage and selection operator) for variable selection and regularization [27] with tenfold cross-validation, with the data divided into equal parts using each partition as a test set for the model built in the training set. The lasso method selects a reduced set of covariates by forcing specific coefficients to zero, thereby removing them from the model. Bootstrapping (1000 samples) allowed for a selection process enabling a determination of the overall confidence level for including a variable in the model. This was completed by calculating the proportion of bootstrapped models in which the individual variable was included in the model. Finally, continuous variables were compared between the groups using the Mann–Whitney test.

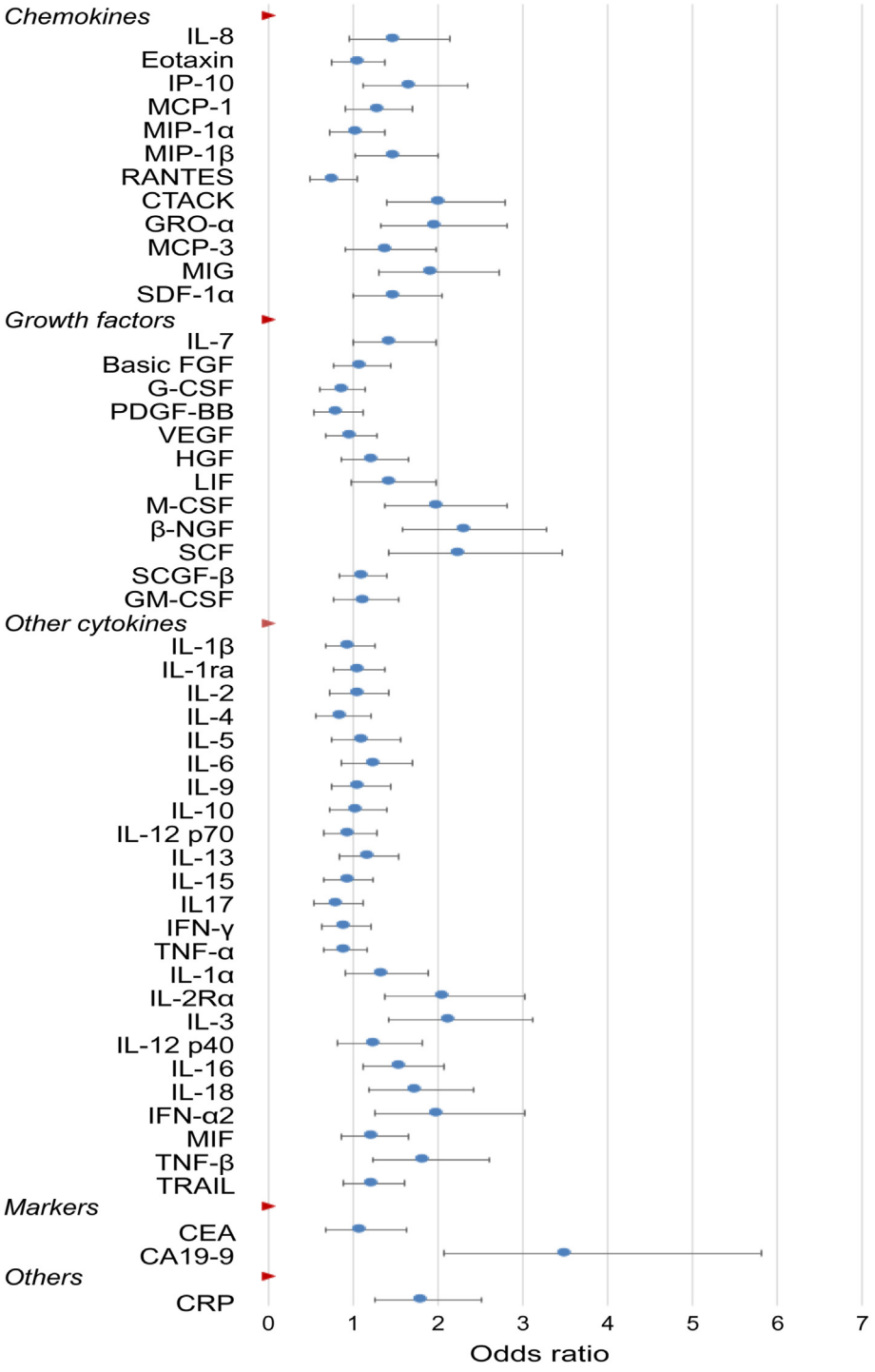

Fig. 1. Univariate logistic regression analysis describing the association between laboratory variables and a PDAC diagnosis in our cohort of PDAC (n = 186) and CP (n = 45) patients. Standardized values were used for each marker.

Table 3
The multivariate model with array data selected using the lasso model.

Multivariate		OR	(lasso OR)[b]	95% CI lower	95% CI upper	p***
Logarithmic values						
	CTACK	1.48	(1.31; 75.0%)	1.00	2.19	0.048
	GRO-α	1.43	(1.03; 75.1%)	0.94	2.19	0.095
	β-NGF	1.73	(1.52; 84.0%)	1.15	2.60	0.009
Dichotomic values						
	CRP[a]	2.25	(1.27; 83.9%)	1.03	4.94	0.042
	CA19-9[a]	3.82	(1.63; 95.6%)	1.78	8.20	0.001

***p values are reported for the unpenalized logistic regression model.
[a] Cut-off points at 1.6 mg/l for CRP and 36 kU/l for CA19-9 obtained by maximizing Youden's index.
[b] The proportion of times the variable was selected in the model in a bootstrapped selection process (1000 repetitions) is shown after the lasso OR value. This demonstrates how confident the selection process is for including the variable in the model. Standardized values were used for continuous variables.

3. Results

Of the 45 CP patients, 44 underwent surgery because of a cancer suspicion. Table 1 summarizes the patient characteristics.

Table 2 presents the univariate logistic regression results, while Fig. 1 illustrates the univariate results graphically. The results describe the association between the laboratory variables and a PDAC diagnosis in our cohort of PDAC (n = 186) and CP (n = 45) patients.

The lasso method identified the four most important diagnostic variables: (logarithmic) CTACK, GRO-α, β-NGF, and (dichotomic) CA19-9. There are no standard levels for these cytokines, but Supplementary Table I presents our results together with those of healthy controls from an earlier study [25]. Together with CRP, these variables formed our new differential diagnostic model (Table 3). The area under the curve (AUC) for the differential diagnostic model was 0.809 (95% CI 0.738–0.880), whereas, for CA19-9 alone, the AUC was 0.791 (95% CI 0.728–0.854), although this difference was not statistically significant (Fig. 2). Cytokines exhibiting more elevated levels in PDAC patients were IP-10, MIP-1β, CTACK, GRO-α, MIG, SDF-1α, IL-7, SCF, M-CSF, β-NGF, IL-2Rα, IL-3, IL-16, IL-18, IFN-α2, and TNF-β. No cytokine level was more elevated in CP patients. Supplementary Table II shows a comparison of cytokines, chemokines, growth factors, and markers among CP and PDAC patients. The differential diagnostic model without CA19-9 would offer an AUC of 0.783 (95% CI 0.704–0.862). When age and sex are added to the differential diagnostic model, the combination would offer an AUC of 0.841 (95% CI 0.780–0.903). The multivariate analyses of these AUCs are presented in Supplemental Tables III and IV and the ROC curves in Supplementary Fig. 1.

4. Discussion

We found that adding the cytokines CTACK, GRO-α, and β-NGF alongside CA19-9 and CRP in diagnostic assessments may improve the accuracy of distinguishing between PDAC and CP. However, the differences in cytokine profiles in PDAC and CP were surprisingly subtle.

All the cytokines selected for our diagnostic model were associated with the pro-inflammatory state. Pro-inflammatory stimuli induce CTACK production, and GRO-α shows apparent pro-inflammatory effects [28,29]. Nerve growth factors (NGFs) are neurotrophic factors that, among other actions, induce chemotaxis [30]. This fits our initial hypothesis that circulating pro-inflammatory cytokines are more typical for PDAC than for CP, a difference that may be observed in the sera of patients. Our results fit well with what is known about cancer-related inflammation.

Previous studies on the differential diagnostic abilities of serum cytokines have yielded mixed results. In combination with tumor markers, the cytokines IL-6, IL-8 with IP-10, M-CSF with SCF, and GDF-15 appear to help differentiate between PDAC and CP [11–14]. Furthermore, a panel of IP-10, IL-6, IL-8, IFN-γ, TNF-α, eotaxin, MCP-1, MIP-1α, MIP-1β, and EGF appeared to provide an impressive differential diagnostic accuracy [15]. Serum interleukin-17, IFNβ IL-17F, and PDGFB has been shown to help differentiate between PDAC and CP [16,17]. However, the results remain inconsistent. For example, higher IL-8 levels have been associated with both PDAC and CP [12,15]. Out of these cytokines, IP-10, M-CSF, SCF, and MIP-1β had statistically significant results in our univariate logistic regression analysis.

One reason for the inconsistencies across previous studies may be statistical. While the number of PDAC patients is often quite limited, numerous cytokines exist, not to mention the number of different cytokine combinations. In other words, coincidental statistical findings and statistical overfitting are genuine risks. We attempted to avoid these problems by selecting variables using the lasso method, which we consider superior to more traditional, step-wise processes. We also benefitted from a more significant number of patients—186 for PDAC and 45 for CP—and used FDR for multiple comparisons.

CA19-9 (sialylated Lewis[a] antigen) is the most widely used

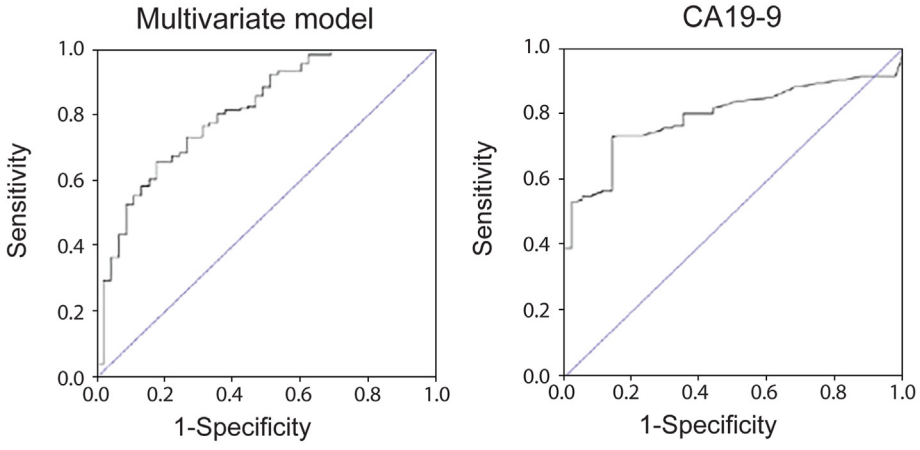

Fig. 2. The receiver operating curves for the multivariate model and pre-operative CA19-9.

diagnostic serum marker for pancreatic cancer but has its limitations. Its sensitivity is estimated to reach 79%, with a specificity of 82% [31]. False-positive values may result from pancreatitis, liver cirrhosis, or nonmalignant obstructive jaundice. In contrast, false-negative values remain an issue among patients with blood group Lewis negativity (impacting ~5–10% of the Caucasian population) since they do not express CA19-9 even with advanced pancreatic cancers [31,32]. To counter problems related to CA19-9, better diagnostic tools need to be developed.

PDAC and CP are both diseases with marked inflammation, but the roles of that inflammation are different. Pancreatitis is thought to arise from impeached apical exocytosis in acinar cells. Malfunctioning acinar cells secrete pancreatic enzymes via the basolateral membrane to the interstitium and the bloodstream, resulting in local inflammation [33]. Inflammation may cause cancer via exposure to anti-apoptotic, angiogenic, and growth-stimulating factors [34], and the balance between pro-inflammatory and anti-inflammatory cytokines is thought to determine whether a cancer develops [35]. In addition, a growing tumor causes direct inflammation, which is believed to accelerate tumor progression [9]. Cachexia and other systemic symptoms associated with advanced PDAC are linked to pro-inflammatory cytokines [36], although cachexia may also be present in CP. Some inflammatory characteristics are also shared. Specifically, both PDAC and CP are characterized by fibrosis, which may lead to hypoxia via the obstruction of the blood flow, thus leading to similar hypoxia-induced inflammation [37].

CP is a significant risk factor for PDAC [2,3]. Moreover, PDAC and CP share some inflammatory etiological factors, such as alcohol and tobacco use, further complicating the analysis of the cause and effect of these two diseases [38]. Considering the multilevel interplay between different inflammatory mechanisms, it is unsurprising that this area of research has featured such diverse results.

We aimed to provide a tool for differentiating PDAC from CP. The lasso method is a sophisticated statistical method that incorporates variable selection and regularization. This also creates the most optimal variable combination for diagnostic assessments. However, one consequence of our model is that it contains CA19-9, which may not work as intended among patients negative for the Lewis antigen.

That said, we could not use a separate validation set for the data in this study, but we performed a bootstrapped analysis to assess the stability of variable selection. Although our results agree with what is known about pro-inflammatory cytokines and cancer, they require validation in other cohorts. Our analysis comprised a large number of patients (186 PDAC and 45 CP patients), and to our knowledge, no similar studies among a similar-sized sample have been previously published.

Our PDAC patients were all treated surgically, and we can only assume that the results also apply to more advanced disease. We excluded PDAC patients who received neoadjuvant therapy since such treatment may alter the tumor microenvironment and skew the results. In addition, many of our PDAC patients were treated in the 2000s, when neoadjuvant therapy was less common. Thus, we were allowed to study serum inflammation markers unaffected by chemo- or radiotherapy.

5. Conclusions

To conclude, we demonstrated the diagnostic value of the serum CTACK, GRO-α, and β-NGF combined with serum CA19-9 and CRP levels. We expect our results to benefit the differential diagnosis for PDAC and CP, and we recommend further studies to validate these findings.

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Ethics approval

This study was approved by the Helsinki University Hospital Surgical Ethics Committee and the participating surgical departments. Because this is a retrospective study, the Finnish National Supervisory Authority for Health and Welfare granted permission to use archived materials. The cytokine levels were measured without access to patient data. Statistical analyses included complete patient data, including clinicopathological and survival data, and all data were anonymized.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2023.07.004.

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