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Microsatellite Instability (MSI-H vs MSS) and Mismatch Repair Gene Alterations in Hospital-Based Studies of Colorectal Cancer in Sub-Saharan Africa: A Systematic Review and Meta-Analysis

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Abstract

Background: The rising incidence of colorectal cancer (CRC), driven by an ageing population and ongoing epidemiological transition, underscores the need for improved surveillance strategies. In sub-Saharan Africa (SSA), however, limited access to molecular diagnostics and fragmented genomic data hinder the characterization of mismatch repair deficiency (MMRd). These constraints contribute to delayed detection, with most cases diagnosed at advanced stages, thereby compromising prognosis and the effective delivery of oncologic care. **Objectives:** This study aimed to estimate the pooled hospital-based proportion of CRC across SSA, characterize the molecular architecture of mismatch repair genes (MLH1, MSH2, MSH6, PMS2), stratify tumor aggressiveness according to microsatellite instability (MSI/MSS) status, and

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evaluate overall survival following diagnosis. **Methods:** A systematic review and meta-analysis were conducted in accordance with PRISMA guidelines and registered in PROSPERO(CRD420261341249). A comprehensive search was conducted across six databases (PubMed, Scopus, Embase, ScienceDirect, Google Scholar, and HINARI) to identify studies published between 2009 and 2025 in 18 SSA countries. Egger's test was performed using Stata 17; Kaplan-Meier survival curves were generated using Python3.13. **Results:** A total of 47 studies were included from 1074 identified records. The findings revealed a CRC profile distinct from that observed in Western populations. The mean age at diagnosis was 52.52 years (95% CI: 49.68 - 55.36), with a pooled hospital-based proportion of 44.48% (95% CI: 28.89 - 60.65) reflecting in-hospital recruitment patterns within the sub-Saharan African context. Recurrent alterations were observed in MSH6 (54/126) and MLH1 (14/18). MSI-H colorectal tumors frequently exceeded 40%, suggesting substantial Lynch syndrome contribution and immunotherapy responsiveness potential; the pooled MSI-H proportion in sub-Saharan Africa was 25.71% (95% CI: 16.32 - 36.34) (I^2 = 92.10%; $p < 0.001$). Despite a lower reported pooled hospital-based proportion of colorectal cancer compared with Western regions, outcomes remain poor, with a 5-year overall survival of 31.13% (95% CI: 22.10 - 40.93**). Conclusion**: The pooled proportion of MSI-H in colorectal cancer in sub-Saharan Africa was characterized by high inter-study heterogeneity and poor 5-year survival, emphasizing the urgent need to improve molecular diagnostic capacity to enable personalized and precision oncology.

Keywords

Colorectal Cancer, Mismatch Repair Deficiency, Microsatellite Instability, Survival Analysis, Pooled Hospital-Based Proportion, Sub-Saharan Africa

1. Introduction

1.1. Global Epidemiological Dynamics and Oncological Transition

Global cancer epidemiology is undergoing a profound structural transformation. According to the GLOBOCAN 2022 estimates, published in 2024, this shift reflects an unprecedented epidemiological transition [1]. In 2022, the global cancer burden was estimated at approximately 19.96 million new cases and 9.7 million deaths. Analyses from the International Agency for Research on Cancer and the American Cancer Society indicate that lung cancer remains the most frequently diagnosed malignancy worldwide (12.4%), followed by breast cancer (11.6%) and colorectal cancer (CRC), which accounts for 9.6% of global incidence [1].

This upward trajectory is expected to intensify substantially, with projections indicating a 77% increase in global cancer incidence by 2050, reaching approximately 35 million new cases annually [2]. This expansion reflects the interplay of the ageing demographic genetic and epigenetic susceptibilities, and sustained exposure to environmental and lifestyle-related risk factors [3]. Currently, cancer

ranks as the first or second leading cause of premature mortality (before age 70) in 112 countries. Globally, the lifetime risk of developing cancer is now estimated at one in five individuals, with a mortality risk of one in nine men and one in twelve women [4].

Beyond descriptive epidemiological metrics, the characterization of tumor distribution patterns provides critical insight into the complex interplay between genomic architecture, epigenetic regulation, and socio-environmental determinants of carcinogenesis. In this context, colorectal cancer (CRC) emerges as a key epidemiological sentinel, with its incidence closely reflecting the extent of demographic and epidemiological transition [5]. This results in a heterogeneous global epidemiological landscape, with marked disparities in cancer incidence. Indeed, geographic variation remains substantial, with incidence rates differing by up to a 20-fold gradient between low-burden regions and high-incidence areas such as Central Europe, where rates exceed 40 cases per 100,000 inhabitants [6].

This disparity places the African continent at the forefront of a distinct and evolving public health challenge. Rapid environmental changes and the progressive westernization of lifestyles have disrupted historical disease patterns. Previously underestimated due to limitations in cancer registries and diagnostic infrastructure, the true burden of cancer in Africa is now emerging. Projections indicate that countries with a low Human Development Index (HDI) may experience up to a 142% increase in cancer incidence by 2050 [1]. This epidemiological shift reflects a complex transition in which the persistent burden of infectious diseases increasingly coexists with a rising incidence of non-communicable malignancies, particularly cancers of the prostate, breast, and colorectum.

In Africa, the age-standardized incidence of colorectal cancer (CRC) exhibits marked heterogeneity, ranging from 0.2 per 100,000 population in Sierra Leone to 20.7 per 100,000 in South Africa. Ranking fourth in incidence and fifth in cancer-related mortality, CRC accounted for 46,087 deaths across the continent in 2022 [7]. This excess mortality is largely attributable to late-stage diagnosis, with a high proportion of cases presenting at metastatic stages. It also reflects the impact of a rapid nutritional transition, characterized by a shift from traditional fiber-rich diets toward ultra-processed foods, particularly among younger urban populations [8].

Beyond these environmental and clinical determinants, improving survival and optimizing care in sub-Saharan Africa depend on a deeper understanding of the underlying biological mechanisms driving this disease. In the context of clinically observed tumor aggressiveness, it is essential to define population-specific genomic signatures to transition from generalized management strategies to precision oncology approaches.

1.2. Three Molecular Pathways of Colorectal Carcinogenesis: MSI, CIN and Serrated Pathways

At the genomic level, colorectal carcinogenesis is driven by three principal and

largely distinct molecular pathways: chromosomal instability (CIN), microsatellite instability associated with mismatch repair deficiency (MSI/dMMR), and the serrated pathway, frequently linked to the CpG island methylator phenotype (CIMP).

1.2.1. Microsatellite Instability and Mismatch Repair Deficiency (MSI/dMMR)

The MSI pathway accounts for approximately 15% of colorectal cancers (CRC) and arises from defects in the DNA mismatch repair (MMR) system [9]. This deficiency results from inactivation of key MMR genes (*MLH*1, *MSH*2, *MSH*6, *and PMS*2), either through germline mutations, as observed in Lynch syndrome, or through somatic alterations, most commonly epigenetic silencing via MLH1 promoter hypermethylation [10]. Loss of MMR function leads to the accumulation of insertion-deletion mutations within microsatellite regions, defining the MSI-high (MSI-H) phenotype. Clinically, MSI-H tumors are preferentially located in the proximal (right) colon and are associated with a favorable prognosis in localized disease, despite relative resistance to adjuvant 5-fluorouracil-based chemotherapy, particularly in stage II [11]. Conversely, these tumors exhibit marked sensitivity to immune checkpoint inhibitors, owing to their high mutational burden and increased neoantigen load, making MSI/dMMR a critical predictive biomarker for immunotherapy response [12].

1.2.2. Chromosomal Instability (CIN Pathway)

The microsatellite stable (MSS) pathway accounts for approximately 80% - 85% of colorectal cancers (CRC) and is predominantly associated with chromosomal instability (CIN) (9). This pathway follows the classical adenoma-carcinoma sequence, characterized by the stepwise accumulation of genetic alterations [13]. Tumor progression within the CIN pathway is driven by dysregulation of key oncogenic signaling networks, notably the EGFR/MAPK axis, frequently involving mutations in KRAS and BRAF, as well as the PI3K/AKT/mTOR pathway [14]. In addition, activation of the hepatocyte growth factor (HGF)/MET signaling axis promotes tumor proliferation, survival, and invasiveness through downstream pathways including PI3K/AKT, RAS/MAPK, and STAT [15].

1.2.3. Serrated Pathway and the CpG Island Methylator Phenotype (CIMP)

The serrated pathway represents a distinct molecular route of colorectal carcinogenesis, diverging from the conventional adenoma-carcinoma sequence. It originates from specific precursor lesions, including sessile serrated adenomas/polyps, and is frequently initiated by the oncogenic BRAF V600E mutation. This pathway is closely associated with the CpG island methylator phenotype (CIMP), characterized by widespread promoter hypermethylation and epigenetic silencing of tumor suppressor genes. Among these, inactivation of MLH1 through promoter hypermethylation is a critical event, leading to the emergence of mismatch repair deficiency (dMMR) and subsequent microsatellite instability-high (MSI-H) tu-

mors. This trajectory illustrates the intricate interplay between genetic mutations and epigenetic alterations in colorectal tumorigenesis [16].

While understanding these molecular mechanisms offers important therapeutic perspectives, their practical implementation reveals a marked disparity between advances in precision oncology and effective diagnostic capabilities in Africa. It is precisely at the intersection of this biological potential and the operational constraints of the continent that the diagnostic, prognostic, and clinical challenges of this study are situated.

1.2.4. Clinical Implications and Study Objectives

The identification of instability profiles results from either sporadic mechanisms, primarily MLH1 promoter hypermethylation, or germline mutations characteristic of Lynch syndrome [17]. In sub-Saharan Africa, the implementation of MMR/MSI testing faces a significant gap between global innovation and local operational realities, including the cost of reagents and the limited availability of molecular biology platforms [8] [18]. This diagnostic deficit severely compromises patient prognosis: overall survival is particularly poor in sub-Saharan Africa, decreasing from approximately 55% at one year to 18% at five years [8] [18].

In response to the need for a transition toward precision oncology, the present study sets four main objectives: i) to estimate the pooled hospital-based proportion of colorectal cancer (CRC) in sub-Saharan Africa; ii) to characterize the molecular architecture of MMR genes (MLH1, MSH2, MSH6, and PMS2); iii) to stratify tumor aggressiveness according to MSI/MSS status; and iv) to assess post-diagnosis overall survival using Kaplan-Meier analysis. The systematic integration of molecular screening would enable the identification of both sporadic and hereditary forms, thereby optimizing targeted therapeutic strategies and access to immunotherapy, and ultimately improving survival outcomes in sub-Saharan Africa.

2. Methodology

2.1. Study Design

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring transparency and reliability in the synthesis of evidence. To prevent duplication and ensure methodological rigor, the protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under the registration number CRD420261341249 (https://www.crd.york.ac.uk/PROSPERO/view/CRD420261341249). The review focused on studies conducted in sub-Saharan African countries and published between January 2009 and December 2025.

2.2. Eligibility Criteria

2.2.1. Inclusion Criteria

Studies were included if they involved adult patients aged ≥18 years residing in

sub-Saharan African countries with histopathologically confirmed colorectal cancer (CRC). Eligible publications comprised original observational studies, including cohort, case-control, and cross-sectional studies, population-based cancer registry studies, and documented case series published in English between January 2009 and December 2025.

Eligibility was determined according to the specific outcomes investigated. For epidemiological analyses, studies were eligible if they reported extractable data on the hospital-based proportion of CRC, with appropriate hospital-based numerators and denominators, or population-based incidence estimates. Population-based cancer registry studies were eligible for incidence analyses, whereas only studies providing appropriate hospital-based data were considered for the hospital-based proportion analysis. For survival analyses, studies reporting Kaplan-Meier estimates or survival rates at 1, 3, or 5 years were included. For molecular analyses, studies were eligible if they evaluated the DNA mismatch repair (MMR) system, including *MLH*1, *MSH*2, *MSH*6, and *PMS*2 genes or their corresponding proteins, and/or reported microsatellite instability (MSI) or microsatellite stability (MSS) status. Molecular testing was mandatory only for studies contributing to the molecular analyses and was not required for studies reporting epidemiological or survival outcomes. Studies were included if they provided extractable data for at least one of these outcomes.

2.2.2. Exclusion Criteria

Studies conducted outside sub-Saharan Africa, those involving African populations residing in the diaspora, and studies exclusively involving patients younger than 18 years were excluded. Articles addressing digestive or gastrointestinal cancers without separately extractable CRC-specific data were also excluded. Studies that did not provide extractable data for any of the predefined epidemiological, survival, or molecular outcomes were considered ineligible.

For molecular analyses, studies without an assessment of the MMR system or an explicit classification of MSI/MSS status were excluded. However, the absence of molecular testing did not constitute grounds for exclusion from epidemiological or survival analyses when relevant data were available. Population-based registry studies without extractable hospital-specific numerators and denominators were excluded from the hospital-based proportion analysis but remained eligible for incidence or survival analyses, as appropriate. Literature reviews, previous meta-analyses, editorials, letters to the editor, and conference abstracts without accessible full text were excluded, as were experimental studies conducted exclusively in animal models or in vitro cell lines.

To avoid duplication, reports involving overlapping patient cohorts were excluded when the same outcome data were more comprehensively described in another included study.

2.3. Article Search Strategy

Based on predefined eligibility criteria, a comprehensive literature search was

conducted across multiple electronic databases, including PubMed, Scopus, Embase, ScienceDirect, Google Scholar, and HINARI. The search strategy combined relevant keywords with Boolean operators. The following terms were used: "colorectal cancer", "microsatellite instability", "MSI", "MSH2", "MSH6", "MLH1", "PMS2", "survival", and "sub-Saharan Africa". An example of a search query is: "Microsatellite instability" OR MSI AND MLH1 OR MSH2 OR MSH6 OR PMS2 OR "colorectal cancer" AND "sub-Saharan Africa". The search strategy was adapted to each database to optimize sensitivity and relevance.

2.4. Study Selection

Following the literature search, all retrieved references were imported into the reference management software Zotero (version 8). Titles, abstracts, and full-text articles were screened, and a structured Microsoft Excel database was created to compile data from each selected study.

2.5. Data Extraction

Titles and abstracts were independently reviewed by at least two of the three authors (Aminata Dickel Sidibe, R. Alice Ouedraogo, and Denise P. Ilboudo). Data were initially extracted by the first author and subsequently verified by the co-authors. The extracted information included study characteristics, first author, year of publication, country (sub-Saharan Africa), sample size, age, sex, and reported pooled hospital-based proportion of MMR genes (MLH1, MSH2, MSH6, and PMS2), as well as microsatellite instability (MSI) or microsatellite stability (MSS) status, and post-diagnosis overall survival trajectories.

2.6. Quality Assessment

The methodological quality of the included studies was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Tool [19]**.** The evaluation covered inclusion and exclusion criteria, sample selection and size, data reliability and validity, and the appropriateness of statistical analyses. Discrepancies between reviewers were resolved through discussion among ADS, DPI, and RAO. The quality assessment process was overseen by JS.

2.7. Procedures for Sample Analyses

The diagnosis and classification of colorectal cancer (CRC) rely on a complementary approach integrating histopathology and molecular biology. Immunohistochemistry (IHC) enables visualization of the nuclear expression of the four key proteins of the mismatch repair (MMR) system (MLH1, MSH2, MSH6, and PMS2). Loss of nuclear staining in tumor cells, in the presence of a positive internal control, defines a mismatch repair-deficient (dMMR) status, indicating functional impairment of the repair system [18]. In parallel, analysis of microsatellite instability (MSI) using polymerase chain reaction (PCR) or next-generation se-

quencing (NGS) confirms the functional consequences of this deficiency at the genomic level. This approach compares microsatellite sequences in tumor tissue with those in corresponding normal tissue. A significant difference in sequence length defines the MSI-high (MSI-H) phenotype, whereas identical profiles indicate microsatellite stability (MSS) [20].

In clinical practice, this dual approach is essential [21]. IHC identifies the specific defective protein, thereby guiding genetic evaluation toward either Lynch syndrome or a sporadic origin. MSI-H status also represents a major predictive biomarker, particularly for response to immune checkpoint inhibitors (anti-PD-1 therapies), and informs the adaptation of chemotherapy regimens (such as FOLFOX or CAPOX), notably by avoiding fluoropyrimidine monotherapy in cases where it may be ineffective.

2.8. Data Synthesis and Statistical Analysis

Data were extracted using Microsoft Excel 2016 and analyzed with Stata software (version 17; StataCorp, TX, USA) and Kaplan-Meier survival curves were generated using Python3.13. Meta-analysis was performed using a random-effects model based on the DerSimonian and Laird method (1986) [22]. Individual and pooled hospital-based proportion estimates were calculated with 95% confidence intervals (95% CI) according to the method described by Nyaga *et al.* [23]**.** Between-study heterogeneity was assessed using Cochran's Q test and quantified with the I^2 statistic as described by Higgins and Thompson (2002) [24].

The following thresholds were applied: low ($I^2 < 25\%$), moderate ($25\% \leq I^2 < 50\%$), high ($50\% \leq I^2 < 75\%$), and very high ($I^2 \geq 75\%$). Heterogeneity was considered statistically significant at $p < 0.05$. Pooled estimates of CRC hospital-based proportion and survival outcomes were presented as forest plots. Publication bias was assessed by visual inspection of funnel plots and confirmed using Egger's regression test, with $p > 0.05$ indicating no significant publication bias [25].

3. Results

3.1. Results of the Electronic Search

The initial search of electronic databases identified 1074 articles. During the initial screening phase, 291 publications were excluded for the following reasons: duplicates (n = 205), inadequate titles (n = 49), non-relevant works (n = 19), conference abstracts (n = 1), inaccessible articles (n = 3), studies conducted outside sub-Saharan Africa (n = 4), and theses (n = 10). A further 117 publications were excluded after abstract screening due to the absence of an abstract (n = 4), content not aligned with the study objectives (n = 97), case reports (n = 7), and reviews or meta-analyses (n = 11). Finally, 619 articles were excluded for not meeting specificity criteria, including the absence of CRC hospital-based proportion estimates in sub-Saharan Africa, lack of analysis of MMR system genes (MLH1, MSH2, MSH6, and PMS2), absence of MSI/MSS stratification, or lack of post-diagnosis overall survival assessment (PRISMA flow diagram, **Figure 1**).

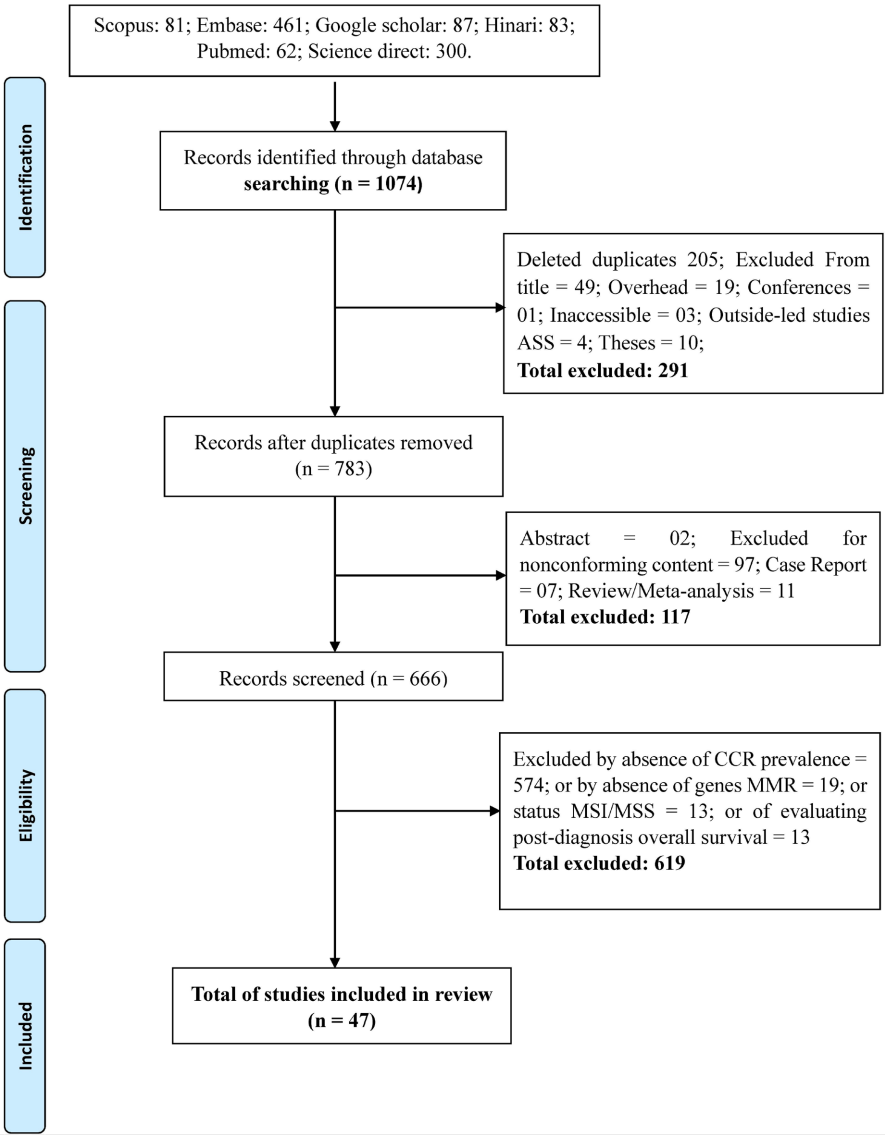


Figure 1. PRISMA flow diagram.

At the end of the selection process, 47 articles were included in the systematic review and meta-analysis. Among these, 11 cohort studies were retained for post-diagnosis survival analysis. The temporal distribution of publications ranged from 2009 to 2025, with a marked increase from 2019 onward (n = 28 articles between 2019 and 2025). The included studies covered 18 sub-Saharan African countries: Benin, Burkina Faso, Cameroon, Congo Brazzaville, Democratic Republic of the Congo, Ethiopia, Ghana, Ivory Coast, Kenya, Mozambique, Nigeria, Rwanda, Senegal, South Africa, Togo, Uganda, Zambia, and Zimbabwe. Overall, these studies involved a total of 31945 participants, including 10332 cases of colorectal cancer (CRC) (Table 1).

3.2. Assessment of Methodological Quality

Assessment using the Joanna Briggs Institute (JBI) critical appraisal tool indicated

Table 1. Sociodemographic characteristics of the population.

First Author Surname (year)	Country	Study Design	Data Source	Mean Age	Nb CRC Cases	Sample Size	Men:Women	Risk of Biais
Abdulkareem *et al.* 2009 [35]	Nigeria	Retrospective case series	Laboratory records	49.5 ± 15.3	402	713	410:303	🟡
Abudu *et al.*, 2016 [36]	Nigeria	Retrospective case series	Laboratory records	58.0 ± 7.7	36	67	51:16	🟡
Yeboah *et al.*, 2017 [37]	Ghana	Retrospective case series	Laboratory records	54.0 ± 16.8	89	221	127:94	🟢
Alain *et al.*, 2024 [38]	DR Congo	Retrospective case series	Laboratory records	50.8 ± 15.25	55	129	89:40	🟢
Alatise *et al.*, 2018 [39]	Nigeria	Retrospective case series	Laboratory records	64.8 ± 12.5	66	362	236:126	🟢
Alatise *et al.*, 2021 [32]	Nigeria	Retrospective case series	Laboratory records	59.3 ± 14.8	107	380	202:178	🟢
Alatise *et al.*, 2022 [40]	Nigeria	Prospective case series	Screening Prospective	56.8 ± 2.2	285	432	111:174	🟢
Alatise *et al.*, 2022 [41]	Nigeria	Retrospective case series	Laboratory records	54.0 ± 15.5	263	347	188:159	🟢
Alatise *et al.*, 2022 [41]	South Africa	Retrospective case series	Laboratory records	56.8 ± 13.7	264	515	269:246	🟢
Aldera *et al.*, 2025 [27]	South Africa	Prospective case series	Hospital records	51.3 ± 2.8	32	32	18:14	🟡
Asombang *et al.*, 2018 [42]	Zambia	Retrospective case series	Hospital records	48.6 ± 16.7	234	234	145:89	🟡
Atinafu *et al.*, 2020 [43]	Ethiopia	Retrospective case series	Hospital records	46.9 ± 13.9	360	360	208:152	🟢
Baldwin *et al.*, 2024 [44]	Rwanda	Retrospective case series	Hospital records	54.6 ± 13.0	46	74	45:29	🟢
Bang *et al.*, 2021 [45]	Cameroon	Cross-sectional multicentre study	Hospital records	49.7 ± 16.9	68	68	37:31	🟢
Bienfait *et al.*, 2020 [46]	Ivory Coast	Retrospective case series	Hospital records	53.5 ± 20.0	11	83	45:38	🟢
Blokhuis, *et al.*, 2010 [47]	South Africa	Retrospective case series	Hospital records	50.0 ± 5.2	21	208	208	🟡
Brand *et al.*, 2018 [48]	South Africa	Retrospective case series	Hospital records	61.5 ± 12.7	2267	3412	1862:1550	🟡
Cronjé *et al.*, 2009 [26]	South Africa	Prospective case series	Hospital records	53.5 ± 14.3	961	961	528:433	🟢
Dakubo *et al.*, 2010 [49]	Ghana	Prospective observational	Hospital records	46.3 ± 10.2	359	359	192:167	🟡
Dakubo *et al.*, 2014 [50]	Ghana	Prospective observational	Hospital records	64.8 ± 8.2	579	579	310:269	🟢
Darré *et al.*, 2014 [51]	Togo	Retrospective case series	Hospital records	50.8 ± 16.3	57	57	34:23	🔴

Continued

Degu *et al.*, 2022 [52]	**Kenya**	**Retrospective case series**	**Hospital records**	**54.1 ± 13.3**	**231**	**232**	**126:106**	
Etissa *et al.*, 2021 [53]	Ethiopia	Retrospective case series	Hospital records	46.0 ± 25.0	422	722	262:460	
Gullickson *et al.*, 2021 [54]	Uganda	Retrospective case series	Hospital records	58.1 ± 3,4	45	149		
Irabor *et al.*, 2014 [55]	Nigeria	Prospective cohort	Hospital records	50.8 ± 11.2	120	120	56:64	
Irabor *et al.*, 2017 [31]	Nigeria	Retrospective case series	Hospital records	51.8 ± 11.5	83	83	40:43	
Katsidzira *et al.*, 2015 [56]	Zimbabwe	Retrospective case series	Gastroenterology	55.0 ± 16.0	85	460	242:218	
Katsidzira *et al.*, 2019 [21]	Zimbabwe	Retrospective case series	Hospital records	52.3 ± 14.9	90	101	55:46	
Katsidzira *et al.*, 2016 [57]	Zimbabwe	Prospective case series	Hospital records	52.9 ± 16.6	847	886	471:415	
Konate *et al.*, 2012 [58]	Senegal	Retrospective case series	Hospital records	50.0 ± 16.0	44	71	41:30	
Kpossou *et al.*, 2025 [59]	Benin	Retrospective case series	Hospital records	52.5 ± 6.0	194	13857	110:84	
Lukanu *et al.*, 2021 [60]	DR Congo	Prospective descriptive	Hospital records	55.2 ± 14.5	90	914	283:631	
McCabe *et al.*, 2019 [34]	South Africa	Retrospective case series	Hospital records	56.0 ± 14.0	39	262	23:16	
McCabe *et al.*, 2022 [29]	South Africa	Retrospective case series	Hospital records	57.0 ± 14.0	428	428		
Okon *et al.*, 2012 [61]	Ivory Coast	Retrospective observational	Hospital records	47.4 ± 17.05	19	270	165:105	
Ossibi *et al.*, 2022 [62]	Congo Brazzaville	Prospective descriptive	Hospital records	55.13 ± 13.25	30	738	393:345	
Ouedraogo *et al.*, 2019 [63]	Burkina Faso	Prospective and descriptive study	Hospital records	35.4 ± 4.6	45	116	70:46	
Parker *et al.*, 2019 [64]	Kenya	Retrospective case series	Hospital records	55.4 ± 16.7	150	165	84:66	
Raskin *et al.*, 2013 [28]	Ghana	Retrospective case series	Hospital records	53.0 ± 19.0	36	89	37:52	
Saidi *et al.*, 2011 [65]	Kenya	Prospective case series	Hospital records	51.8 ± 14.8	159	233	137:96	
Selemane *et al.*, 2025 [30]	Mozambique	Retrospective case series	Hospital records	54.8 ± 10.3	30	30	11:19	
Teka *et al.*, 2021 [66]	Ethiopia	Retrospective case series	Hospital records	45.9 ± 14.5	151	161	59:102	
Tiruneh *et al.*, 2022 [67]	Ethiopia	Retrospective case series	Hospital records	51.3 ± 5.8	367	367	204:163	

Continued

Wekha *et al.*, 2021 [68]	**Uganda**	**Retrospective case series**	**Hospital records**	**45.3 ± 19.8**	**138**	**1476**	**979:497**	
Wismayer *et al.*, 2022 [69]	Uganda	Prospective case series	Hospital records	53.8 ± 5.8	247	247	115:132	
Wismayer *et al.*, 2025 [18]	Uganda	Prospective case series	Hospital records	54.3 ± 6.3	127	127	69:58	
Yildiz *et al.*, 2023 [70]	South Africa	Retrospective case series	Hospital records	35.6 ± 8.7	27	107	54:53	

that only one study presented a high risk of bias, whereas the remaining studies were classified as having moderate to low risk of bias (Table 1).

3.3. Mean Age at Diagnosis

The forest plot in Figure 2(a) summarizes the distribution of mean age at diagnosis across the 47 included studies. The pooled mean age was 52.52 years (95% CI: 49.68 - 55.36). The absence of publication bias was confirmed by the visual symmetry of the funnel plot and Egger's regression test p = 0.9538 (Figure 2(b)).

3.4. Hospital-Based Proportion of Colorectal Cancer

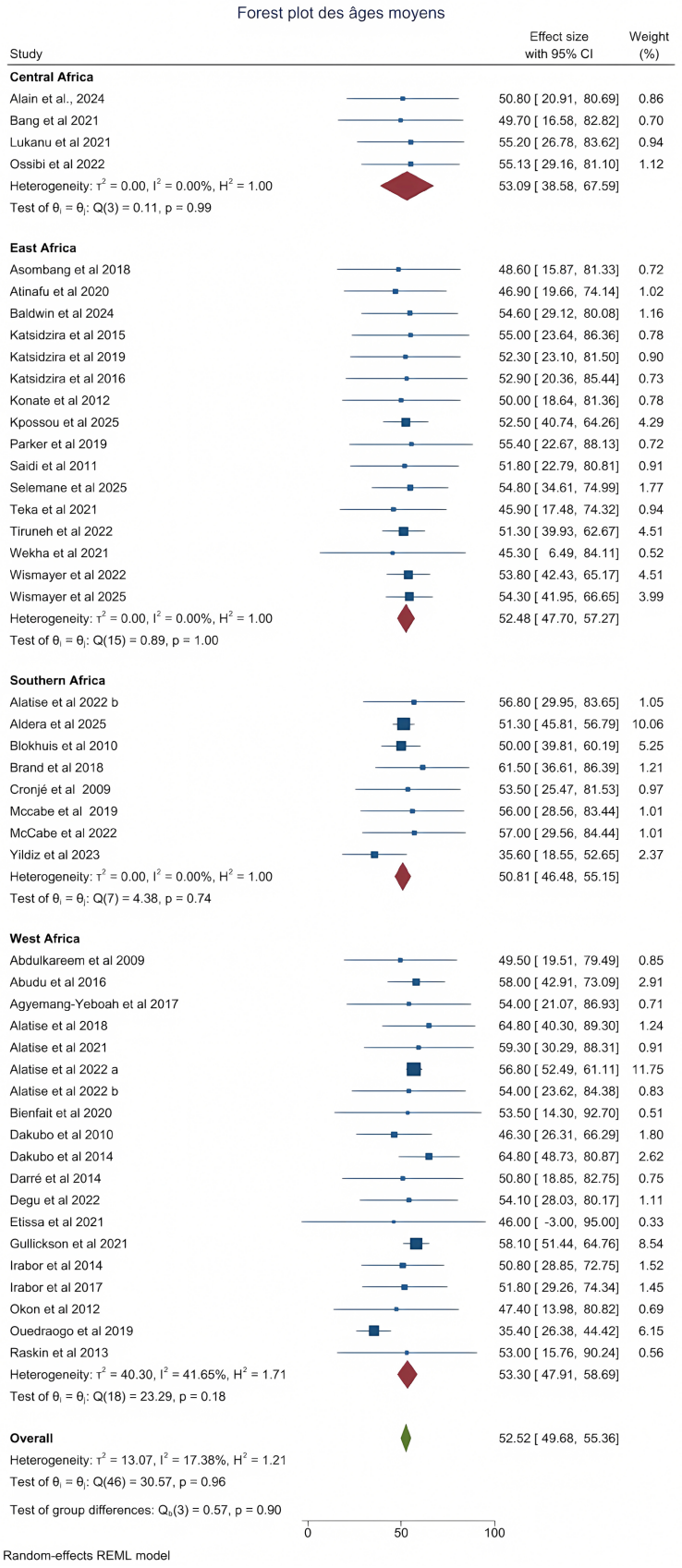
The forest plot in Figure 3(a) presents the pooled hospital-based proportion of colorectal cancer (CRC) reported in the selected studies. This analysis represents a central component of the meta-analysis, quantifying the burden of the disease in sub-Saharan Africa. The pooled hospital-based proportion was 44.48% (95% CI: 28.89 - 60.65), with substantial heterogeneity (I^2 = 99.83%, p < 0.001). However, the Egger test performed, which has a p-value of 0.5392 (Figure 3(b)), does not indicate a statistically significant bias.

3.5. Expression Profile of MMR System Proteins

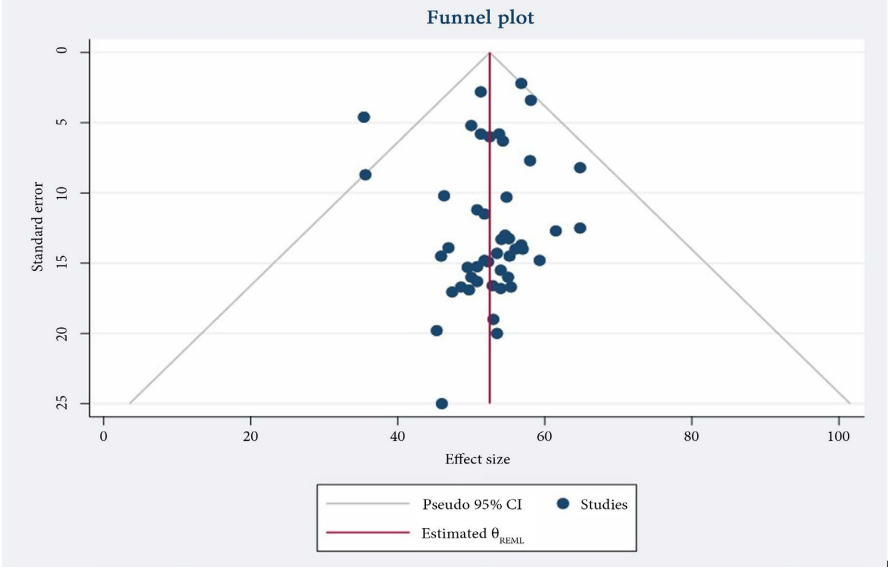
Table 2 presents a detailed analysis of the loss of expression of mismatch repair (MMR) proteins (MLH1, MSH2, MSH6, and PMS2) across different sub-Saharan African cohorts. The data reveal marked heterogeneity in mismatch repair deficiency (dMMR) status across studies and geographic regions. For example, Cronjé *et al.* (2009) [26] reported a high hospital-based proportion of loss of MSH6 expression (43%; 54/126). In contrast, more recent work by Aldera *et al.* (2025) [27] highlighted a predominance of MLH1 loss, observed in 77.78% of patients (14/18).

3.6. Microsatellite Instability (MSI) Analysis

Analysis of microsatellite status in CRC across sub-Saharan Africa (Table 3) shows a predominance of the microsatellite stable (MSS) phenotype, with frequencies ranging from 38.57% in Raskin *et al.* (2013, Ghana) [28] to 86.21% in McCabe *et al.* (2022, South Africa) [29]. Conversely, microsatellite instability (MSI) cases display a more heterogeneous distribution, ranging from 11% in Selemane *et al.* (2025, Mozambique) [30] to 43% in Irabor *et al.* (2017, Nigeria) [31]. Across cohorts,

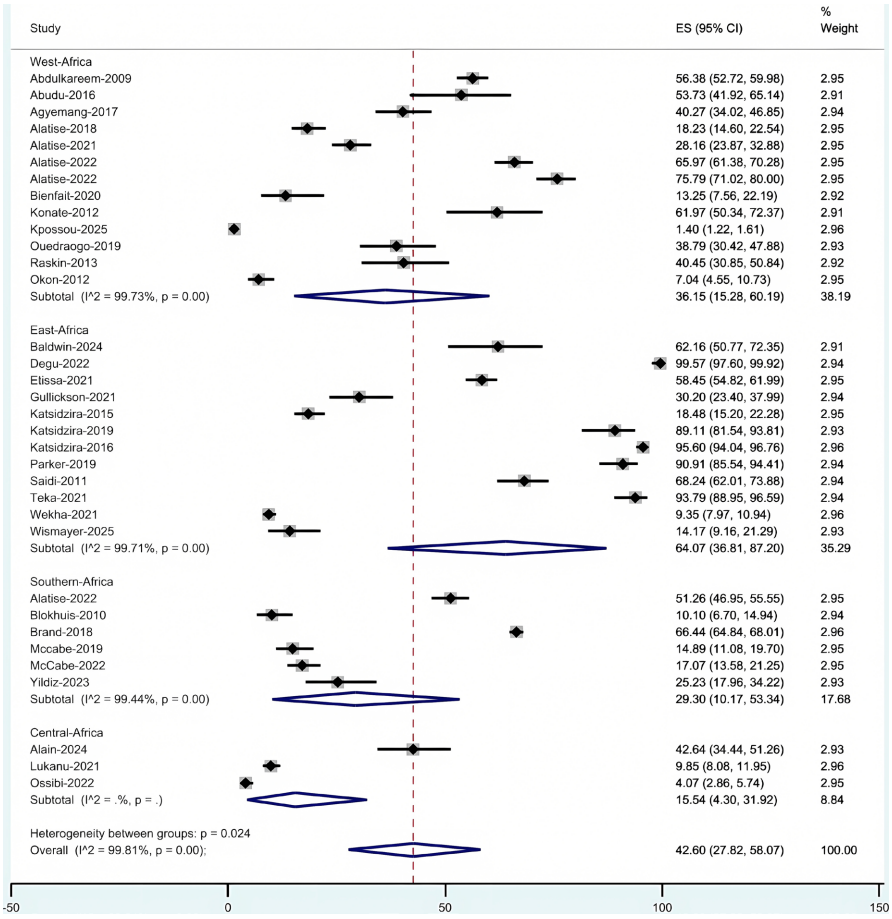

Forest plot des âges moyens
Study
Effect size with 95% CI
Weight (%)
Central Africa
Alain et al., 2024 50.80 [20.91, 80.69] 0.86
Bang et al 2021 49.70 [16.58, 82.82] 0.70
Lukanu et al 2021 55.20 [26.78, 83.62] 0.94
Ossibi et al 2022 55.13 [29.16, 81.10] 1.12
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 53.09 [38.58, 67.59]
Test of θi = θj: Q(3) = 0.11, p = 0.99
East Africa
Asombang et al 2018 48.60 [15.87, 81.33] 0.72
Atinafu et al 2020 46.90 [19.66, 74.14] 1.02
Baldwin et al 2024 54.60 [29.12, 80.08] 1.16
Katsidzira et al 2015 55.00 [23.64, 86.36] 0.78
Katsidzira et al 2019 52.30 [23.10, 81.50] 0.90
Katsidzira et al 2016 52.90 [20.36, 85.44] 0.73
Konate et al 2012 50.00 [18.64, 81.36] 0.78
Kpossou et al 2025 52.50 [40.74, 64.26] 4.29
Parker et al 2019 55.40 [22.67, 88.13] 0.72
Saidi et al 2011 51.80 [22.79, 80.81] 0.91
Selemane et al 2025 54.80 [34.61, 74.99] 1.77
Teka et al 2021 45.90 [17.48, 74.32] 0.94
Tiruneh et al 2022 51.30 [39.93, 62.67] 4.51
Wekha et al 2021 45.30 [6.49, 84.11] 0.52
Wismayer et al 2022 53.80 [42.43, 65.17] 4.51
Wismayer et al 2025 54.30 [41.95, 66.65] 3.99
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 52.48 [47.70, 57.27]
Test of θi = θj: Q(15) = 0.89, p = 1.00
Southern Africa
Alatise et al 2022 b 56.80 [29.95, 83.65] 1.05
Aldera et al 2025 51.30 [45.81, 56.79] 10.06
Blokhuis et al 2010 50.00 [39.81, 60.19] 5.25
Brand et al 2018 61.50 [36.61, 86.39] 1.21
Cronjé et al 2009 53.50 [25.47, 81.53] 0.97
Mccabe et al 2019 56.00 [28.56, 83.44] 1.01
McCabe et al 2022 57.00 [29.56, 84.44] 1.01
Yildiz et al 2023 35.60 [18.55, 52.65] 2.37
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 50.81 [46.48, 55.15]
Test of θi = θj: Q(7) = 4.38, p = 0.74
West Africa
Abdulkareem et al 2009 49.50 [19.51, 79.49] 0.85
Abudu et al 2016 58.00 [42.91, 73.09] 2.91
Agyemang-Yeboah et al 2017 54.00 [21.07, 86.93] 0.71
Alatise et al 2018 64.80 [40.30, 89.30] 1.24
Alatise et al 2021 59.30 [30.29, 88.31] 0.91
Alatise et al 2022 a 56.80 [52.49, 61.11] 11.75
Alatise et al 2022 b 54.00 [23.62, 84.38] 0.83
Bienfait et al 2020 53.50 [14.30, 92.70] 0.51
Dakubo et al 2010 46.30 [26.31, 66.29] 1.80
Dakubo et al 2014 64.80 [48.73, 80.87] 2.62
Darré et al 2014 50.80 [18.85, 82.75] 0.75
Degu et al 2022 54.10 [28.03, 80.17] 1.11
Etissa et al 2021 46.00 [-3.00, 95.00] 0.33
Gullickson et al 2021 58.10 [51.44, 64.76] 8.54
Irabor et al 2014 50.80 [28.85, 72.75] 1.52
Irabor et al 2017 51.80 [29.26, 74.34] 1.45
Okon et al 2012 47.40 [13.98, 80.82] 0.69
Ouedraogo et al 2019 35.40 [26.38, 44.42] 6.15
Raskin et al 2013 53.00 [15.76, 90.24] 0.56
Heterogeneity: τ² = 40.30, I² = 41.65%, H² = 1.71 53.30 [47.91, 58.69]
Test of θi = θj: Q(18) = 23.29, p = 0.18
Overall 52.52 [49.68, 55.36]
Heterogeneity: τ² = 13.07, I² = 17.38%, H² = 1.21
Test of θi = θj: Q(46) = 30.57, p = 0.96
Test of group differences: Qb(3) = 0.57, p = 0.90
0
50
100
Random-effects REML model

(a)

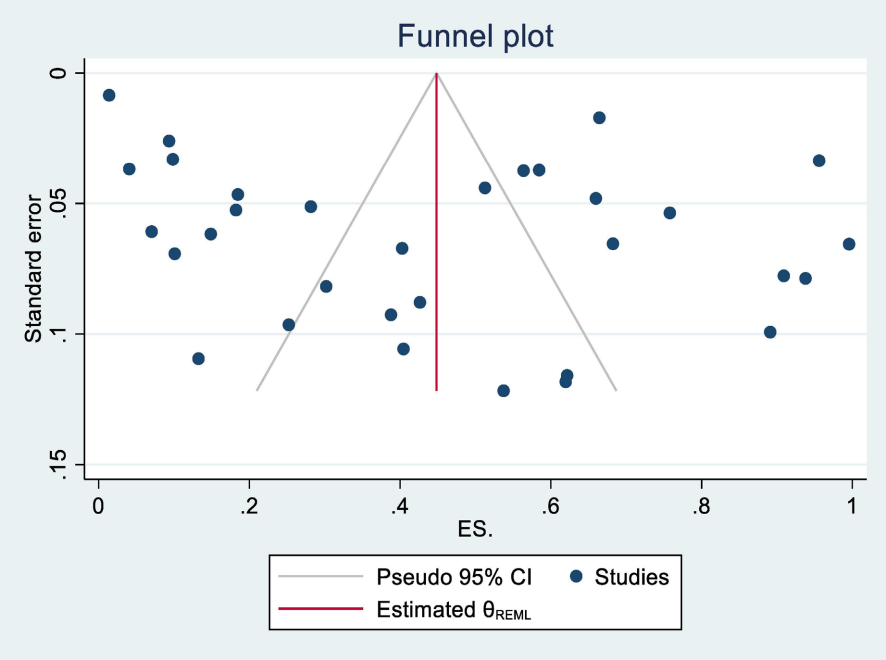


(b)

Figure 2. (a) Forest plot of the pooled mean age at diagnosis of colorectal cancer across hospital-based studies in sub-Saharan Africa regions; (b) Funnel plot for publication bias assessment of hospital-based studies of mean age at diagnosis of colorectal cancer in Sub-Saharan Africa (Egger's test: meta bias, Egger; Prob > |z| = 0.9538).



(a)



(b)

Figure 3. (a) Forest plot of the pooled proportion of colorectal cancer in hospital-based studies across sub-Saharan African regions; (b) Funnel plot for publication bias assessment of colorectal cancer in hospital-based studies (Egger's test: meta bias, Egger; Prob > |z| = 0.2832).

Table 2. Proportion of mismatch repair (*MMR*) gene alterations across hospital-based colorectal cancer studies in sub-Saharan Africa. (Egger's test: meta-bias, Egger; Prob > |z| = 0.2832).

Authors	MLH1	MSH2	MSH6	PSM2	MLH1/ PSM2	MSH2/ MSH6
Alatise *et al.*, 2021 [32]	3/64 (4.69%)	1/64 (1.56%)	NA	NA	NA	NA
Wismayer *et al.*, 2025 [18]	14/127 (11.02%)	30/127 (23.62%)	26/127 (20.47%)	NA	NA	NA
Mccabe *et al.*, 2019 [34]	13/31 (41.93%)	10/31 (32.26%)	1/31 (3.23%)	NA	NA	NA
Aldera *et al.*, 2025 [27]	14/18 (77.78%)	5/8 (62.50%)	1/4 (25.00%)	NA	NA	NA
Cronjé *et al.*, 2009 [26]	29/128 (22.66%)	16/129 (12.40%)	54/126 (42.86%)	NA	NA	NA
M. Mccabe *et al.*, 2019 [34]	13/31 (41.94%)	10/31 (32.26%)	1/33 (3.03%)	2/33 (6.06%)	NA	NA
Katsidzira *et al.*, 2019 [21]	1/89 (1.12%)	1/89 (1.12%)	NA	NA	4/89 (4.49%)	1/89 (1.12%)

NA: Not Available.

Table 3. Distribution of MSS and MSI statuses across hospital-based colorectal cancer studies.

Authors	Countries	MSS/	MSI-low	MSI-high
Irabor *et al.*, 2017 [31]	Nigeria	20/35 (57.14%)	NA	15/35 (42.86%)
McCabe *et al.*, 2022 [29]	South Africa	369/428 (86.21%)	NA	59/428 (13.79%)
Wismayer *et al.*, 2025 [18]	Uganda	75/127 (59.06%)	NA	52/127 (40.95%)
Mccabe *et al.*, 2019 [34]	South Africa	191/267 (71.54%)	45/267 (16.85%)	31/267 (11.61%)
Selemane *et al.*, 2025 [30]	Mozambique	NA	NA	2/18 (11.11%)

Continued

Raskin *et al.*, 2013 [28]	Ghana	27/70 (38.57%)	14/70 (20.00%)	29/70 (41.43%)
Katsidzira *et al.*, 2019 [21]	Zimbabwe	44/53 (83.02%)	3/53 (5.66%)	6/53 (11.32%)
Alatise *et al.*, 2021 [32]	Nigeria	46/64 (71.87%)	NA	18/64 (28.12%)
Irabor *et al.*, 2014 [55]	West African country	NA	NA	35/86 (40.70%)

NA: Not Available.

MSI-high (MSI-H) rates were frequently elevated, often exceeding 40%. Figure 4 shows the pooled proportion of MSI-H status in colorectal cancer in sub-Saharan Africa. Nine hospital-based studies were pooled (random-effects model): the pooled proportion was 25.71% (95% CI: 16.32 - 36.34), with very high heterogeneity ($I^2 = 92.10\%$, $p < 0.001$).

3.7. Stratification of CRC Aggressiveness and Management Challenges

Table 4 summarizes the stratification of clinical aggressiveness and barriers to colorectal cancer (CRC) management in sub-Saharan Africa. Data from Alatise *et al.* (2021) [32] and Li *et al.* (2026) [33] indicate a predominance of aggressive

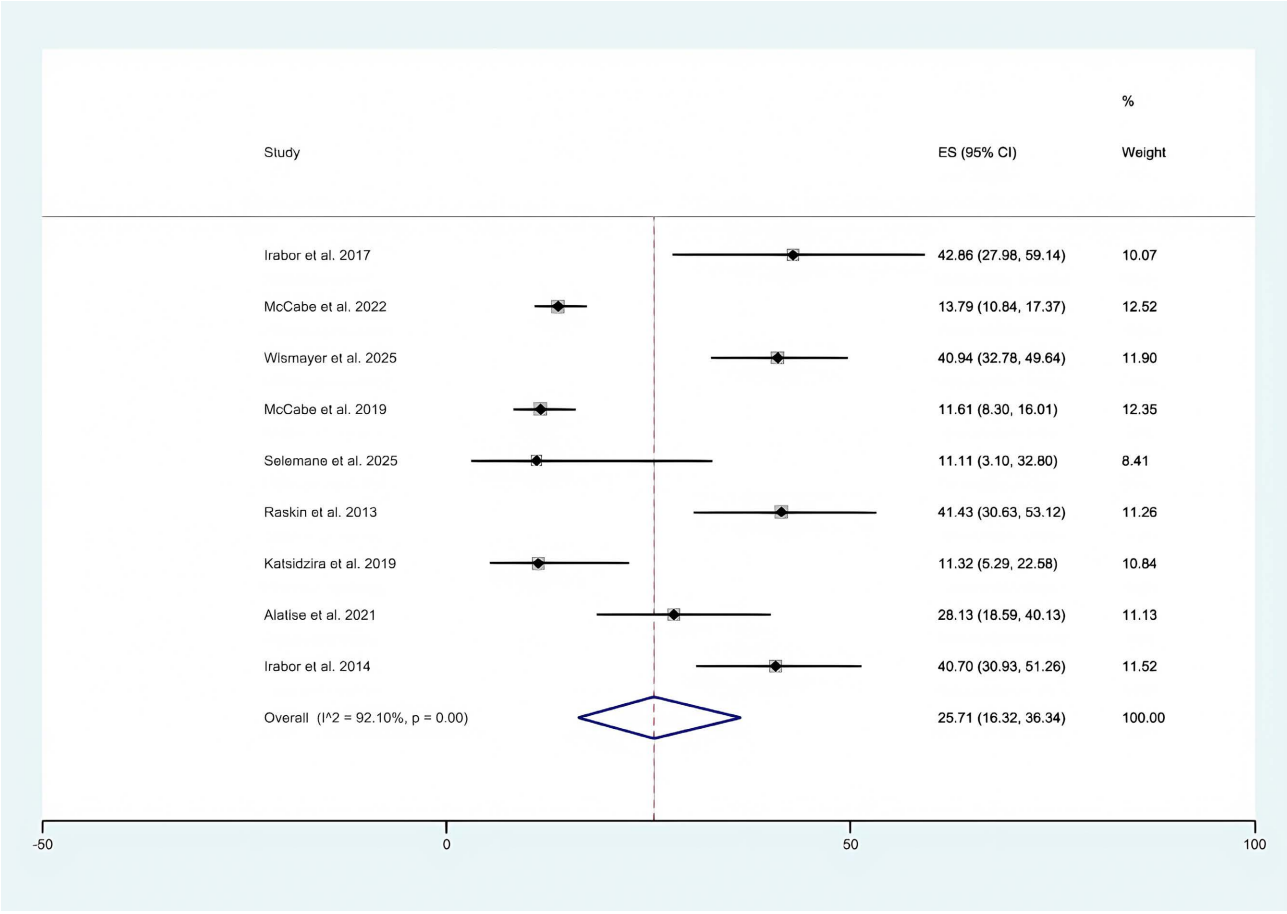


Figure 4. Pooled proportion of MSI-H colorectal cancer in hospital-based studies in sub-Saharan Africa (random-effects model, k = 9).

Table 4. Aggressiveness and management of colorectal cancer across hospital-based studies in sub-Saharan Africa.

	Parameter	MSI-H/dMMR profile (~26%)		MSS/pMMR profile (~74%)	
N°		Phenotypic Parameters and Therapeutic Implications of Colorectal Cancer dMMR	References	Phenotypic Parameters and Therapeutic Implications of Colorectal Cancer dMMR	References
1	Age at diagnosis	Early onset (often <50 years)	Irabor 2017 [31]; McCabe 2019 [34]; Wismayer 2025 [18].	Later onset (generally > 55 - 60 years)	Raskin *et al.* 2013 [28]; Katsidzira 2019 [21]
2	Sex	Female predominance or parity-associated trend	McCabe 2022 [29]; Alatise 2021 [32]	Marked male predominance	Katsidzira 2019 [21]
3	Tumor location	Right-sided/proximal colon (caecum, ascending colon)	Alatise 2021 [32].	Left-sided/distal colon and rectum	Katsidzira 2019 [21]
4	Stage (TNM)	Advanced stages (III - IV), frequent late diagnosis	Selemane 2025 [30]; Alatise 2021 [32].	Advanced stages (III~IV), often metastatic	Raskin 2013 [28]
5	Clinicopathological features	Mucinous histology; signet ring cell carcinoma; high lymphocytic infiltration	Alatise *et al.* 2021 [32] Raskin *et al.* 2013 [28]	Increased early-onset cases in Africa; frequent mutations (APC, TP53, KRAS)	McCabe *et al.* 2022 [29]; McCabe *et al.* 2019 [34]; Wismayer *et al.* 2025 [18]
6	Aggressiveness and prognosis	Lower histological heterogeneity; generally better prognosis in early stages; relative resistance to 5-FU but strong sensitivity to immunotherapy	Alatise *et al.* 2021 [32]	Higher aggressiveness at diagnosis; increased metastatic risk; overall poorer prognosis compared with MSI-H tumors	Wismayer *et al.* 2025 [18] Selemane *et al.* 2025 [30] Katsidzira *et al.* 2019 [21]
7	Preferred treatment	Immunotherapy (anti-PD-1)	Wismayer 2025 [18]; McCabe 2022 [29]	Chemotherapy (FOLFOX/CAPOX)	Katsidzira 2019 [21]
8	Therapeutic response	Relative resistance to 5-fluorouracil (stage II)	Alatise 2021 [32] McCabe 2019 [34]	Limited efficacy of immunotherapy alone	Raskin 2013 [28] Selemane 2025 [30]

histological subtypes, including poorly differentiated tumors and signet ring cell carcinomas. Clinically, diagnosis is most often established at advanced stages (stage III or IV), as reported in studies by Irabor (2017) [31] and McCabe (2019, 2022) [29] [34].

3.8. Overall Survival after Diagnosis

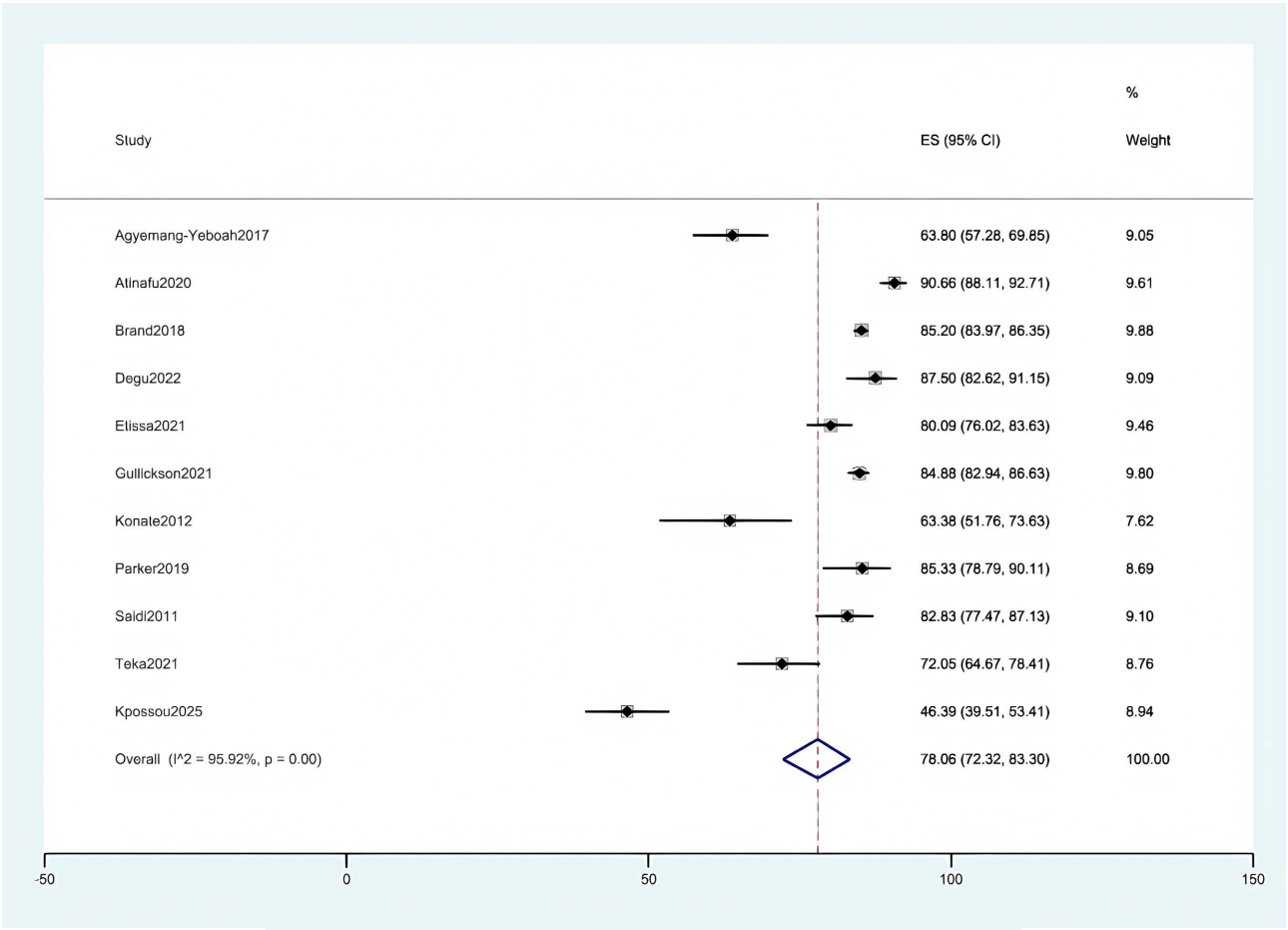
The forest plots in **Figures 5(a)-(c)** illustrate the prognostic dimension of this meta-analysis and provide a longitudinal assessment of survival among patients with CRC in sub-Saharan Africa. This analysis includes data from 11 studies (supplementary **Table 1**).

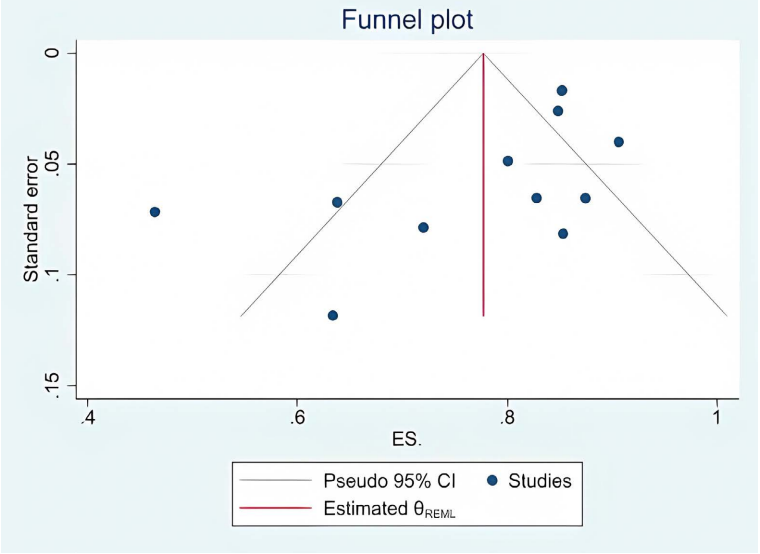
The pooled analysis reveals a progressive decline in survival rates:

At 1 year: Overall survival was 78.06% (95% CI: 72.32 - 83.30; $I^2 = 95.92\%$, $p < 0.001$) (**Figure 5(a)**), reflecting the relative effectiveness of initial management, primarily surgical; At 3 years: Survival decreased to 47.25% (95% CI: 38.93 - 55.63; $I^2 = 97.50\%$, $p < 0.001$) (**Figure 5(b)**), indicating substantial early mortality; At 5 years: Survival further declined to 31.13% (95% CI: 22.10 - 40.93; $I^2 = 98.36\%$, $p < 0.001$) (**Figure 5(c)**).

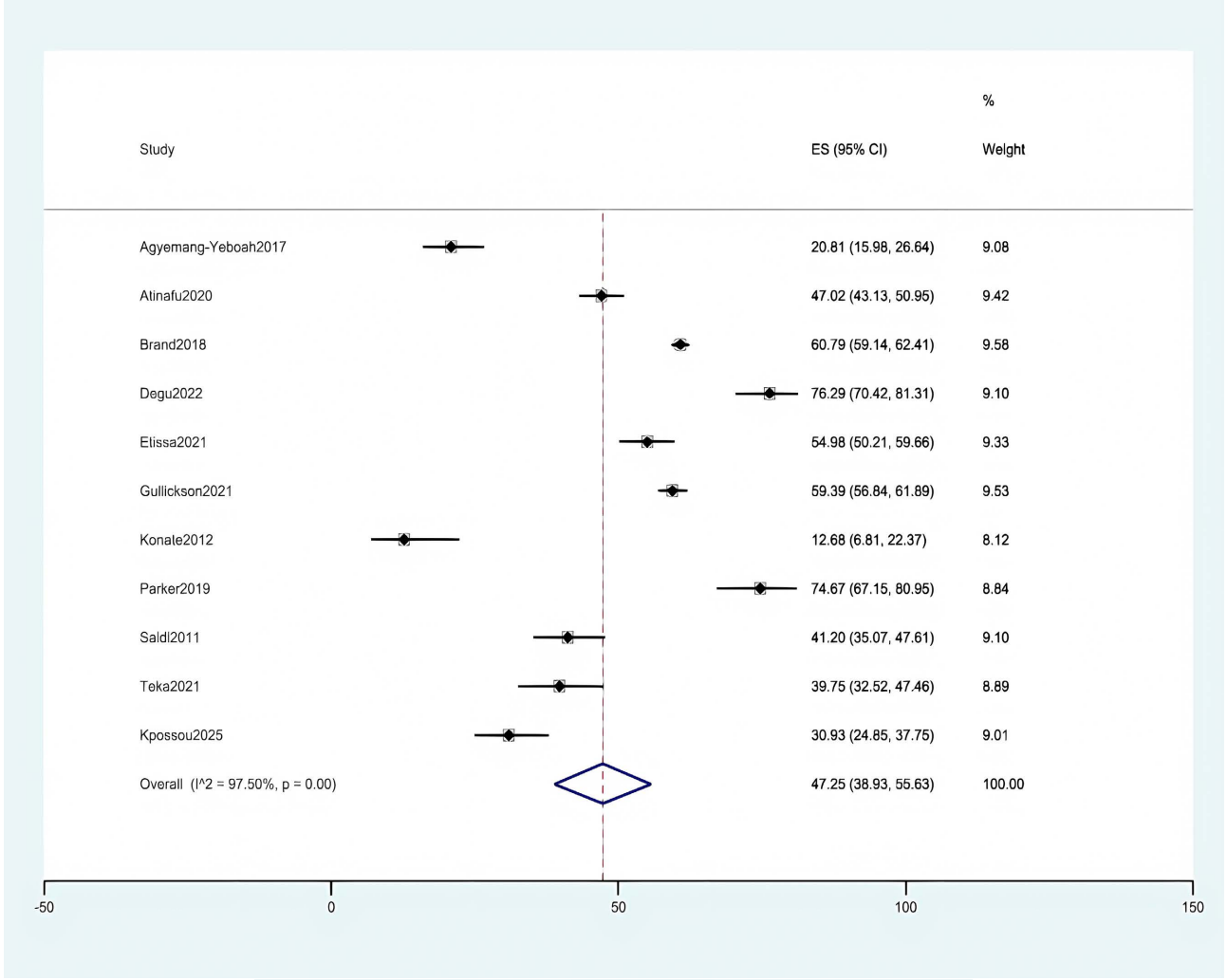
Consistent with these findings, the aggregated Kaplan-Meier survival curves

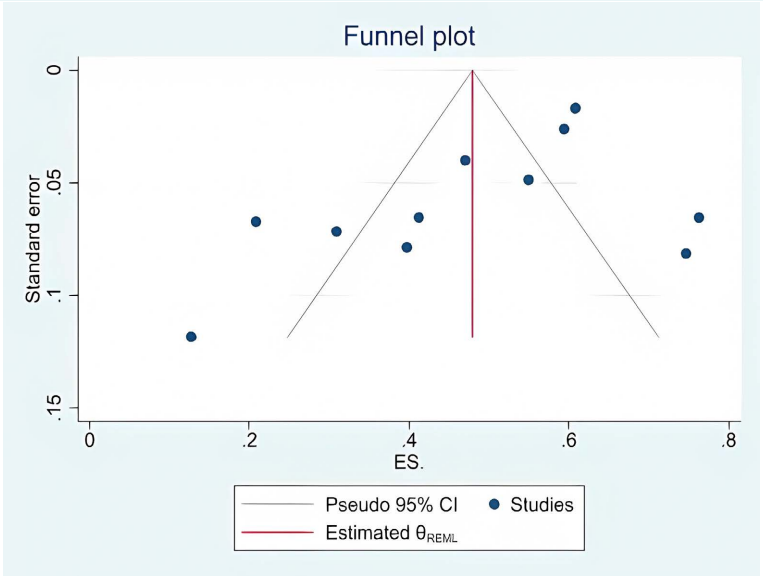
(Figures 6(a)-(b)) demonstrate a progressive decrease in survival probability over time, with estimated survival rates of 78.1% at 1 year, 47.3% at 3 years, and 31.1% at 5 years. These results reflect increasing mortality, accompanied by widening confidence intervals over the follow-up period.



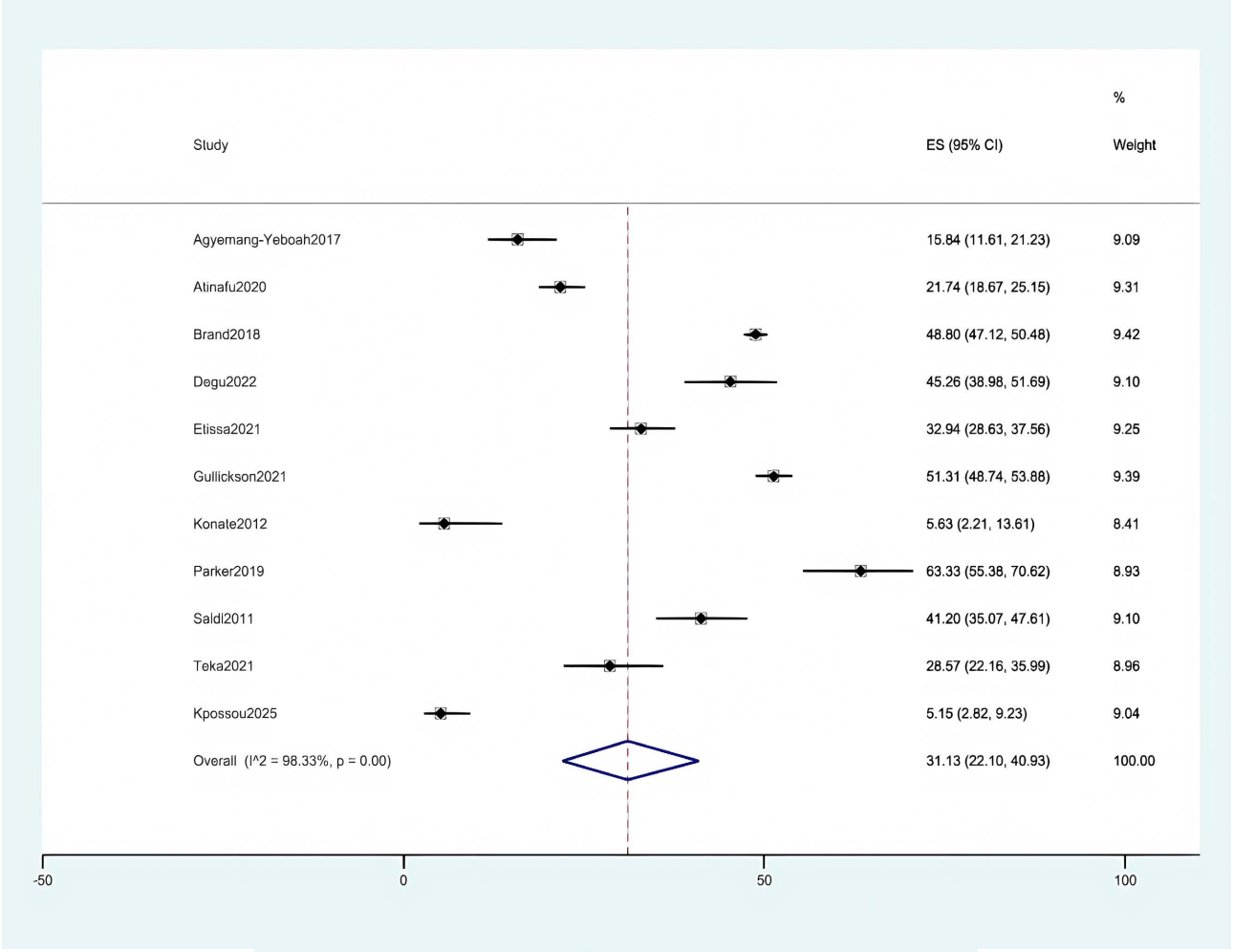


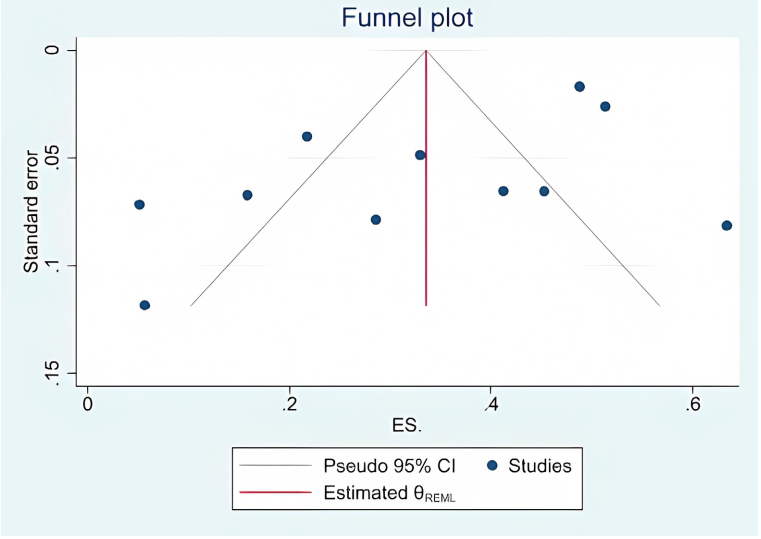
(a)


Study
ES (95% CI)
%
Weight
Agyemang-Yeboah2017
20.81 (15.98, 26.64)
9.08
Atinafu2020
47.02 (43.13, 50.95)
9.42
Brand2018
60.79 (59.14, 62.41)
9.58
Degu2022
76.29 (70.42, 81.31)
9.10
Elissa2021
54.98 (50.21, 59.66)
9.33
Gullickson2021
59.39 (56.84, 61.89)
9.53
Konate2012
12.68 (6.81, 22.37)
8.12
Parker2019
74.67 (67.15, 80.95)
8.84
Saldl2011
41.20 (35.07, 47.61)
9.10
Teka2021
39.75 (32.52, 47.46)
8.89
Kpossou2025
30.93 (24.85, 37.75)
9.01
Overall (I^2 = 97.50%, p = 0.00)
47.25 (38.93, 55.63)
100.00
-50
0
50
100
150


Funnel plot
Standard error
0
.05
.1
.15
0
.2
.4
.6
.8
ES.
Pseudo 95% CI
Studies
Estimated θREML

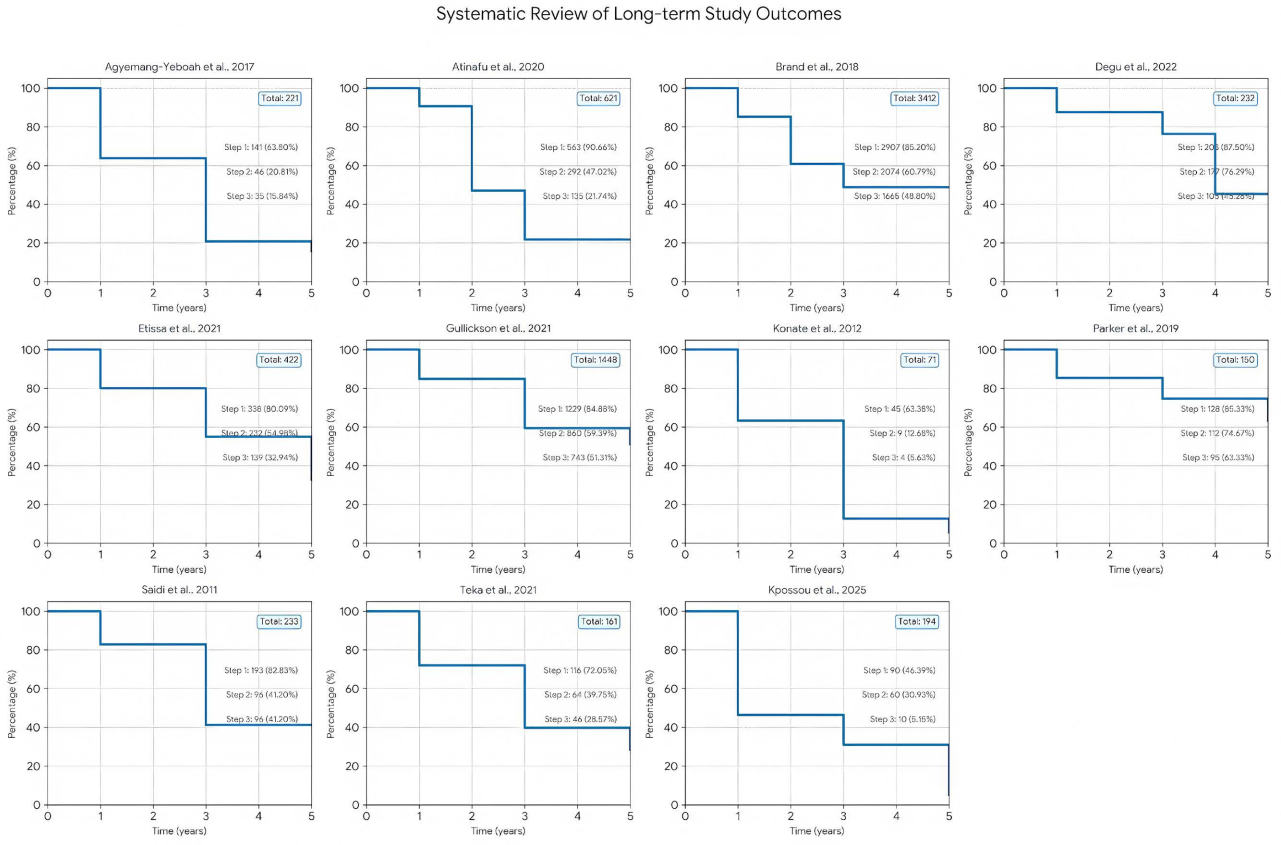
(b)



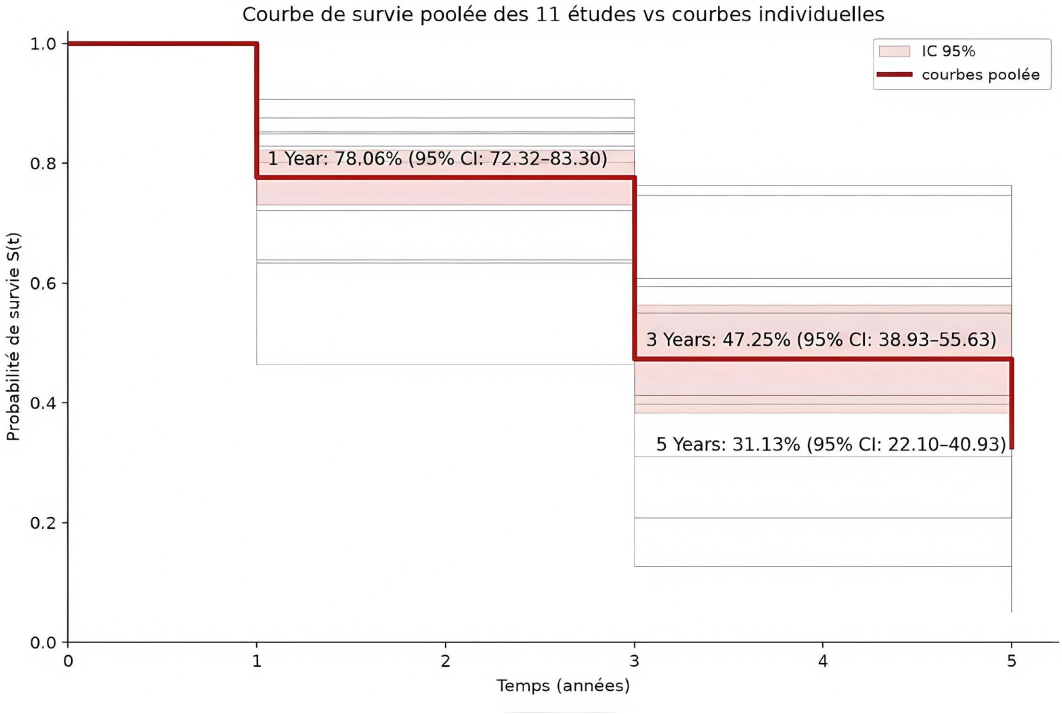


(c)

Figure 5. (a) Forest plots indicating the 1-year survival rates of colorectal cancer patients in sub-Saharan Africa (Egger's test: meta bias, Egger; Prob > |z| = 0.0578); (b) Forest plots indicating the 3-year survival rates of colorectal cancer patients in sub-Saharan Africa (Egger's test: meta bias, egger; Prob > |z| = 0.0993); (c) Forest plots indicating the 5-year survival rates of colorectal cancer patients in sub-Saharan Africa (Egger's test: meta bias, egger; Prob > |z| = 0.0708).



(a)



(b)

Figure 6. (a) 11 Kaplan-Meier curves of the 11 cohorts; (b) Pooled Kaplan-Meier survival curve across included cohorts.

4. Discussion

4.1. Electronic Search Results and Methodological Quality Assessment

The systematic search, conducted in accordance with PRISMA guidelines, resulted in the inclusion of 47 articles out of the 1074 initially identified across six international databases. The exclusion process targeted non-peer-reviewed work and non-relevant publications. Although a geographical imbalance was observed in favor of Anglophone sub-Saharan Africa, potentially introducing a risk of selection bias, the methodological quality assessment, performed using the Joanna Briggs Institute (JBI) tool for hospital-based proportion studies, indicated overall robustness of the evidence. Specifically, 72.34% of studies (34/47) were classified as having a low risk of bias, 25.53% (12/47) as moderate risk, and 2.13% (1/47) as high risk.

4.2. Age of Patients

Forest plot analysis (**Figure 2(a)**) revealed a mean age at diagnosis of 52.52 (95% CI: 49.68 - 55.36) years. This finding supports a major epidemiological pattern, namely the earlier occurrence of colorectal cancer (CRC) in sub-Saharan Africa (SSA) compared with global trends. This "early-onset" pattern is particularly evident in the present study, with patients presenting at an age approximately 15 years younger than their Western counterparts. However, this overall mean conceals substantial heterogeneity across regions. Marked disparities were observed, ranging from 35.4 years in Burkina Faso(63) to 64.8 years in Nigeria (39)**.** Such variation suggests a significant influence of genetic factors, particularly inherited syndromes such as Lynch syndrome, as well as environmental factors specific to certain geographic contexts [21]. Comparison with regional data shows consistency with previous reports. Similar findings were reported by Katsidzira *et al.* (2017) [71] and Brand *et al.* (2018) [48]**,** who documented mean ages ranging from 52 to 56 years and 52.7 years, respectively.

Furthermore, a systematic review and meta-analysis by Matovu *et al.* (2025) [72] estimated the mean age at diagnosis of CRC in Africa at 53.5 years (95% CI: 51.9 - 55.0), a range that encompasses the estimate observed in the present study.

Conversely, some studies report even earlier ages at diagnosis. For instance, Musa *et al.* (2021) reported a mean age of 43.86 ± 18.36 years [73]**,** highlighting the potential aggressiveness of the disease in certain contexts. At the global level, the contrast is striking. Mean ages reported in Europe by Sung *et al.* (2021) [4] aging from 70 to 72 years, and in North America by Siegel *et al.* (2020) [74]**,** ranging from 67 to 69 years, are substantially higher than those observed in SSA.

Overall, these intercontinental differences in age at diagnosis likely reflect a multifactorial interplay between demographic structure, genetic predisposition, disparities in access to screening, and rapidly evolving lifestyle factors.

4.3. Pooled Hospital-Based Proportion of Colorectal Cancer

The meta-analysis of 47 hospital-based studies yielded a pooled hospital-based

proportion of colorectal cancer (CRC) of 44.48% (95% CI: 28.89 - 60.65). Substantial heterogeneity was observed ($I^2 = 99.83\%$), indicating marked variability across the included studies. However, Egger's test ($p < 0.001$) did not indicate significant publication bias. These findings suggest that the pooled hospital-based proportion estimates vary considerably according to geographic context, population genetic background, sampling characteristics, study period, and screening practices.

4.3.1. Comparative Analysis of Pooled Hospital-Based Proportion of Colorectal Cancer

In this study, the pooled effect size of CRC proportions among symptomatic patients presenting for consultation at a diagnostic health center in the overall meta-analysis was 44.48% (95% CI: 28.89 - 60.65) This is accompanied by a significant between-study heterogeneity ($I^2 = 99.83\%$; $p < 0.001$), and a wide range of individual estimates from 1.40% (Kpossou *et al.*, 2025) [59] to 100.00% (Dakubo *et al.*, 2010) [49]. This difference is due to the heterogeneity of the methodology of the included studies (some studied the frequency of biomarkers, some the proportion of advanced stages and some survival) and to the heterogeneity of the genetic, environmental and socio-economic characteristics of the study populations. The proportions reported from hospital-based studies by Holowatyj *et al.* (2016) in Nigeria (20.0%) [75], Admassu *et al.* (2023) in Ethiopia (19.0%) [76] and Alsumait *et al.* (2020) in Oman (11.9%) [77] are much lower than the present study. Furthermore, Bocioaga *et al.* (2026) [78] reported a 63.7% proportion of histopathologically confirmed colorectal cancers among a cohort of symptomatic patients in Romania, a value substantially higher than the pooled proportion observed in our study (44.48%). This concordance can be explained by the fact that both studies were performed in symptomatic patients and not in a screening setting. However, the data reported by Gullickson *et al.* (2021) [54] for sub-Saharan Africa suggest a much higher proportion (up to 98.1% in the Seychelles), a figure that probably reflects a very selected population. Macro-geographically, some African countries show instability in CRC proportion studies and health systems that are rarely equipped with early screening programs. This means that most of the studies in this area are based on symptomatic individuals so that the proportions are high, maximum values close to 100% due to a selection bias toward late metastatic stages (stages III and IV). However, these diagnostic proportions, derived from symptomatic patients, should be distinguished from detection rates in screening settings. CRC detection rates are considerably lower in Western European and North American countries where diagnoses are most often made within the framework of organized screening programs. Uebel *et al.* (2023) in Europe report several studies with detection rates of 3.1% - 7.7% in the United Kingdom, 7.7% - 8.0% in Italy and up to 16.4% in Sweden [79]. Similarly, the ratio of histopathologically confirmed diagnoses of colorectal adenocarcinoma in the United States is between 5.0% and 10.5% [80] [81]. Ultimately, this global divide is a structural health divide. Diagnosis and treatment are more effective in high income countries. There are operational and detection challenges in low-capacity settings.

4.3.2. Explanatory Factors of Heterogeneity

The observed epidemiological variability of colorectal cancer (CRC) reflects the interaction between demographic, biological, and environmental determinants. In sub-Saharan Africa (SSA), the relatively young population structure contrasts with ageing populations in Western countries, where CRC incidence is closely associated with cellular senescence [5]. From a biological perspective, mechanisms such as microsatellite instability (MSI) and Lynch syndrome contribute to earlier tumorigenesis, further influenced by epigenetic alterations and intestinal dysbiosis associated with a pro-inflammatory nutritional transition. This systemic inflammatory context, combined with the absence of systematic screening, contributes to delayed diagnosis. Overall, SSA is experiencing a rapidly evolving epidemiological transition, characterized by the convergence of genetic susceptibility (notably MSI) and changing environmental exposures, in contrast to Western settings where disease burden is mitigated by established prevention and early detection strategies [73].

4.4. MMR Gene Analysis and Public Health Perspectives

The analysis of mismatch repair (MMR) proteins and genes (MLH1, MSH2, MSH6, and PMS2) is important for understanding the specific biology of colorectal cancer (CRC) in sub-Saharan Africa (SSA). Defects of this system result in microsatellite instability (MSI), a key factor in tumorigenesis. The molecular profiling of SSA reveals considerable heterogeneity. The MLH1/MSH2 axis dominates with alteration rates (mostly detected by immunohistochemical [IHC] loss of protein expression) often exceeding 30% in multiple cohorts [34]. These proteins are the main drivers of the MMR-deficient (dMMR) and microsatellite instability-high (MSI-H) phenotypes. However, the present analysis also emphasizes the significance of MLH1, MSH2 and MSH6 with reported IHC protein loss frequencies of 22.66%, 12.40% and 42.86%, respectively [26].

Limiting the analysis to the MLH1/MSH2 axis alone would therefore risk an underestimation of the true hospital-based proportion of dMMR/MSI tumors in this population. It is worth noting that a loss of protein expression on IHC or MSI-H phenotype is not synonymous with germline-confirmed Lynch syndrome. These markers are used for primary screening, but the dMMR/MSI-H phenotype may also be caused by sporadic epigenetic mechanisms, especially somatic hypermethylation of the MLH1 promoter, and double somatic mutations.

Clinically, the pooled proportion of MSI-H status in this SSA hospital-based cohort (25.71%; 95% CI: 16.32% - 36.34%) is considerably higher than Western benchmarks (~15%) [82]. There was extreme heterogeneity (I^2 = 92.10%, $p < 0.001$), indicating large differences in patient selection, sample size and diagnostic methodology (IHC vs. PCR/sequencing).

This biological difference could account for the earlier age of diagnosis noted in SSA, because impaired DNA repair leads to increased accumulation of somatic mutations, thereby decreasing the latency period from the initial cellular transfor-

mation to the development of an invasive tumor. This evidence collectively calls for a structural transformation of healthcare systems in SSA. A transition from reactive care to preventive and genomic medicine, incorporating somatic *BRAF* testing or *MLH*1 promoter methylation assays alongside confirmatory germline sequencing, is essential to integrate local molecular specificities and improve patient management.

4.5. Stratification of CRC Aggressiveness and Management in Sub-Saharan Africa

In sub-Saharan Africa (SSA), the MSI/MSS molecular profile has emerged as a key biomarker for tumor stratification and therapeutic decision-making. In contrast to Western settings [74], SSA is characterized by a relatively high pooled hospital-based proportion of MSI-H phenotypes (up to 43%) [31], reflecting the prominent role of MMR deficiency (dMMR) in early tumorigenesis. In parallel, microsatellite stable (MSS) tumors, although predominant in several series [34], typically evolve through the chromosomal instability (CIN) pathway and exhibit pronounced clinical aggressiveness at advanced stages [82]. This pattern of accelerated carcinogenesis necessitates adaptation of public health strategies. Primary prevention should focus on reducing systemic inflammation, particularly through the promotion of fiber-rich diets. In addition, the increasing pooled hospital-based proportion of MSI underscores the need for systematic cascade screening to enable early identification of Lynch syndrome within affected families.

From a strategic perspective, lowering the screening age to 40 years is warranted, given a median age at diagnosis of 54 years in SSA. The integration of fecal immunochemical testing (FIT) with molecular characterization (MSI status) is essential to guide access to immunotherapy (anti-PD-1 agents), whose therapeutic benefit exceeds that of 5-fluorouracil in these molecular subgroups [83]. Overall, reducing CRC-related mortality in SSA requires an urgent transition toward precision oncology and proactive surveillance tailored to the biological characteristics of the region.

4.6. Analysis of Overall CRC Survival in Sub-Saharan Africa

Pooled survival analysis revealed a marked decline in survival rates from the first year of follow-up. Overall survival was estimated at 78.06% at one year, decreasing substantially to 47.25% at three years, and reaching a critically low level of 31.13% at five years. The reliability of these estimates is supported by statistical robustness analyses. The absence of publication bias was confirmed by the symmetry of funnel plots and Egger's tests, with $p > 0.05$ at all three time points (1, 3, and 5 years), supporting the methodological rigor of this meta-analysis.

Beyond statistical significance, detailed analysis of survival trajectories highlights critical disruptions in the continuum of care. The abrupt decline observed in Kaplan-Meier curves reflects substantial diagnostic delay. This pattern is con-

sistent with a predominance of diagnoses at advanced clinical stages (stage IV or presentation with obstructive complications), which markedly limits eligibility for curative therapeutic strategies at the time of initial management.

This early vulnerability is followed by an equally concerning intermediate-term survival dynamic. The steep decline between the first and third years corresponds to a critical period for metastatic relapse [9] [72]. The absence of a survival plateau during this interval suggests two major contributing factors:

- Systemic barriers: Persistent challenges in access to adjuvant chemotherapy, particularly standard regimens such as FOLFOX, are often limited by drug shortages or prohibitive costs for patients [83].
- Biological factors: Potential intrinsic tumor aggressiveness or resistance associated with molecular profiles specific to the sub-Saharan African context. These outcomes likely result from the combined impact of structural barriers to care and underlying biological determinants, including the high pooled hospital-based proportion of the dMMR/MSI phenotype [84]. These survival patterns contrast sharply with international benchmarks, highlighting a significant global disparity. While 5-year survival for **colorectal cancer (CRC)** generally exceeds **65%** in high-income countries, it remains between **20% and 30%** in sub-Saharan Africa, with notable exceptions reported by Saidi *et al.* (2011) [65] and Parker *et al.* (2020) [64]. These findings underscore the urgent need for integrated strategies, including strengthening early detection through fecal immunochemical testing (FIT) and developing specialized oncology centers to improve continuity and quality of care.

4.7. Strengths of the Study

This systematic review and meta-analysis is supported by several methodological and scientific strengths that enhance the validity of its conclusions for oncology in sub-Saharan Africa.

Methodological rigor and level of evidence: Adherence to PRISMA guidelines and prospective registration in PROSPERO (CRD420261341249) ensures transparency and reproducibility. By integrating heterogeneous primary data, this study provides weighted and statistically robust estimates of the epidemiology and molecular characteristics of colorectal cancer (CRC).

The article demonstrates excellent methodological rigor by transparently addressing its own biases, particularly by highlighting the limited statistical power of Egger's test ($p = 0.2832$) in the context of high between-study variance.

Comprehensiveness of molecular profiling: Unlike approaches restricted to MLH1/MSH2, the systematic inclusion of all four MMR proteins (MLH1, MSH2, MSH6, and PMS2) enables a more precise characterization of microsatellite instability (MSI). This approach highlights the contribution of MSH6 and PMS2, which are often underreported in African cohorts.

Translational relevance and public health implications: The study establishes a link between molecular phenotype and clinical outcomes. The reported mean age

at diagnosis (52.52 years) and 5-year survival (31.13%) provide a rationale for lowering the screening age to 40 years and for the systematic integration of MMR status into clinical decision-making algorithms.

Geographic scope: By synthesizing data across multiple regions of sub-Saharan Africa (West, East, and Southern Africa), this study addresses an important gap in global datasets and contributes to the development of precision medicine approaches adapted to the regional context.

Overall, the combination of statistical power and detailed molecular analysis positions this study as a reference for advancing precision medicine in sub-Saharan Africa and for optimizing resource allocation through improved biological stratification.

4.8. Limitations of the Study

Despite its methodological rigor, this meta-analysis presents several limitations inherent to the available data in sub-Saharan Africa.

Heterogeneity and selection bias: Substantial statistical heterogeneity ($I^2 > 90\%$) was observed, reflecting geographic and clinical variability across the region. Although a random-effects model was applied to account for this variability, the predominance of hospital-based studies, often conducted in tertiary care centers, introduces a risk of selection bias with potential overrepresentation of advanced-stage cases. Nevertheless, the absence of significant publication bias (Egger's test, $p > 0.05$) supports the robustness of the findings.

Technical variability and clinical follow-up: Variability in molecular characterization methods (IHC, PCR, sequencing) may influence the sensitivity of MSI/MMR detection. In addition, survival analyses based on Kaplan-Meier estimates may be affected by incomplete follow-up and loss to follow-up, which are common in resource-limited healthcare settings.

Geographic representativeness: An imbalance in regional representation, with a predominance of studies from Anglophone East and Francophone West Africa, may limit the generalizability of the molecular profiles at the continental level.

5. Conclusion

This systematic review and meta-analysis provide a comprehensive mapping of the molecular epidemiology of colorectal cancer (CRC) in sub-Saharan Africa. The findings highlight a concerning clinical burden, characterized by a pooled hospital-based proportion of 44.48% and a low five-year survival rate (31.13%), reflecting the challenges associated with a disease frequently diagnosed at advanced stages in a relatively young population. A key contribution of this work lies in characterizing the molecular features of CRC across the region. The frequency of microsatellite instability-high (MSI-H) varied considerably across the included cohorts, with substantial inter-study heterogeneity. Alterations involving mismatch repair (MMR) proteins, particularly MLH1 and MSH2, as well as MSH6 and PMS2, were also reported. These findings underscore the molecular heterogeneity

of CRC in sub-Saharan Africa and highlight the importance of strengthening molecular characterization to better understand regional disease patterns. The relatively early age at diagnosis (mean age: 52.52 years) and poor survival outcomes further emphasize the need to investigate the potential contributions of genetic susceptibility, environmental exposures, and changing lifestyle factors to CRC development and progression. In light of these findings, a paradigm shift in public health strategies is required, prioritizing earlier detection, improved access to molecular diagnostics, and the integration of precision oncology into CRC management across sub-Saharan Africa.

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Author Contributions

Conceptualization, S.A.D. and I.D.P., O.R.A.; methodology, Z.S.V., O.A.K.; software, S.F., B.VBE; validation, O.A.R., Z.A.A., and T.M.Z.; formal analysis, D.F.W.; investigation, S.A.D. and I.D.P.; resources, S.J.; data curation, O.A.K.; writing—original draft preparation, Sidibe, A.D., Ilboudo, D.P., Ouedraogo, R.A., Simpore, A.; writing-review and editing, D.O.Y., F.S.; Ouattara, A.K.; visualization. M.G., O.R.A.; supervision, C.O.; O.L., S.J.; project administration, S.J.; All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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