Brief Report

Spatial Epidemiology of Signet-ring Cell Colorectal Cancer in India

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Abstract

Background: Signet-ring cell colorectal carcinoma (SRCC) is an extremely aggressive yet uncommon histologic subtype of colorectal cancer (CRC) with an unknown etiology. There is a stark difference in the prevalence of signet cancers between Western countries and the Indian subcontinent; however, India itself is a vast and diverse country with variable cancer incidence.

Objective: To study the spatial epidemiology of SRCC in India for identifying regions with high prevalence.

Methods: This retrospective study included all patients diagnosed with colorectal adenocarcinoma at Tata Memorial Hospital, the largest colorectal cancer referral unit in India, between January 2020 and December 2022. Geocoding based on the location of the residence was done to map the incidences. Comparisons were performed between the proportion of signet cell and non-signet colorectal cancers.

Results: A total of 4100 patients with colon or rectal adenocarcinomas were included, of which signet cell histology was found in 624 (15%) patients. SRCC accounted for the highest proportions of CRCs in the Central (19%) and Northern (19%) regions, and the lowest in the North-Eastern (10%) and Western (12%) regions of India ($P < 0.001$), with non-overlapping confidence intervals. Compared with patients with non-signet CRCs, those with SRCC more commonly had colon cancers (22% vs. 17%; $P = 0.003$) and belonged to a lower socioeconomic background (67% vs. 59%; $P < 0.001$).

Conclusions: This study found that SRCCs accounted for a significant proportion of CRC cases in India, but there was no substantial disparity in distribution across regions.

Keywords: Colorectal cancer, demography, epidemiology, geography, India, population spatial distributions, signet-ring cell carcinoma

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INTRODUCTION

Colorectal cancers (CRC) are the third most common cancer and the second leading cause of cancer deaths in the world.[1] Signet-ring cell carcinomas (SRCCs) are an extremely aggressive yet uncommon variant of CRC. Worldwide, SRCC constitutes 1% of all cases of CRC;[2]

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however, in the Indian subcontinent, SRCC is more common, accounting for 15%–20% of all cases of CRC.[3] Yet, very little is known about the etiology, molecular and genetic basis, and reasons for the stark geographical difference in the incidence of SRCC.

The study of SRCC is limited because of its rarity; nonetheless, it is feasible and important to study this cancer in high-incidence areas such as India. However, the Indian subcontinent itself is a very diverse land covering nearly 30 degrees of latitude and longitude, and with great variation in the terrain, ethnicity, culture, lifestyle, and access to quality health care. The regional variations in cancer subtypes in India are exemplified by gall bladder cancers, where the highest incidence in the world is in the Gangetic belt of the Sub-Himalayan areas.[4] Similarly, regional variations also exist for other cancers in India.[5] Thus, there also exists a possibility of differences in the distribution of SRCC across India. Identification of such regions would allow concentrated efforts in the affected regions.

Ideally, national cancer registries should be queried for questions about epidemiology. However, the national cancer registry program of India covers <10% of the Indian population through 27 population-based cancer registries. Moreover, these databases do not record histological subtypes of cancers. Thus, the current study was conducted at an apex referral cancer institute in India with the aim of determining the regional variations and the demography of SRCC compared with conventional adenocarcinomas.

METHODS

Study design, settings, and participants

This retrospective study included all patients diagnosed with colorectal adenocarcinoma at Tata Memorial Hospital, Mumbai, India, between January 01, 2020, and December 31, 2022. Tata Memorial Hospital is one of the largest tertiary referral cancer centers in India that registers 65,000 new cancer patients a year.

Patients with appendiceal cancers, non-adenocarcinoma histology (squamous cancer, neuroendocrine tumors, gastrointestinal stromal tumors, sarcomas, and lymphomas), and primary peritoneal cancers without an identifiable primary site in the colon or rectum were excluded.

All data were retrieved from the electronic medical records of the hospital. No patients were contacted physically, telephonically, or electronically for data collection. The study was approved by the Institutional Ethics Committee of Tata Memorial Hospital.

Variables

The variables recorded were age, gender, religion, paying category (general or private), site of the primary tumor (colon or rectum), histologic subtype (signet cell vs. non-signet cell), and geographical location of residence. The primary site of the tumor was reported based on colonoscopy. Tumors with their lower edge ≤15 cm from the anal verge were labeled as rectal cancers, while the others were treated as colonic tumors. Histology was dichotomized as signet cell and non-signet-ring cell cancers. SRCC was defined as any percentage of signet-ring cells within the tumor.

Geocoding

The full address of the residence along with pin codes was used for geocoding to latitudes and longitudes to the fourth decimal place on the World Geodetic System version 84 Web Mercator projection (WGS 84; EPSG 4326). The coordinates generated were projected on the maps from OpenStreetMaps (https://www.wiki.openstreetmap.org/wiki/About_OpenStreetMap). Choropleth maps were further generated to demonstrate an aggregate summary of characteristics using color distribution within spatial units. Spatial units used in choropleth projections were the individual states and Union territories of India. For statistical comparative analysis, Indian states were clustered into regions (Northern, North-Eastern, Central, Eastern, Western, and Southern) based on the zonal councils for the administrative division of India and the States Reorganization Act, 1956 (Act Number 37 of 1956), Revised in 2012.

Statistical methods

Data were collected in Microsoft Excel 2021 and geocoding was performed from open-source extensions by Google Inc. Analysis was carried out using MS Excel and the R Project for Statistical Computing. Continuous data were presented as medians and interquartile ranges, while categorical data were represented as numbers, proportions, and 95% confidence intervals. Comparisons for numerical data were performed using the Mann–Whitney *U* test, and for categorical data, using Fisher's Chi-square test. A *P* value <0.05 was considered statistically significant. Correction for false discovery rate with multiple comparisons was represented by q values using the q value package of the R project. A q-value of <0.05 was considered statistically significant.

RESULTS

A total of 4100 patients with colon or rectal adenocarcinomas were included [Supplementary Figure 1]. The median age of the patients was 52 years, with about two-thirds being

male [Supplementary Figure 2]. The majority of referrals to our hospital were rectal cancers (3373 patients; 82%) and SRCC (624 patients; 15%). Most patients were from the Eastern region (43%), followed by the Western (31%) and Central (16%) regions of India [Table 1].

Signet cell versus non-signet cell colorectal cancers

The median age at presentation was significantly lower in patients with SRCC compared with non-SRCCs (41 years vs. 54 years; $P < 0.001$). SRCC accounted for the highest proportion of CRC cases from the Central (19%) and Northern (19%) regions, and the least from the North-Eastern (10%) and Western (12%) regions ($P < 0.001$), with non-overlapping confidence intervals [Figures 1 and 2; Supplementary Figure 3].

Compared with patients with non-signet CRCs, those with SRCC more commonly had colon cancers (22% vs. 17%; $P = 0.003$) and belonged to a lower socioeconomic background (67% vs. 59%; $P < 0.001$). There was no difference based on religion between the two groups [Supplementary Table 1].

DISCUSSION

The present study evaluated the spatial epidemiology of SRCC to determine regional variations in the proportion of CRCs across India. More than 4000 CRC patients referred to an apex tertiary cancer center in India were mapped based on the geographical location of their residence, and it was found that the proportion of SRCC among CRC cases varied from 10% in the North-East region to 19% in the Central and Eastern parts of India, with non-overlapping confidence intervals. However, despite the statistically significant differences across regions, these findings should be interpreted with caution, given the relatively moderate sample size of the study.

The median age of our population was 52 years, with differing median ages at presentation for SRCC (41 years) and non-SRCC cohorts (54 years). These findings are in line with the younger age at onset in SRCC cases and the overall younger demographic of India compared with the more developed parts of the world.[3,6-8] Notably, colon cancers were less represented in our cohort compared with rectal cancers (18% vs. 82%). However, it should be noted that this does not necessarily represent the incidence of colon cancers in India, but rather signifies the referral patterns to tertiary cancer centers. The majority of colon cancers are treated by community surgeons, while rectal cancers tend to get referred to specialized CRC units.

The number of patients within the geographical regions further represents the pattern of referral to our institute and should not be interpreted as the incidence of CRC in India. According to the national and population-based cancer registries, the incidence of CRC is highest in the

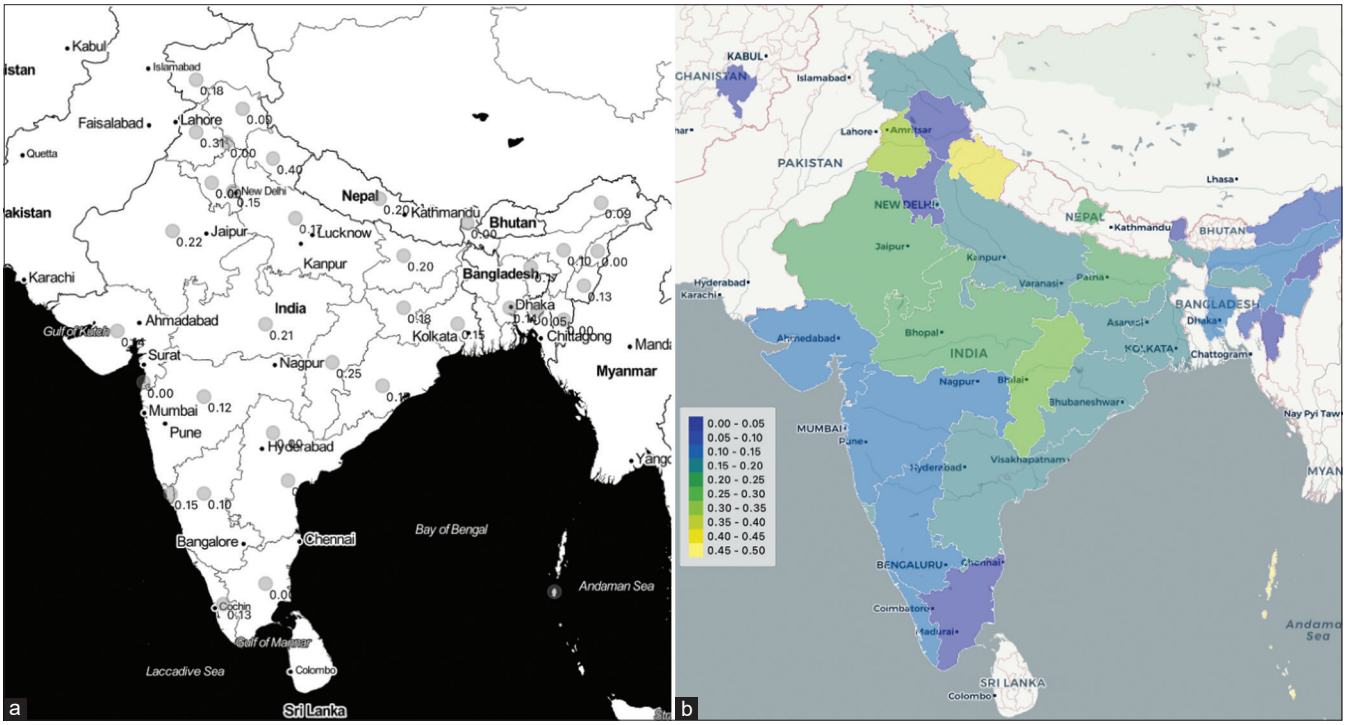
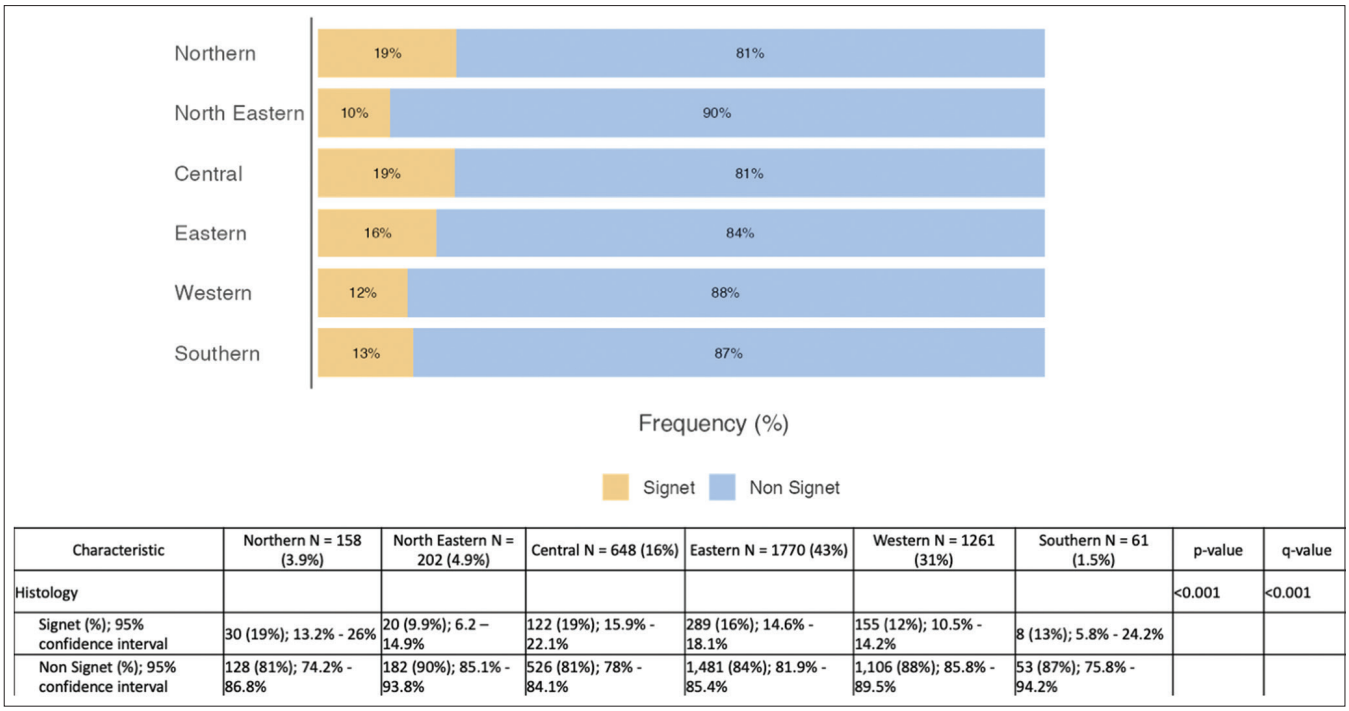


Figure 1: (a) Proportion of signet-ring cell cancer within the states of India. (b) Choropleth maps of signet-ring cell colorectal cancer proportions in India



Characteristic	Northern N = 158 (3.9%)	North Eastern N = 202 (4.9%)	Central N = 648 (16%)	Eastern N = 1770 (43%)	Western N = 1261 (31%)	Southern N = 61 (1.5%)	p-value	q-value
Histology							<0.001	<0.001
Signet (%); 95% confidence interval	30 (19%); 13.2% - 26%	20 (9.9%); 6.2 – 14.9%	122 (19%); 15.9% - 22.1%	289 (16%); 14.6% - 18.1%	155 (12%); 10.5% - 14.2%	8 (13%); 5.8% - 24.2%		
Non Signet (%); 95% confidence interval	128 (81%); 74.2% - 86.8%	182 (90%); 85.1% - 93.8%	526 (81%); 78% - 84.1%	1,481 (84%); 81.9% - 85.4%	1,106 (88%); 85.8% - 89.5%	53 (87%); 75.8% - 94.2%		

Figure 2: Distribution of proportional difference in signet cell and non-signet cell colorectal cancers by regions of India

Table 1: Demographic differences in signet cell and non-signet cell colorectal cancers

Characteristic	All patients (*N*=4100), *n* (%)	Signet cell carcinoma (*n*=624; 15%), *n* (%)	Non-signet cell carcinoma (*n*=3476; 85%), *n* (%)	*P*	*Q*
Age (years)	52 (40–63)	41 (33–53)	54 (42–64)	<0.001	<0.001
Gender					
Male	2708 (66)	423 (68)	2285 (66)	0.32	0.35
Female	1392 (34)	201 (32)	1191 (34)		
Site					
Colon	727 (18)	137 (22)	590 (17)	0.003	0.004
Rectum	3373 (82)	487 (78)	2886 (83)		
Category					
General	2474 (60)	416 (67)	2058 (59)	<0.001	<0.001
Private	1626 (40)	208 (33)	1418 (41)		
Religion					
Hinduism	3266 (80)	490 (79)	2776 (80)	0.35	0.35
Islam	645 (16)	109 (17)	536 (15)		
Others	189 (4.6)	25 (4.0)	164 (4.7)		
Region					
Northern	158 (3.9)	30 (4.8)	128 (3.7)	<0.001	<0.001
North-Eastern	202 (4.9)	20 (3.2)	182 (5.2)		
Central	648 (16)	122 (20)	526 (15)		
Eastern	1770 (43)	289 (46)	1481 (43)		
Western	1261 (31)	155 (25)	1106 (32)		
Southern	61 (1.5)	8 (1.3)	53 (1.5)		

North-East and Southern regions of India, while that of early-onset CRC is highest in Central and Northern India;[9,10] the results of the current study corroborate these findings. Thus, we hypothesize that the rise in early-onset cancers might result from increased SRCC proportions in these regions.

The underlying causes of the geographical variation of cancer incidence are complex and multifactorial. Some of the reasons include environmental factors, level of pollutants, infectious agents, lifestyle factors (diet, physical activity, tobacco consumption, and alcohol use), genetic factors, screening and diagnostic variations, and access to health care.[2,7,11,12] The present study was not designed to investigate these factors, rather it was meant only to explore the regional variations. However, the current study showed geographical disparities in SRCC incidence, indicating the need for further studies to substantiate

these findings, and thus help policymakers determine the way forward.

Limitations and future perspectives

The primary limitation of the study is that the sampled population is from a single tertiary center, and thus may not be representative of the population of the country. Thus, a strong referral bias exists that cannot be eliminated from the present study. Future studies should include collaborations across various referral units in the country to confirm the findings of this study. Another limitation is that the percentage of signet-ring cells was not available in the pathology reports; nonetheless, as any proportion of signet cells (<50% or ≥50%) within the tumor portends an adverse prognosis,[2,7,13] this is a weak limitation.

A substantial amount of research is required regarding SRCC, which afflicts the young and is associated with very poor outcomes.[6] Investigation for SRCC should be two-pronged: to determine the molecular basis of SRCC for identifying the genetic drivers and novel targets for effective therapy, and to determine the putative environmental and host susceptibilities to possibly reduce the burden of SRCC, especially in high-incidence countries such as India. With regards to epidemiology, this is the first study that attempted to map the spatial distribution of SRCC in India and found that its distribution is similar to that of early-onset CRCs in the country.

CONCLUSIONS

This study found that the Central and Northern regions of India had the highest proportion of SRCCs in India, while in the remaining regions, SRCCs accounted for 10% to 16% of all CRC cases.

Ethical considerations

This study was approved by the Institutional Ethics Committee of Tata Memorial Hospital, Mumbai, India (Ref. no.: OIEC/4319/2023). The study adhered to the principles of the Declaration of Helsinki, 2013.

Peer review

This article was peer-reviewed by two independent and anonymous reviewers.

Data availability statement

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

Author contributions

Conceptualization: M.K., N.C.; Methodology: M.K.; Data analysis: M.K.; Data Collection: H.P., A.J., S.D., S.N.; Writing–original draft preparation: M.K.; Writing – review and editing: M.K., A.D., A.S.; Supervision: A.S.

All authors have read and agreed to the published version of the manuscript.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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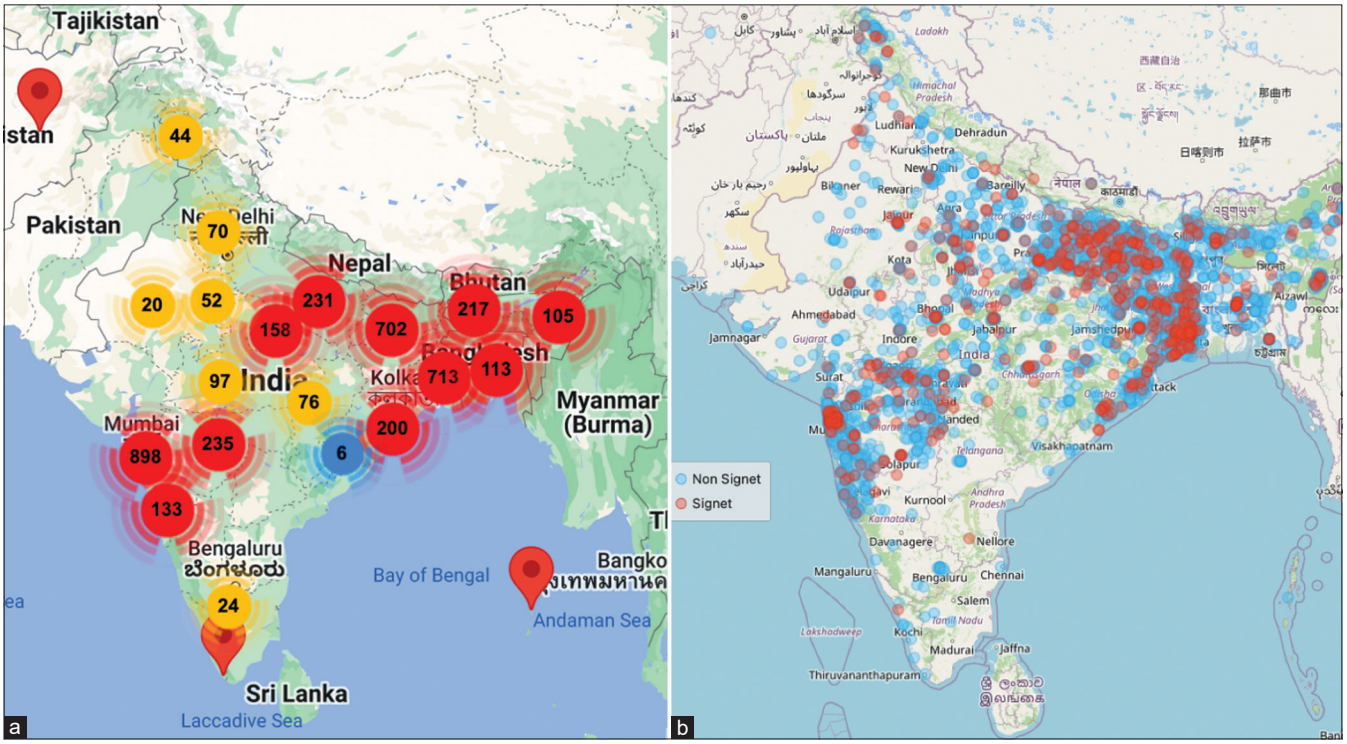
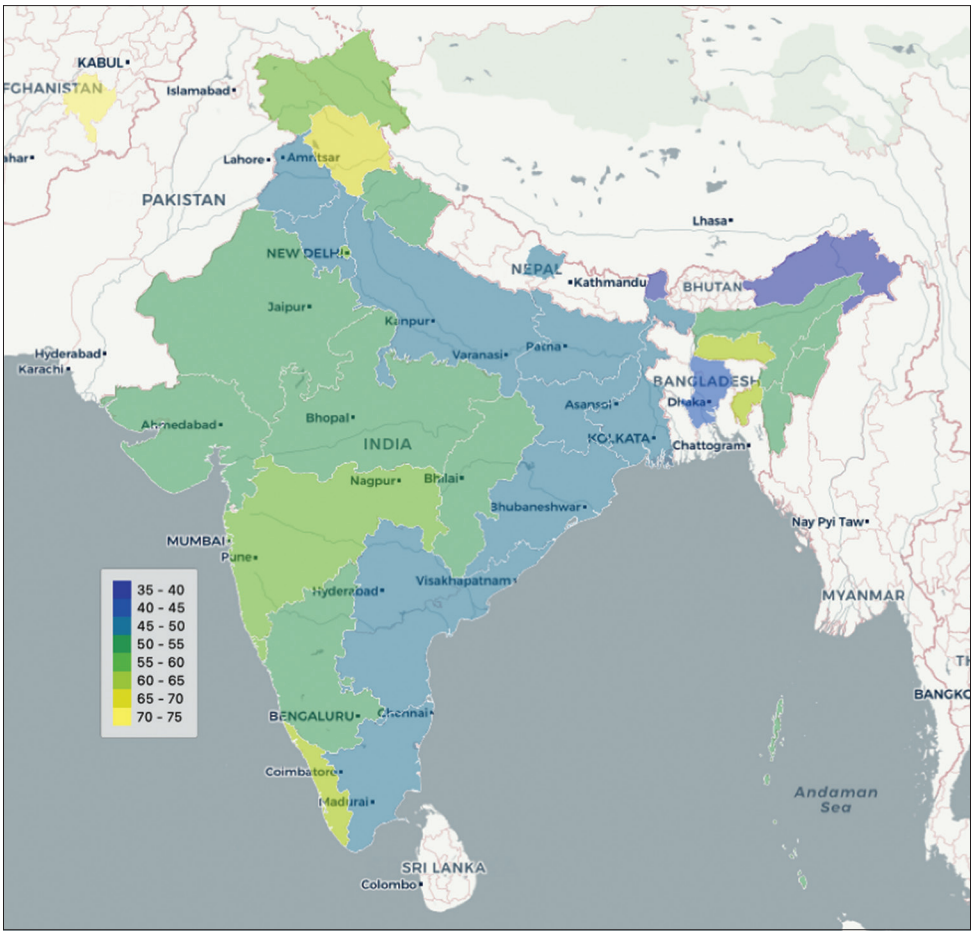
Supplementary Table 1: Regional variations in the demography of colorectal cancer in India (*N* = 4100)

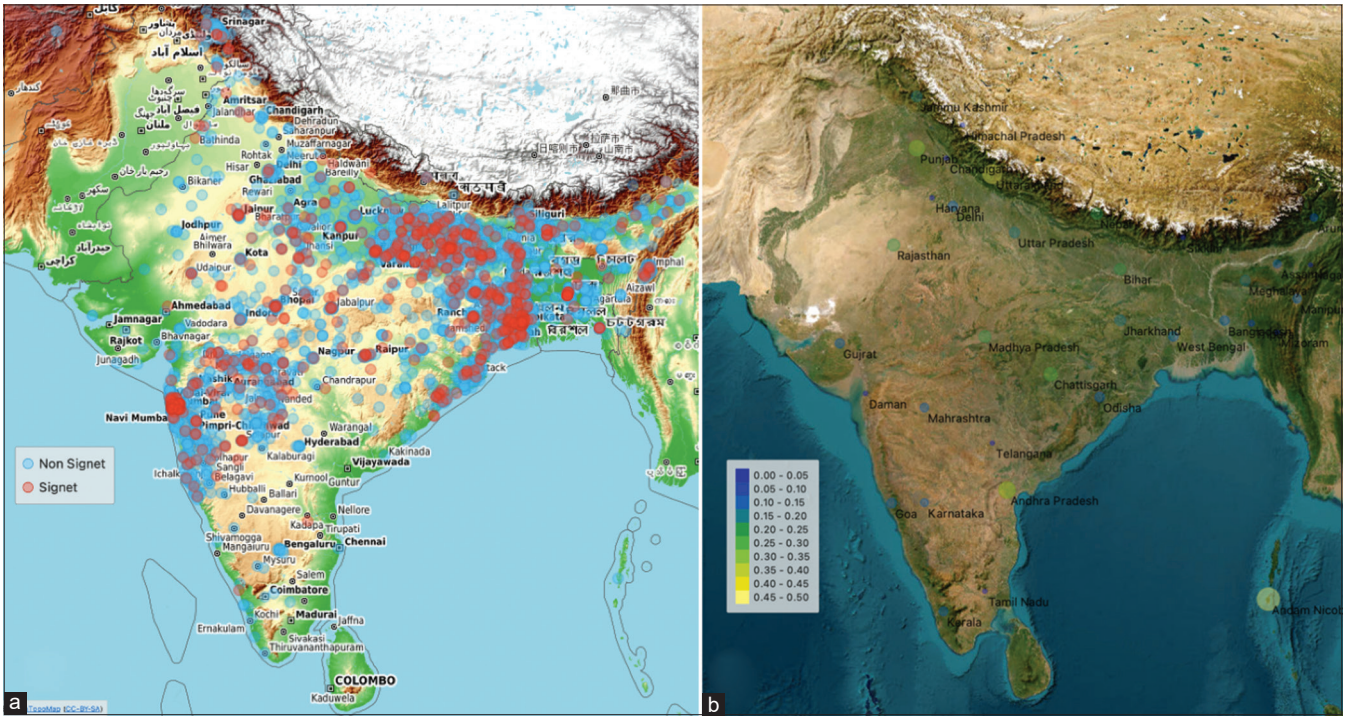
Characteristic	Northern (*n*=158; 3.9%), *n* (%)	North Eastern (*n*=202; 4.9%), *n* (%)	Central (*n*=648; 16%), *n* (%)	Eastern (*n*=1770; 43%), *n* (%)	Western (*n*=1261; 31%), *n* (%)	Southern (*n*=61; 1.5%), *n* (%)	*P*	*Q*
Histology								
Signet cell	30 (19)	20 (9.9)	122 (19)	289 (16)	155 (12)	8 (13)	<0.001	<0.001
Non-signet cell	128 (81)	182 (90)	526 (81)	1481 (84)	1106 (88)	53 (87)		
Age	52 (40–66)	54 (44–63)	49 (38–60)	48 (38–59)	57 (45–68)	53 (42–66)	<0.001	<0.001
Sex								
Male	119 (75)	127 (63)	427 (66)	1204 (68)	791 (63)	40 (66)	0.006	0.008
Female	39 (25)	75 (37)	221 (34)	566 (32)	470 (37)	21 (34)		
Site								
Colon	25 (16)	31 (15)	128 (20)	291 (16)	239 (19)	13 (21)	0.23	0.23
Rectum	133 (84)	171 (85)	520 (80)	1479 (84)	1022 (81)	48 (79)		
Category								
General	49 (31)	94 (47)	365 (56)	1118 (63)	835 (66)	13 (21)	<0.001	<0.001
Private	109 (69)	108 (53)	283 (44)	652 (37)	426 (34)	48 (79)		
Religion								
Hinduism	92 (58)	151 (75)	529 (82)	1379 (78)	1071 (85)	44 (72)		
Islam	41 (26)	25 (12)	93 (14)	375 (21)	102 (8.1)	9 (15)		
Others	25 (16)	26 (13)	26 (4.0)	16 (0.9)	88 (7.0)	8 (13)		



Supplementary Figure 1: (a) Number of colorectal cancer patients referred from different parts of India. (b) Point distribution of signet cell and non-signet cell colorectal cancers



Supplementary Figure 2: Choropleth maps of the distribution of median age at presentation of colorectal cancer in India



Supplementary Figure 3: Distribution of signet cell colorectal carcinoma proportions in (a) a topographical and (b) a satellite map of India