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Epidemiology and clinical characteristics of colorectal cancer and advanced adenoma: a single center experience in Jordan

Nadia Khamees[1,2], Abdallah Al-Ani[2,3,4], Tarek A. Tamimi[1,2], Omar Sarhan[2], Yazan Matouq[2], Dana Laswi[2], Dima Arabiyat[2], Nadin Rayyan[2], Mustafa Rami Ali[2,3], Abdalrahman I. Al-slaimieh[2] and Yaser M. Rayyan[1,2*]

Abstract

Objectives We evaluated the epidemiology and clinical characteristics of colorectal polyps to formulate an appropriate screening program.

Methods A retrospective chart review was conducted on all patients who underwent complete colonoscopy at Jordan University Hospital from January to September 2018. Demographics, comorbidities, lifestyle habits, medication history, family history of cancer, laboratory parameters, quality of bowel preparation, and polyp characteristics were evaluated. Binary logistic regression was utilized to find predictors of colorectal polyps.

Results A total of 965 patients were included in the study, with a mean age of 53.9 ± 17.1 years and a male predominance (52.7%). Polyps were detected in 28.1% of patients, with 18% having one polyp, 10.4% having two polyps, and 3.3% having more than two polyps. Multivariate analysis demonstrated that older age, high BMI, male gender, diabetes mellitus, dyslipidemia, ischemic heart disease, and family history of CRC were positive predictors of polyps. The right colon (cecum and ascending colon) was the most common location for polyps (51%), followed by the sigmoid colon (24.8%). The most common histologic subtype of polyps was tubular adenoma (48.2%). The prevalence of CRC was 18.65 per 1000 patients.

Conclusion We highlight the fair prevalence of colorectal polyps and CRC in a Jordanian cohort. Awareness campaigns, screening strategies, and promotion of healthy lifestyles could help alleviate the burden of the disease, particularly among patients with classical risk factors for CRC.

Keywords Colorectal Cancer, Polyps, Jordan, Risk, Epidemiology

*Correspondence:
Yaser M. Rayyan
y.rayyan@ju.edu.jo
[1]Department of Internal Medicine, Section of Gastroenterology, Jordan University Hospital, Amman, Jordan
[2]School of Medicine, The University of Jordan, Amman, Jordan
[3]Office of Scientific Affairs and Research, King Hussein Cancer Center, Amman, Jordan
[4]King Hussein Cancer Center, Amman, Jordan

Introduction

Colorectal cancer (CRC) is the second and third most common cancer in women and men globally, and respectively, accounting for 10% of all annual cancer diagnoses and cancer-related deaths [1]. It is the third and fourth most common cause of death in women and men, with mortality rates 25% lower in females than in males [1, 2]. Incidence and mortality rates vary geographically, with Asia having the highest rates among all ages and genders [3]. While the incidence of CRC is stabilizing or decreasing in developed countries, it is increasing in developing countries due to "westernization of diet," lack of consistent screening strategies, and low uptake of screening colonoscopy [3, 4].

In Jordan, neoplasms are the second leading cause of death, accounting for 16.4% of all deaths, with CRC being the second most common neoplasm [5, 6]. Recent data from Jordan shows an increasing trend in CRC rates, currently standing at 16.3/100,000 for both genders [5]. Diagnosis and treatment delays in Jordanian CRC patients are high, with delay rates of 68.1% and 32.6%, respectively, attributed to lack of knowledge of cancer symptoms, delayed physician referral, and patients' reluctance to seek medical care [7]. Additionally, poor knowledge and lack of awareness regarding early CRC detection exist among the Jordanian population [8].

Colorectal cancer originates in precancerous polyps, which is an abnormal cell growths projecting through the intestinal lumen [9]. The progression of polyps to cancer takes years, requiring genetic mutations to invade the submucosa of the bowel wall and metastasize. The size of polyps is a significant determinant of progression, with high-grade dysplasia and invasiveness being the most relevant histologic characteristics [10]. Polypectomy is the standard treatment, which reduces the risk of CRC progression and CRC-related deaths by 53% [11].

Given the limited data on CRC in the Middle East and rising CRC rates in Jordan, this study aims to report the epidemiology and clinical characteristics of patients with colonic adenoma and CRC to develop appropriate screening guidelines for the Jordanian population.

Materials and methods

This retrospective chart review study included all patients who underwent a complete colonoscopy at Jordan University Hospital between January 2018 to September 2018, with exclusion criteria being a known history of colonic cancer, colonic resection, active colitis, active diverticulitis, or inflammatory bowel disease. The study collected data on patients' demographics (age, gender, BMI), comorbidities (diabetes mellitus, hypertension, dyslipidemia, ischemic heart disease, renal diseases, etc.), smoking and alcohol status, family history of CRC, relevant medication history (dose, frequency, and duration), colonoscopy indication, quality of bowel preparation, presence and number of colorectal polyps, and characteristics of polyps (histopathological subtypes).

The study obtained characteristics of polyps, including size, location, histological type and degree of differentiation, from the patients' histology reports. Two independent pathology experts assessed the reports to minimize inter- and intra-observer bias, with disagreements resolved by referring to a third expert when applicable. Bowel preparation was evaluated using the Aronchick scale for bowel cleansing [12]. Additionally, laboratory tests, including hemoglobin levels (normal: male 13.2–16.6 g/dL, female 11.6–15 g/dL), mean corpuscular volume (normal: 80–96), ferritin (normal: male 24–336 mcg/L, female 11–307 mcg/L), iron (normal: 60–170 mcg/dL), total iron binding capacity (normal: 240–450 mcg/dL), and presence of stool hemoccult, were reviewed from patients' charts. Adenoma Detection Rate (ADR) was calculated as the number of examinations with adenomas divided by the number of total examinations [13].

Statistical analysis

Data were cleaned using Microsoft Excel and analyzed using the Statistical Package for Social Sciences (SPSS) version 23 (SPSS Inc., Chicago, IL, USA). Continuous variables were reported as means, medians, and standard deviations, while categorical variables were reported as frequencies [n (%)]. Chi-square was used to detect associations between the presence of polyps and different clinical characteristics. The Student t-test was used to detect mean differences between categorical variables and the number of polyps. To determine predictors of having colorectal polyps, a binary logistic regression model was computed. A p-value of less than 0.05 was considered statistically significant for all associations.

Ethical considerations

The study's protocol and proposal were reviewed and approved by both the Jordan University Hospital's Institutional Review Board (IRB) and the University of Jordan's research ethics committee. The study's protocol adheres to the guidelines of the Declaration of Helsinki.

Results

A retrospective chart review was conducted on the medical records of 965 patients who underwent a complete colonoscopy at Jordan University Hospital. The study's cohort had a mean age of 53.9 ± 17.1, with a female-to-male ratio of 1:1.1 (47.3%:52.7%) and a mean BMI of 27.9 ± 6.7. The most common comorbidities observed were hypertension (36.6%), diabetes mellitus (32.5%), dyslipidemia (23.5%), ischemic heart disease (13.2%), and renal disease (2.8%). Current or ex-smokers

represented 27% of the sample, with an average pack year of 32.4 ± 27.1, while only 1% reported alcohol ingestion. Family history of CRC was reported by 110 participants (11.4%), with 80.9% and 18% reporting CRC in first- and second-degree relatives, respectively. Family history of other gastrointestinal cancers was reported by 6.5% of the cohort. The characteristics of the cohort are reported in Table 1.

Laboratory and medication characteristics

Of the 249 participants with complete laboratory records, hemoglobin was 13.0 ± 3.4, MCV 83.2 ± 8.7, ferritin 90.9 ± 294.3, serum iron 151.6 ± 141.4, TIBC 203.5 ± 160.4, and the positive hemoccult rate was 32.5%. The most frequently used medications among the study's participants were aspirin (28.3%), metformin (16.8%), statins (11.8%), beta blockers (8.6%), and calcium channel blockers (4.8%).

Factors associated with colorectal polyps

Males were significantly more likely to have polyps ($p = 0.005$), and patients on aspirin or metformin were significantly associated with a higher number of polyps ($p < 0.01$). Similarly, smoking status was significantly associated with the prevalence of polyps ($p = 0.027$), and patients with diabetes mellitus, hypertension, dyslipidemia, and ischemic heart disease had significantly more polyps (all, $p < 0.01$). On the other hand, none of the laboratory measures significantly correlated with the number of detected polyps (all, $p > 0.05$), nor were any significant differences in laboratory measures between participants with and without detected polyps (all $p > 0.05$).

Table 1 Characteristics of study participants

Variables		*n* (%)	Patients with polyps	*p*-value*
Gender	Male	509 (52.7%)	109	**0.005**
	Female	456 (47.3%)	163	
Comorbidities	Diabetes Mellitus	314 (32.5%)	139	**< 0.001**
	Hypertension	352 (36.6%)	152	**< 0.001**
	Dyslipidemia	227 (23.5%)	105	**< 0.001**
	Ischemic Heart Disease	127 (13.2%)	66	**< 0.001**
	Renal disease	27 (2.8%)	12	0.080
	Others	9 (0.9%)	--	**--**
Smoking status	Current/Past	257 (26.6%)	86	**0.027**
	Non-smoker	679 (70.4%)		
	Unknown	29 (3%)		
Alcohol ingestion		5 (1%)	2	0.618
Medications	Paracetamol	10 (1%)	1	0.298
	Anticoagulants	31 (3.2%)	12	0.103
	ARBS	28 (2.9%)	15	**0.005**
	ACEI	11 (1.1%)	7	**0.015**
	CCB	46 (4.8%)	23	**0.001**
	Alpha blockers	4 (0.4%)	1	1.000
	Aspirin	273 (28.3%)	108	**< 0.001**
	Beta blockers	83 (8.6%)	37	**0.001**
	Diuretic	16 (1.7%)	4	1.000
	Insulin	33 (3.4%)	18	**0.001**
	Iron supplements	20 (2.1%)	5	0.220
	Laxatives	3 (0.3%)	--	--
	Metformin	162 (16.8%)	74	**< 0.001**
	NSAIDS	4 (0.4%)	1	1.000
	PPI	51 (5.3%)	8	0.054
	Statins	114 (11.8%)	46	**0.003**
	Thyroxine	27 (2.8%)	6	0.707
	Vitamin D supplements	12 (1.2%)	--	--
	Antidiabetics	8 (0.8%)	3	0.694
	Steroids	5 (0.5%)	2	0.625
	Others	33 (3.4%)	--	--
Family history of CRC		110 (11.4%)	36	0.258

*Chi-square testing was done to test significant associations between clinical variables and presence of polyps.

Table 2 Characteristics of detected polyps

Variables		*n* (%)
Location	Right Colon	162 (39.5%)
	Transverse Colon	62 (15.1%)
	Left Colon	158 (38.5%)
	Rectum	53 (12.9%)
Histologic Subtype	Non-adenomatous	71 (17.3%)
	Normal	15 (3.6%)
	Adenomatous	255 (62.1%)
	n/a*	59 (14.3%)
	Others	10 (2.4%)
Degree of dysplasia of adenomatous polyps	High	3 (1.2%)
	Low	245 (96.1%)
	n/a*	7 (2.7%)

*n/a refers to information that was not reported nor found

Table 3 Binary logistic regression model of variables predicting having polyps

	Odds ratio	95% CI	B	S.E. of B	*p*-value
Age	1.026	1.01–1.04	0.025	0.006	**< 0.001**
BMI	1.006	1.01–1.01	0.006	0.003	**0.032**
Gender (Male)	1.589	1.12–2.25	0.463	0.178	**0.009**
DM Type II	1.634	1.13–2.37	0.491	0.189	**0.009**
Hypertension	1.454	0.99–2.12	0.374	0.193	0.052
Dyslipidemia	1.534	1.06–2.22	0.428	0.189	**0.024**
Ischemic Heart Disease	1.666	1.09–2.55	0.511	0.217	**0.019**
Renal Disease	0.905	0.37–2.16	-0.100	0.445	0.823
Family History of CRC	1.608	1.01–2.58	0.475	0.241	**0.049**
Smoking Status	1.261	0.87–1.83	0.232	0.191	0.226

Characteristics of complete colonoscopy

The indication for complete colonoscopy in the cohort was symptoms of anemia (22.1%), abdominal pain (17.8%), changes in bowel habit (16.2%), screening for CRC (14.6%), bleeding per rectum (11.8%), abdominal bloating (3.1%), weight loss (2.4%), and personal history of colon polyps (2.1%). Among the study participants, excellent, good, and fair bowel preparation was reported in 6.5%, 60.1%, and 27.2% of participants, respectively. On the other hand, 5.9% participants had poor bowel preparation while 0.3% had inadequate bowel preparation which warranted repeat colonoscopy.

The study found that the polyp detection rate was 28.1%. About 18% of the study's cohort had at least one polyp, 10.4% had two polyps, and 3.3% of all participants had more than two polyps. Characteristics of detected polyps are reported in Table 2. Polyps were detected in 32% of males and 23.9% of females. When stratified by age groups, polyp detection rate was 13.6% in participants younger than 50 years, 31.5% in those aged between 51 and 65, and 43.0% in those older than 66 years.

ADR for the entire cohort was 18.1%. Female participants had an ADR of 15.1%, while males had an ADR of 20.8%. Males were significantly more likely to have higher rates of ADR ($p = 0.022$). Participants with diabetes mellitus, hypertension, dyslipidemia, and ischemic heart disease were significantly more likely to have higher rates of ADR (all, $p < 0.001$). Furthermore, higher rates of ADR were significantly associated with patients smoking ($p = 0.026$), consuming aspirin ($p < 0.001$), beta blockers ($p = 0.008$), insulin ($p < 0.001$), metformin ($p < 0.001$), and statins ($p = 0.031$).

Screening patients' subgroup

Participants who underwent a complete colonoscopy to screen for CRC represented 14.9% of the cohort, 55.6% were males with a mean age of 59.0 ± 11.7 years. Polyp detection rate was 34.0%. of which participants had one, two, and three or more polyps were 19.4%, 11.1%, and 3.5%, respectively. The polyps were most prevalent in the following locations along the colon: transverse colon (32.6%), sigmoid colon (30.6%), ascending colon (28.6%), descending colon (24.5%), cecum (22.4%), rectum (10.2%), and hepatic flexure (6.1%). Furthermore, the prevalence of adenomas within detected polyps was 71.4%, 16.3%, and 8.2% for tubular adenomas, serrated adenomas, and tubulovillous adenomas, respectively.

Prevalence of CRC

CRC was detected in 18 participants out of 965 undergoing complete colonoscopy resulting in a prevalence rate of 18.65 per 1,000. Fifteen cases were adenocarcinomas, of which three were invasive. Moreover, one was poorly differentiated, 14 were moderately differentiated, and one was well differentiated while the histological characteristics of two cases could not be retrieved.

Multivariate analysis

Multivariate analysis revealed that DM, dyslipidemia, ischemic heart disease, age, BMI, family history of CRC, and male gender were significant predictors of having polyps (Table 3**).** Renal disease and smoking were not significant predictors of colorectal polyps in the regression model.

Discussion

Based on the latest reports from the Jordanian Ministry of Health and the World Health Organization (WHO), colorectal cancer (CRC) is the second most common cause of cancer death in males and females [1, 6]. The overall 5-year and 10-year survival rates for Jordanian patients with CRC are estimated to be 58.2% and 51.8%, respectively [5]. This rate is relatively higher than its neighboring Middle Eastern countries, but lower than western countries and US, due to Jordan's advanced cancer care, which is evident in the form of well-trained

physicians and specialized tertiary cancer centers, such as the King Hussein Cancer Center (KHCC) [14]. However, lower survival rates are associated with increased age, poor differentiation, advanced stage, and presence of CRC in the ascending colon [5]. Diagnosis and treatment delays have also been reported [7]. Therefore, devising a national screening program tailored for Jordanians is essential, as early detection and removal of adenomatous polyps may prevent the majority of CRC cases and reduce mortality rates [9].

In order to design a suitable screening program, the characteristics of polyps, including their prevalence, histology, age at detection, and gender predilection, must be explored. Our study showed that the prevalence of polyps in patients was 28.1%, with a significant gender predilection towards males. This rate is higher than what was reported in two Saudi Arabian reports, China, and Egypt, yet lower than that of an Italian multicenter cohort and two American databases [15–20]. Additionally, the gender predilection towards males is demonstrated in a Jordanian cohort, a Saudi cohort, and the GLOBOCAN 2020 [1, 5, 15]. While such differences may be attributed to genetic, dietary, or lifestyle differences, the recent Jordanian literature supports a precedent for poor uptake and accessibility of endoscopy [21–23]. Multiple studies demonstrated that Jordanians, eligible for CRC screening, are unaware of proper screening practices or do not perceive the risk and seriousness of CRC. The latter is a phenomenon can be best explained by the health belief model, which, in the case of CRC, demonstrated that the lack of perceived benefits, reduced perception of susceptibility, and improper cues to action (e.g., physician recommendation) were the most commonly associated constructs with intention to screen [24].

It is worth noting that the average age of patients with polyps in the study was relatively young, with an average of 53.9 years, which is similar to the average age of patients with CRC reported at the King Hussein Cancer Center (50.6 years). These average age numbers are lower than what is reported by neighboring Middle Eastern nations such as Saudi Arabia or the United Arab Emirates [17, 25]. However, this trend was noted among Iraqi patients with CRC as patients in the 25–50 range were significantly more likely to have CRC [26]. Interestingly, Chen et al., demonstrated that patients younger than 50 years of age were more likely to present with advanced CRC compared to their older counterparts [27]. The National Cancer Institute acknowledge such a trend as it reported a steady decline in incidence of CRC among those aged 50 years or older, and an opposite trend for young patients [28]. A review by Cirarrochi and Amicucci declares CRC in young patients as a distinct entity owing to its biological aggressiveness and advanced stage at presentation [29]. This phenomenon may be attributed to genetic variability as multiple reports indicated that CRC in the young is dominated by microsatellite instability, while other classical suppressor pathways are more prevalent in CRC of older populations [30]. It should be noted that despite these differences, prognosis between those two age stratifications remains similar. We have also observed increased polyp detection rates with incrementing age groups, being at its lowest in the >50 years age group (13.6%) and rising up to a peak in the >65 years age group (43.0%). This is in line with the literature as the risk of colorectal polyps and CRC increases with age [31].

The study showed that polyps were most abundant in the right colon, cecum, and ascending colon combined (51%), followed by the sigmoid colon (24.8%), and were most commonly tubular adenomas (48.2%). Moreover, most polyps had low-grade dysplasia (61.7%). These observations are in line with the latest Middle Eastern cohort on the epidemiology of colorectal polyps and that of a recently published Iranian cohort [17, 32]. Associations between different medications (e.g., antihypertensives, antidiabetics, and statins) and polyps are probably a manifestation of confounding variables such as metabolic syndrome. Nonetheless, several meta-analyses have demonstrated that insulin insensitivity and hyperinsulinemia are associated with a higher risk for CRC and colorectal adenomatous polyps [33]; this may explain the aforementioned associations with antidiabetic medications. Yet, it is unknown whether CRC occurrence or progression is directly involved with either insulin resistance or hyperinsulinemia [34, 35]. In addition, there is a strong significant association between those who take aspirin and higher numbers of colorectal polyps [36]. Such observation is expected as aspirin had proven its effectiveness in reducing risk of CRC and CRC-related morality across both observational studies and randomized controlled trials [36]. However, it appears that such protective effect is bound to long-term usage. One critical issue under inspection is the dosing of aspirin as randomized controlled trials demonstrated a dose-independent effect which was not observed in observational studies. Finally, the literature a COX-dependent and COX-independent mechanisms for such effect. The earlier is mediated through the suppression of prostaglandins (i.e., COX-1) and the restoration of antitumor activity by platelet inactivation (i.e., COX-2) [37, 38]. On the other hand, in vitro data supports COX-independent mechanisms such as the direct modulation of oncogene-induced expression of transcription factors or the indirect modulation of polyamine catabolism [39, 40]. However, these mechanisms are only bound to extremely high doses that may not be physiologically relevant in humans.

Smoking is a well-established risk factor for colorectal polyps and cancer, as it is known to have a dose-response relationship to polyp risk, and can induce DNA

alterations, enzyme mutations, and genetic polymorphisms that may lead to carcinogenesis [41]. Consistent with the findings of several meta-analyses linking smoking with CRC [42], our study found that smokers had a significantly higher number of colorectal polyps. However, this effect was masked when included in the multivariate model, which may be due to some form of social desirability bias. Patients were personally contacted for their smoking and alcohol ingestion histories, which may have overestimated the proportions of non-smokers in our cohort, and subsequently impacted our statistical analysis. Furthermore, we failed to find any association between alcohol ingestion and colorectal polyps, which may be attributed to the low levels of alcohol consumption in our region due to lifestyle and religious differences.

Considering the burden of CRC in Jordan and the evidence on lack of proper awareness towards the disease, we believe that it is imperative to enforce a screening program that is accommodating to the Jordanian context. While Jordan had an advanced screening program for breast cancer, it lacks a national program and vision for colorectal cancer. This makes the initiation of a screening program a vital priority for policy makers concerned with prevention. As aforementioned, the rate of CRC in Jordan is significant among individuals younger than 50 years of age. Thus, screening programs should start earlier, which is best exemplified in the updated guidelines of the US Preventive Services Task Force, of which updated guidelines started incorporating adults aged 45 to 49 years [21]. Our results also noted a lower ADR than published benchmarks [43]. Low ADR sheds light on another issue experienced by the Jordanian healthcare system within the context of CRC as it reflects lower colonoscopy quality. This phenomenon might be attributed to inadequate bowel preparation, incomplete examinations resulting in missed lesions, and suboptimal endoscopist skills or technique [43, 44]. However, this variance in ADR may reflect clinical differences at the population level and calls for benchmarking that is relevant for the Jordanian population [45].

Such screening program should not prove resource intensive as Saudi Arabia, a country with lower incidence of colorectal cancer, demonstrated reasonable thresholds of cost-effectiveness for either colonoscopy or fecal immunochemical test screening [46]. Nonetheless, Shamseddine et al., noted that a number of barriers to CRC screening should be dealt with simultaneously [47]. These barriers include financial return of screening programs, deficits in cancer awareness, and human displacement. The latter is especially relevant to Jordan as it hosts a large number of refugees and is a prime safe haven during times of armed conflicts or political crises.

Our findings should be interpreted within the context of the following limitations: Our study is a retrospective, single-centered investigation. Contacting participants for missing information about their lifestyle habits and medications could have resulted in recall bias. Additionally, the study lacked information regarding the gross character of the found polyps. Moreover, the colonoscopy reports that were reviewed were not uniform and consistent in their reporting, which led to some outcome variables being imputed. Potential confounders that may directly affect CRC were not investigated (e.g., diet, physical activity). Similarly, due to the reliance on retrospective electronic records, detailed information on family history of cancer was not available. Finally, we were not able to study the factors affecting CRC within the context of survival analysis. This is mainly due to the fact that survival data is contained on another registry outside of our jurisdiction.

Conclusion

In conclusion, our study demonstrated that multiple socio-demographic and clinical factors are associated with higher prevalence of colorectal polyps. Despite the lack of a national screening program, patients with conditions associated with CRC, such as diabetes, should be approached for screening and subjected to individualized awareness sessions. Moreover, considering high prevalence of colorectal cancer in Jordan among younger adults, and the potential for early detection and prevention, it may be necessary to lower the screening age to 40–45 years and raise patients' awareness of the importance of regular screening. Finally, special attention should be allocated by policymakers and healthcare workers towards to patients who smoke, as smoking is an already established risk factor for CRC with a dose-response relationship. This is particularly important as Jordan is characterized by one of the highest smoking and nicotine consumption rates in the world.

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Author contributions
Conceptualization: Nadia Khamees, Yaser M. RayyanFormal analysis: Abdallah Al-Ani, Abdalrahman I. Al-slaimiehMethodology: Omar Sarhan, Abdalrahman. I Al-slaimiehSupervision: Nadia Khamees, Yaser M. RayyanWriting – original draft: Nadia Khamees, Abdallah Al-Ani, Tarek A. Tamimi, Omar Sarhan, Yazan Matouq, Dana Laswi, Dima Arabiyat, Nadin Rayyan, Mustafa Rami Ali, Abdalrahman I. Al-slaimieh, Yaser M. RayyanWriting – review & editing: Nadia Khamees, Yaser M. Rayyan, Abdallah Al-Ani, Omar Sarhan.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and informed consent to participate
This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of University of Jordan approved this study and waived its need for an informed consent.

Consent for publication
Not applicable.

Competing interests
The authors have no competing interests to declare that are relevant to the content of this article.

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