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Research article

Targeted variant prevalence of FBXW7 gene mutation in colorectal carcinoma propagation. The first systematic review and meta-analysis

Hafeez Abiola Afolabi [a], Salzihan Md Salleh [b,*], Zaidi Zakaria [a], Ch'ng Ewe Seng [h], Norasikin Mohd Nafi [i], Ahmad Aizat Bin AbdulAziz [c], Yusuf Wada [d,g], Ahmad Adebayo Irekeola [d], Sameer Badri Al-Ml-hanna [e], Ali Mussa [f,j]

[a] *Department of General Surgery, School of Medical Sciences, Hospital Universiti Sains Malaysia (HUSM), Health Campus, Universiti Sains Malaysia (USM), Kubang Kerian, Kelantan, 16150, Malaysia*
[b] *Department of Pathology, School of Medical Sciences, Hospital Universiti Sains Malaysia (HUSM), Health Campus, Universiti Sains Malaysia (USM), Kubang Kerian, 16150, Kelantan, Malaysia*
[c] *Department of Human Genome Centre, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kubang Kerian, 16150, Kelantan, Malaysia*
[d] *Department of Medical Microbiology and Parasitology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kubang Kerian, 16150, Kelantan, Malaysia*
[e] *Department of Exercise Physiology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kubang Kerian, 16150, Kelantan, Malaysia*
[f] *Department of Biology, Faculty of Education, Omdurman Islamic University, Omdurman, P.O. Box 382, Sudan*
[g] *Department of Zoology, Ahmadu Bello University, Zaria, Kaduna, Nigeria*
[h] *Department of Pathology, Advanced Medical & Dental Institute, Universiti Sains Malaysia (USM), Kepala Batas, 13200, Malaysia*
[i] *Department of Pathology, School of Medical Sciences, Universiti Sains Malaysia (USM), Health Campus, Kubang Kerian, 16150, Malaysia*
[j] *Department of Haematology, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, 16150, Kelantan, Malaysia*

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ABSTRACT

FBXW7 is a tumour suppressor gene that functions as E3-ubiquitin-ligase, targeting numerous oncoproteins for degradation, i.e., Cyclin-E, c-Myc, and Notch. FBXW7 performs a pivotal role in regulating cell cycle progression. FBXW7 mutation is frequently implicated in various cancers.

Methodology: A systematic review and meta-analysis done on several studies using "Preferred Reporting Items for Systemmatic Reviews and Meta-Analysis (PRISMA)" criteria and registered with PROSPERO (registration-number-CRD42023388845). The preliminary search comprises 1182 articles; however, 58 studies were subsequently chosen after eliminating non-eligible studies. To explore the prevalence of FBXW7 mutation among colorectal cancer patients, data were analysed using "OpenMeta Analyst and comprehensive meta-analysis-3.0 (CMA-3.0)" software.

Results: This meta-analysis involves 13,974 respondents; most were males 7825/13,974, (56.0 %). Overall prevalence of FBXW7 mutations was 10.3 %, (95%CI: 8.6–12.4), I2 = 90.5 %, ($P < 0.001$). The occurrence of FBXW7 mutations was highest in Russia [19.0 %, (95%CI: 9.8–33.7)]

* Corresponding author.
E-mail addresses: afolabihafeez68@gmail.com (H.A. Afolabi), profsalzihan66@gmail.com, salzihan@usm.my (S.M. Salleh), doczakaria44@gmail.com, drzaidi@usm.my (Z. Zakaria), eschng@usm.my (C.E. Seng), snmn@usm.my (N.M. Nafi), aizataziz@usm.my (A.A. Bin AbdulAziz), wadayusuf34@gmail.com, wadayusuf@student.usm.my (Y. Wada), profahmad007@yahoo.com (A.A. Irekeola), sameerbadri9@gmail.com (S.B. Al-Ml-hanna), alimaha1341989@gmail.com (A. Mussa).

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and Taiwan [18.8 %, (95%CI: 8.7–35.9)], P-values< 0.05 while the least prevalence was reported in Netherland (4 %) and Italy (5 %), both P-values< 0.001. Overall prevalence of FBXW7 abberation was greatest amongst male gender: "53.9 %, (95%CI: 8.3–62.0 %)", Tumour location (colon): 59.8 %, (95%CI: 53.9–65), tumour site (left): 61.6 %, (95%CI: 53.8–68.9), Tumour-grade (Moderate): 65.9 %, (95%CI: 54.9–75.4 %), and Tumour late-stage: 67.9 %, (95%CI: 49.7–84.3 %), all P-values< 0.001. When stratified according to study-period, an increasing trend was noted from 2018 till present with the highest mutation rate recorded in 2022 (15.3 %).
Conclusion: Overall prevalence of FBXW7 mutations was 10.3 % with male gender, left side, and late-stage being most mutated, and these outcomes conform with severally published articles on FBXW7 mutation.

1. Introduction

1.1. Background

Colorectal carcer (CRC) is a noteworthy medical menace worldwide, epitomising a major burden on public healthiness systems and individuals alike. With press release of about two million fresh CRCs detected and almost a million fatalities worldwide in 2018 [1], Colon/colorectal tumour is ranked third in both commonest and causes of cancer-related mortality globally, with substantial morbidity and mortality rates [2]; 10 % of all cancer diagnosed annually [3,4]. CRC arises from precancerous polyps, which are abnormal growths on the inner lining of the colon or rectum. Although, epidemiological studies have identified several risk factors associated with propagation of CRC. The most prominent risk factor is advancing age, family history, and smoking. Diagnosing colorectal cancer involves a series of tests, with colonoscopy being the gold standard for detection [5]. Early detection through regular screenings is essential, especially for individuals with risk factors or a family history of colorectal cancer. Screening tests such as sequencing-based tests can help identify precancerous mutations or early-stage cancer, leading to more effective treatment and improved outcomes.

Over the past years, several identified genetic changes, including mutations such as "APC, BRAF, KRAS, PIK3CA, p53, and F-box and WD repeat domain-containing-7 (FBXW7)" are responsible for the advancement of CRC [6]. Of specific interest is the FBXW7 gene, a member/lineage of the F-box category or clan of proteins, F-box/WD repeat-containing protein 7 (FBXW7) which is also a subunit of the Skp1, Cul1, and F-box protein (SCF) ubiquitin ligase complex. Not until recently that studies stressed the crucial role of FBXW7 in CRC propagation and poor treatment outcomes [7]. By attacking some oncogenic regulators, including "cyclin E, c-Myc, Notch, Mcl-1, c-Jun, and mTORz", Fbxw7 function as a tumour suppressor is loss [8]. Many malignancy mechanisms showed that loss of Fbxw7 in tumour tissues is associated with a poor prognosis and tumorigenesis metastasis and progression [9]. The route for the instigation and advancement of colon cancer culminates from the build-up of numerous mutated genomic and epigenomic variations in the epithelial of the colo-rectum tracts [10]. FBXW7 is a key driver substrate for ubiquitin ligase complex operation in bio-metabolic pathways such as in cell-cycle control, and it is the targeted proto-oncogenes such as "cMYC" and "cyclin E2" for proteasomal breakdown [11]. Revealed data on aberration or deregulation of the miR-182/miR-503–FBXW7 bloc arbitrates malignant transformation in CRC because FBXW7 mutation prevalence in multiple cancers has established the gene as a key element for tumorigenesis [11]. Nonetheless, the comprehension of the genetic influence of FBXW7 mutation in CRC progression remains ambiguous and unclear [12].

Similar to the APC, BRAF, and KRAS genes, the FBXW7 gene aberrations are commonly identified in many cancer types, identified in about 5–10 % of all sequenced cancer cases [13–16], approximately 5–7% in CRCs [17], 30 % in cholangiocarcinoma [13], and 15 % in hepatic cancer [18,19]. An important pitfall hindering cancer-sequencing exploration is the limited headway to substantively detect variant genes with reduced recurrence mutation rate "i.e. 5 % rate of occurrence" [10]. Given the significance and operative role of the FBXW7 genes in the development of colon cancer, FBXW7 mutation is ranked among the nine most often documented mutated genes in colon cancer, including APC, BRAF, KRAS, TCF7L2, EGFR, insulin-like growth factor receptor (IGF1R), FGFR, and CASP8 [20]. Our current research examine the frequency of FBXW7 aberration in individuals with cancer of the colon and rectum using cancer genomic profiling from data from several published research.

Because the development of CRC relies on the multi-genetic alteration of various bio-markers, the discovery and verification of prognosticating bio-markers will enhance cancer management by supplementing the clinicohistopathology information available on the patients [12,21]. Mutation of the FBXW7 gene in the miR-182/miR-503–FBXW7 cascade is crucial among eukaryotes for signal-transduction, cell growth and hormonal regulation [22,23]. Thence, when gene alterations including frameshift insertions, silent mutations, nonsense, and missense mutations take place, they significantly contribute to the proliferation and carcinogenic transformation of cancer cells, as seen in colorectal cancer CRC. Additionally, given that the majority of these aberrations occur inside the WD40 domain, which is crucial for FBXW7 substrate recognition, or produce a termination of the translation propagation before incorporation within this domain, FBXW7 alterations or loss are likely to deactivate the protein translation. These FBXW7 gene mutations at this domain cause uncontrollable cAMP signalling, metastasis, and adenylate cyclase gene activation [24]. The objective of the present research is to examine the global prevalence of FBXW7 gene mutation/aberration in colorectal cancer patients and its association with poor tumorigenesis outcomes.

2. Materials and methods

A systemmatic review and meta-analyses completed inline with the guidelines of "Preferred Reporting Items for Systemmatic

Reviews and Meta-Analyses (PRISMA)", and the study procedure was duly registered in the database of PROSPERO with the registration identity number: CRD42023388845 (https://www.crd.york.ac.uk/prospero/#myprospero) [25].

2.1. Literature search and selection criteria

Our existing study comprises published manuscripts involving five online records [Scopus, Web of Science "WOS", ScienceDirect, PubMed, and Google Scholar]. For assertiveness to achieving the objective of the research, the suitable studies were searched and scrutinised using all-inclusive and appropriate keywords: ["colon cancer" OR "colorectal cancer" OR "metastatic colorectal carcinoma" OR "metastatic colon cancer" OR "metastatic colorectal cancer" OR "CRC" OR "Rectum"] and ["FBXW7" OR "FBXW-7″ OR ″c-FBXW7" OR "CFBXW7"].

Thorough search approaches were carried out and depicted in the Search Strategic Folder (SSF), this ensures a highly reliable and reproducible details. A detailed search string for the utmost relevant studies/articles was undertaken via combing across captions/titles, keynotes and words, and abstracts of a set of published articles. This initial searching comprised 1182 papers/documents (Fig. 1) that was performed in February 2022 via Mendeley software.

The selected articles with available full text that reported on FBXW7 mutation in CRC were downloaded into the software afterwhich, replicates were excluded/removed. The inclusion criteria employed included "cross-sectional [observational]", "cohort" or "case-series" executed to explore the occurrence of FBXW7 aberration in CRC individuals described in "Fresh Frozen, Formalin-Fixed Paraffin-Embedded FFPE" or biopsied colon tumour samples. Also, articles on FBXW7 gene mutation containing greater than a sample

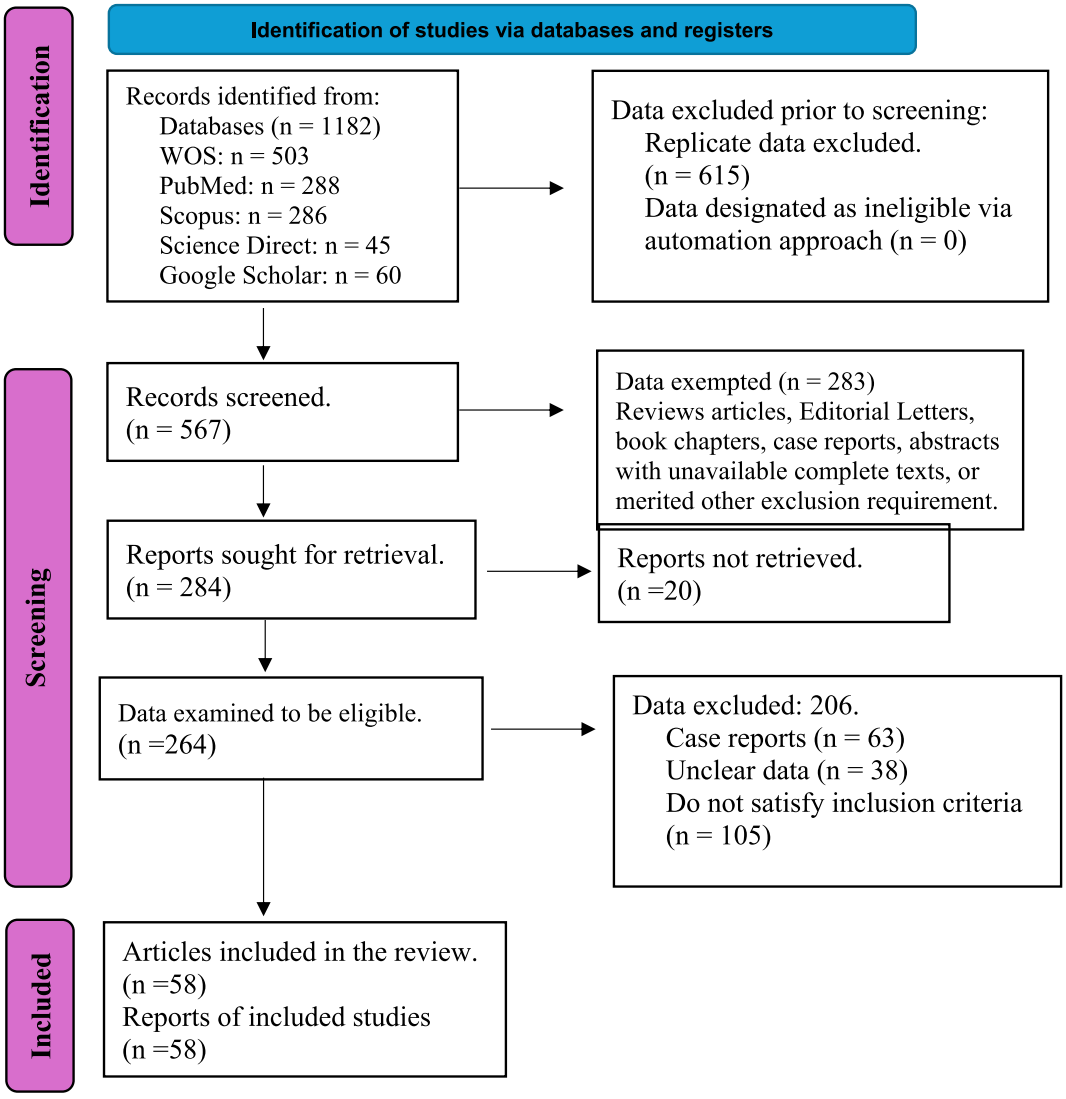

Fig. 1. Summary representation of articles identification and selection process.

Table 1
Comprehensive characteristics of the prevalence of FBXW7 screening studies included in the meta-analysis.

S/N	Author	Year	Location	Male n (%)	Age	Sample Size	Right Colon (%)	Left Colon (%)	Tumour Stage (Early stages 1&2) *	Tumour Stage (Late stage 3&4) *	Tumour Location (colon)*	Tumour Location (Rectum)*	Tumour Grade (Poor)*	Tumour Grade (Moderate)*	Tumour Grade (Well)*	Method	Total FBXW7 Mutation (n)
1	[30]	2014	China	46.2	62 (29–86)	93	NR	NR	NR	NR	11.8	87.1	NR	NR	NR	NGS	10
2	[15]	2007	Austria	NR	NR	31	NR	NR	NR	NR	NR	NR	NR	NR	NR	PCR Amplification	3
3	[31]	2016	USA	60.6	50.8 (20–77)	99	24.2	69.7	3	90.9	37.4	56.5	22.2	66.6	5.1	NGS/PCR	3
4	[32]	2022	Italy	NR	NR	296	NR	NR	NR	NR	NR	NR	NR	NR	NR	NGS	9
5	[33]	2016	Finland	NR	NR	52	NR	NR	NR	NR	39	13	NR	NR	NR	NGS	9
6	[34]	2019	USA	57	61 (24–95)	121	NR	NR	44	33	NR	NR	NR	NR	NR	NGS	5
7	[35]	2015	China	45.1	59 (31–82)	91	NR	NR	49.5	46.2	NR	NR	25.3	64.8	8.8	NGS	9
8	[36]	2021	Italy	43.4	56.4 (47.9–64.7)	152	40.1	59.9	NR	NR	87.5	12.5	NR	NR	NR	NGS	5
9	[37]	2018	Germany	50	62.9	100	56.3	40.2	NR	NR	NR	NR	NR	NR	NR	NGS/PCR	3
10	[38]	2019	China	65.8	7.41 (1–103)	152	13.8	86.2	0.66	99.4	52	48.03	NR	NR	NR	NGS/ Bioanalyzer	17
11	[39]	2019	Brasil	26.1	62.8 + 13	46	32.6	67.4	34.8	65.2	67.4	32.6	NR	NR	NR	NGS	10
12	[40]	2015	China	65.8	70.0 + 11.5	1519	NR	NR	51.7	48.3	69.3	30.7	5.8	NR	NR	NGS	114
13	[41]	2017	China	65.8	70.1 ± 11.5	1475	26.4	35.9	51.5	48.5	62.3	37.7	5.9	NR	NR	(MSI-high)	109
14	[42]	2017	China	75	58 (26–75)	53	53	28	NR	NR	NR	19	NR	NR	NR	NGS	4
15	[43]	2019	Taiwan	62.5	60.47 (35–90)	32	NR	NR	59.4	37.5	75	25	6.25	87.5	6.25	NGS	6
16	[44]	2016	USA	56.3	57 (35–81)	16	NR	NR	18.8	81.3	NR	NR	18.7	NR	81.2	NGS	3
17	[45]	2016	Saudi Arabia	58.6	41 (25–75)	99	27.3	47.5	NR	NR	72.7	27.3	10.1	61.6	16.2	NGS	7
18	[46]	2019	Brasil	53.8	61.18 (29–88)	91	22	78	74.7	22	72.5	35.2	4.4	84.6	11	NGS-MSI	10
19	[47]	2022	USA	49.4	59.8 (30–90)	83	34.9	55.4	33.7	57.8	71.1	24.1	33.7	NR	NR	NGS/MSI	68
20	[48]	2019	China	62.3	61 (53–68)	207	17.9	28	44.9	55.1	45.9	54.1	16.4	82.1	1.4	NGS/PCR	33
21	[49]	2022	Switzerland	59	67 + 12	512	34	59	4	96	NR	NR	22	NR	78	NGS	40
22	[50]	2021	China	60.2	57 (16–96)	630	25.9	74.1	26.5	67.3	NR	NR	NR	NR	NR	NGS/	110
23	[51]	2016	India	NR	NR	112	NR	NR	NR	NR	NR	NR	NR	NR	NR	PCR/NGS	13
24	[52]	2015	Germany	54	61.5 (36–83)	24	25	75	25	75	54	46	NR	NR	NR	NGS	5
25	[53]	2017	USA	NR	NR	32	NR	NR	NR	NR	29	3	NR	NR	NR	NGS	3
26	[54]	2016	Canada	NR	NR	80	NR	NR	NR	NR	NR	NR	NR	NR	NR	TRUSIGHT NGS	5
27	[55]	2019	Poland	37.9	66.448	58	NR	NR	16	42	35	23	55.1	10.3	34.4	NGS	7
28	[56]	2021	USA	54.8	56 (46–65)	504	NR	NR	37.4	92.8	75.6	24.4	13.9	27.4	58.7	NGS	60
29	[57]	2021	USA	56.5	55 (46–62)	476	NR	NR	NR	NR	68.5	31.5	NR	NR	NR	NGS	27
30	[58]	2017	USA	56	55 (22–82)	571	34	66	NR	NR	77.6	22.4	24.7	74.1	0.2	NGS	43
31	[59]	2019	Thailand	42.6	64 (30–89)	108	64.8	33.3	24.1	75.9	82.4	17.6	6.5	86.1	4.6	NGS	16
32	[60]	2017	USA	50	57.5 (30–93)	246	NR	NR	38.2	60.6	NR	NR	NR	NR	NR	NGS	23
33	[61, 61]	2021	S.Korea	46.9	64 (43–87)	49	NR	NR	28.6	71.4	NR	NR	NR	NR	NR	NGS	4
34	[62]	2021	S.Korea	52.4	60.9 (25–88)	145	31	69	17.9	82.1	63.4	36.6	10.3	71.7	8.3	NGS	19

(*continued on next page*)

Table 1 (*continued*)

S/N	Author	Year	Location	Male n (%)	Age	Sample Size	Right Colon (%)	Left Colon (%)	Tumour Stage (Early stages 1&2) *	Tumour Stage (Late stage 3&4) *	Tumour Location (colon)*	Tumour Location (Rectum)*	Tumour Grade (Poor)*	Tumour Grade (Moderate)*	Tumour Grade (Well)*	Method	Total FBXW7 Mutation (n)
35	[63]	2021	S.Korea	66.9	61 (34–89)	142	NR	NR	7	93	24.6	75.4	2.8	93	1.4	NGS	10
36	[64]	2022	Spain	NR	NR	294	NR	NR	NR	NR	NR	NR	NR	NR	NR	NGS	28
37	[65]	2022	China	50.6	55 (29–78)	85	28.2	71.8	NR	NR	68.2	31.8	NR	NR	NR	MSI/NGS	18
38	[66]	2019	China	60.1	57 (15–83)	526	19.2	68.4	NR	NR	50.8	49.2	NR	NR	NR	ION TORENT/ NGS	29
39	[23]	2019	China	47.1	61 (32–84)	17	NR	NR	64.7	35.3	41.2	58.8	5.9	88.2	5.9	Sequencing/ NGS	2
40	[67]	2018	China	57.1	61 (21–91)	509	NR	NR	61.1	38.8	NR	NR	16.3	NR	NR	MSI/IHC	150
41	[68]	2015	Czech Rep	64.6	58 (31–81)	65	10.8	84.6	12.3	87.7	NR	NR	3.1	83	7.6	HISTO/NGS	6
42	[69]	2016	Italy	60.9	66.8 (29–96)	653	NR	NR	NR	NR	NR	NR	NR	NR	NR	PCR	39
43	[70]	2009	Japan	NR	NR	33	NR	NR	NR	NR	NR	NR	NR	NR	NR	NGS	3
44	[71]	2021	Japan	60	72 (54–85)	20	NR	NR	45	55	NR	NR	NR	NR	NR	NGS	1
45	[72]	2016	Czech Rep	41.7	61 (53–73)	24	16.7	83.3	NR	NR	NR	NR	NR	NR	NR	NGS	6
46	[73]	2019	S.Korea	63.1	48 (10–73)	84	NR	NR	NR	NR	3.6	82.1	1.2	25	70.2	NGS	5
47	[74]	2017	Italy	NR	NR	21	NR	NR	NR	NR	NR	NR	NR	NR	NR	PCR/NGS	3
48	[75]	2014	Japan	NR	NR	9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NGS	3
49	[76] A	2020	USA	54.5	59 (16–91)	617	30.6	61.4	NR	NR	68.2	23.8	7.9	49.1	17.8	NGS	80
50	[76] B	2020	USA	54.6	59 (20–93)	348	12.9	14.7	NR	NR	21.3	6.3	3.2	12.6	9.8	NGS	24
51	[77]	2022	Russia	NR	NR	42	NR	NR	NR	NR	NR	NR	NR	NR	NR	NGS	8
52	[78]	2016	Netherland	58.8	69.2 (11.6)	114	40.4	59.6	7	93	NR	NR	6.1	86.8	7.02	NGS	8
53	[79]	2012	Netherland	53.8	68.9 (40–90)	199	NR	NR	NR	NR	73.4	24.6	NR	NR	NR	NGS	4
54	[80]	2022	Canada	52.7	66.1 + 13.4	594	NR	NR	54.5	43.1	74.1	25.9	NR	NR	NR	NGS	90
55	[81]	2021	China	67.7	58 (13–80)	396	17.7	82.3	NR	NR	NR	NR	NR	NR	NR	NGS	43
56	[82]	2018	China	58.8	NR	648	26.1	66.4	NR	NR	NR	NR	7.9	59.7	5.4	NGS	3
57	[83]	2020	China	66.7	65 (58–71)	117	NR	NR	NR	NR	46.2	53.9	NR	NR	NR	NGS	23
58	[84]	2022	Egypt	45	51 (24–76)	62	NR	NR	NR	NR	46	54	5	64	2	ION TORRENT	6

N: Number, NR: Not reported, *: Percentage of all samples, Age is presented in years [(mean +SD/median(range/IQR)/range, HRMS: High resolution melting (HRM)- sequencing, HRMA/P: High resolution melting assay/pyrosequencing, PNAM/PCR and PNAM/PCR/S: Peptide Nucleic Acid-mediated Polymerase Chain Reaction/Sequencing, IHC: immunohistochemistry; W.E.S Whole Exome Sequencing.

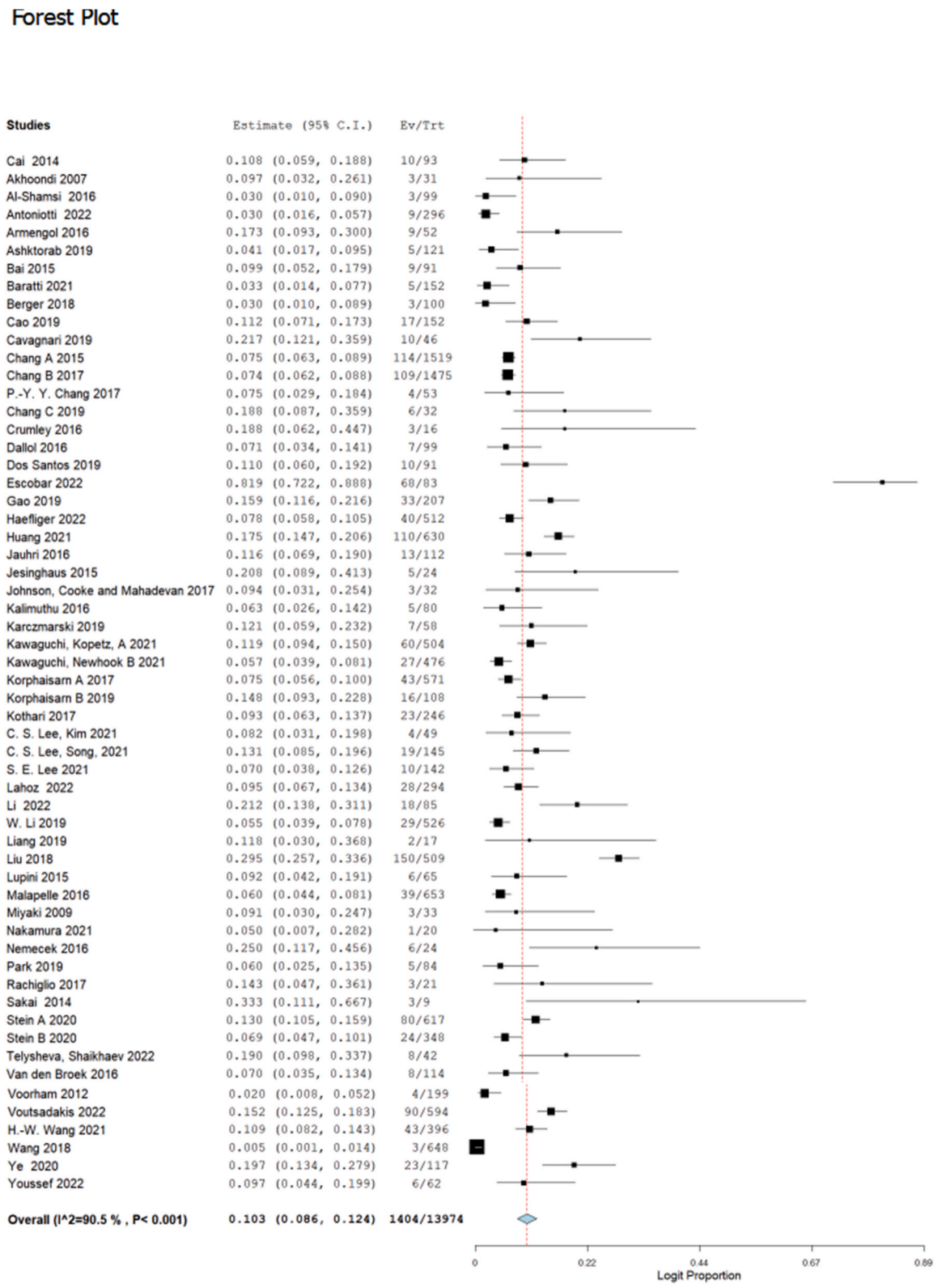

Fig. 2. A Forest plot for the prevalence of FBXW7 mutation in CRC patients.

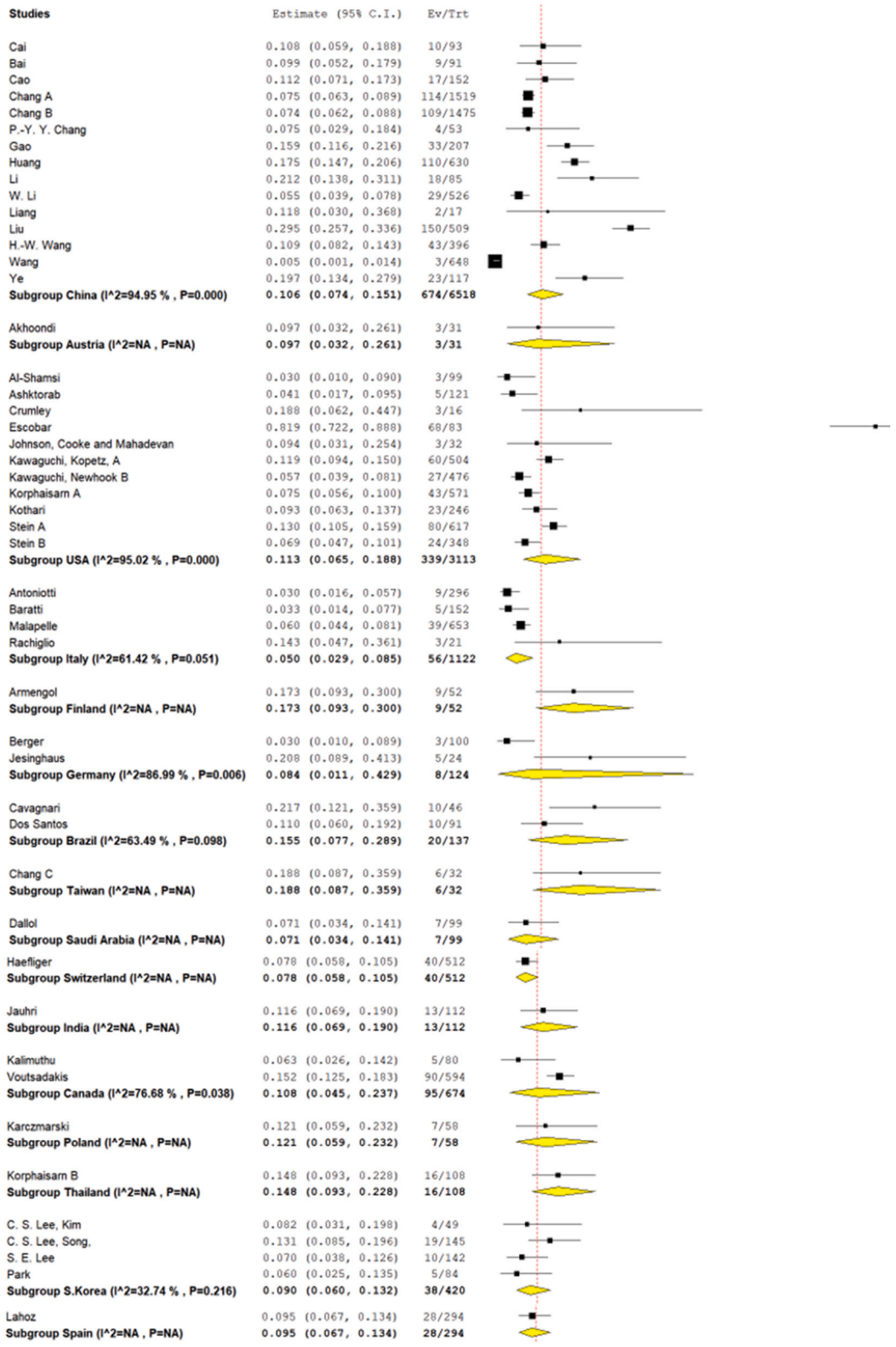

Fig. 3. A Forest plot for the prevalence of FBXW7 mutation in CRC patients by countries.

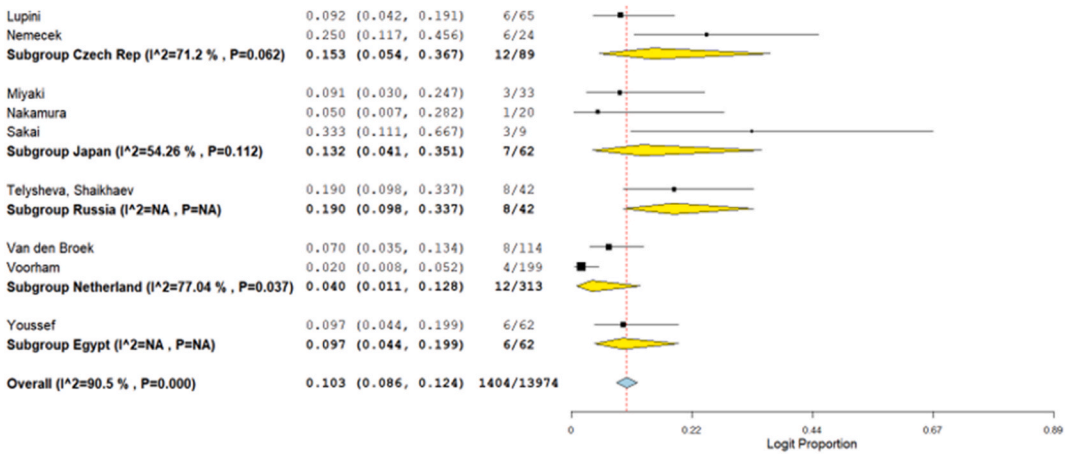

Fig. 3. (*continued*).

size with similar articles published/released from reputable international conferences and/or journals were included. No constraint was put on the method of gene mutation detection. The exclusion criteria are (i) articles not related to the occurrence of FBXW7 gene alteration, (ii) reviews articles and case report; (iii) FBXW7 aberrations that are related to cell cascade downstream and non-human studies/research [26]. All authors/writers partook in the assessment, selection, and assessment process of the study. Two assessors (A. H.A. and S·S.) separately vetted the manuscripts depending on the research's headings and article abstract. Arising discords in the vetting course were resolved via a concession with other co-authors in the research team.

2.2. Data extraction and quality assessment

An Excel spreadsheet was used to extract the data. Two assessors (H.A.A. and S·S.) autonomously read the captions and abstracts and extricated the relevant data, including the study's identity, the year it was published, the time frame and design, the gender, and reports of the occurrence of FBXW7 gene mutations among CRC-diagnosed patients. To prevent bias, any disparities were resoluted by a conversation with a third assessor (A.I.A.), and any inconsistencies were resolved through discussion with additional reviewers. Two assessors (A.H.A. Y.W and I.A.A.) independently evaluated the excellence of the procedural approach for the studies chosen using the "Joanna Briggs Institute (JBI)" critical assessment checklist for incidence information [27] "Supplementary J.B·I file". The sum quality mark, which goes from 0 to 9, was calculated by assigning a score of 1 for "Yes" and a score of 0 for the other factors. Studies were deemed to be of suitable quality if they had a final score of 7–9. The data retrieved part for the meta-analysis comprised the studies that fall in the range of the latter appropriate score array.

2.3. Data synthesis and analysis

OpenMeta Analyst and comprehensive meta-analysis 3.0 (CMA 3.0) tools was employ to analyse the data [28]. In addition to computing the occurrence rate of FBXW7 aberration in colon and rectal cancer patients, data analysis was done on subgroup characteristics such as "tumour location", "gender", "tumour stage", "study year", and "tumour grade". The collective approximates of the documented FBXW7 aberration instances were obtained using a random effect model and the "DerSimonian-Laird meta-analysis"

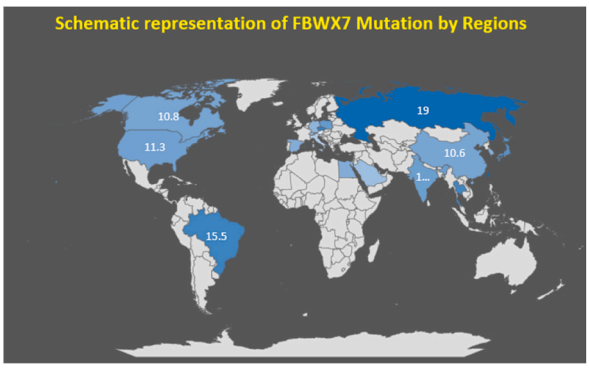

Fig. 4. Geography representation of FBXW7 gene mutation by countries.

Table 2
Subgroup analysis. Prevalence of FBXW7 of patients with colorectal cancer stratified by study location of study.

Subgroup	No of Studies	Prevalence (%)	95 % CI	I^2 (%)	Q	Heterogeneity Test	
						DF	*P*
Study Location							
China	15	10.6	0.074–0.151	94.95	277.12	14	<0.001
Austria	1	9.7	0.032–0.261	NA	NA	NA	NA
USA	11	11.3	0.065–0.188	95.02	200.79	10	<0.001
Italy	4	5.0	0.029–0.085	61.42	7.78	3	0.05
Finland	1	17.3	0.093–0.300	NA	NA	NA	NA
Germany	2	8.4	0.011–0.429	86.99	7.69	1	0.006
Brazil	2	15.5	0.077–0.289	63.49	2.74	1	0.098
Taiwan	1	18.8	0.087–0.359	NA	NA	NA	NA
Saudi Arabia	1	7.1	0.034–0.141	NA	NA	NA	NA
Switzerland	1	7.8	0.058–0.105	NA	NA	NA	NA
India	1	11.6	0.069–0.190	NA	NA	NA	NA
Canada	2	10.8	0.045–0.237	76.68	4.287	1	0.038
Poland	1	12.1	0.059–0.232	NA	NA	NA	NA
Thailand	1	14.8	0.093–0.228	NA	NA	NA	NA
South Korea	4	9.0	0.060–0.132	32.74	4.460	3	0.216
Spain	1	9.5	0.067–0.134	NA	NA	NA	NA
Czech Republic	2	15.3	0.054–0.367	71.2	3.473	1	0.062
Japan	3	13.2	0.041–0.351	54.26	4.373	2	0.112
Russia	1	19.0	0.098–0.337	NA	NA	NA	NA
Netherlands	2	4.0	0.011–0.128	77.04	4.356	1	0.037
Egypt	1	9.7	0.044–0.199	NA	NA	NA	NA
Overall	58	10.3	0.086–0.124	90.5	599.97	57	<0.001
FBXW7 Subgroup by Gender of Study							
Male gender	47	53.9	0.539–0.570	90.45	481.78	46	<0.001
Female gender	47	43.6	0.415–0.458	78.659	215.545	46	<0.001
FBXW7 Subgroup by Period of Study Conduct							
Before 2016	7	8.6	5.8–12.4	60.36	15.136	6	0.019
Between 2015 and 2020	34	9.9	7.7–12.6	89.43	312.319	33	<0.001
After 2020	17	11.8	8.3–16.6	93.32	239.699	16	<0.001
FBXW7 Subgroup by Side of Tumour							
Right side	26	26.4	0.230–0.302	90.15	253.74	25	<0.001
Left side	26	61.6	0.538–0.689	97.27	914.473	25	<0.001
FBXW7 Subgroup by Tumour Stage							
Early Tumour Stage[a]	28	27.6	0.216–0.346	96.94	881.553	27	<0.001
Late Tumour Stage[b]	28	67.9	0.497–0.843	96.56	887.89	27	<0.001
FBXW7 Subgroup by Tumour Location							
Colon	32	59.8	0.539–0.654	95.71	723.094	31	<0.001
Rectum	32	33.9	0.275–0.410	96.83	978.909	31	<0.001
FBXW7 Subgroup by Tumour Grading							
Poor	26	9.7	0.071–0.130	93.22	368.538	25	<0.001
Moderate	20	65.9	0.549–0.754	97.36	719.570	19	<0.001
Well	22	57.5	0.054–0.171	97.25	726.401	21	<0.001
FBXW7 Subgroup by Yearly Rate							
2007	1	9.7	0.032–0.261	NA	NA	NA	NA
2009	1	9.1	0.030–0.247	NA	NA	NA	NA
2012	1	2.0	0.086–0.124	NA	NA	NA	NA
2014	2	17.6	0.052–0.457	69.78	3.309	1	0.069
2015	4	9.6	0.065–0.140	49.43	5.932	3	0.115
2016	8	9.4	0.063–0.137	68.45	25.353	7	<0.001
2017	6	7.8	0.067–0.089	0 %	2.511	5	0.775
2018	3	3.9	0.002–0.436	97.37	76.186	2	<0.001
2019	11	11.0	0.079–0.152	72.7	36.627	10	<0.001
2020	3	12.2	0.072–0.198	86.74	15.082	2	<0.001
2021	9	9.3	0.066–0.129	83.77	49.300	8	<0.001
2022	8	15.8	0.077–0.152	96.24	186.075	7	<0.001

[a] Implies stage 1 &2.
[b] Implies stage 3 & 4.

approach. Additionally, to maintain the standard and validity of our research, potential publication differences [bias] was thoroughly examined by creating a funnel plot. Egger's regression test was used to further analyse the funnel plot's asymmetry [29]. The study-level dissimilarity [heterogeneity] was checked through "Cochran's-Q test and quantified using I^2 - statistics; values of I^2 at 25 %, 50 %, and 75 % were categorised as "Low," "Moderate," and "High" dissimilarity, respectively. A p-value of <0.001 was deemed statistically significant in each test.

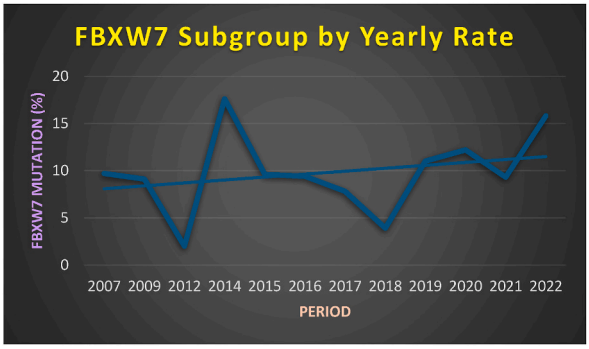

Fig. 5. Graphical representation of FBXW7 gene mutation yearly rate prevalence trend.

3. Result

To ensure a succinct and specific result section, the result arrangement was prepared in subdivisions with each one assigned a subcaption to highlight the experiment/research outcomes and interpretation along with the inferential deduction engraved from the findings.

3.1. Search results and study selection

All 1182 papers used in this study were obtained from five different electronic databases. Some 615 papers were excluded after the duplicates were checked and studies that didn't merit the inclusion conditions were also eliminated, leaving 567 studies for title and abstract screening. Another 284 studies with inconclusive details and those that merited the exclusion criteria were eliminated after the articles underwent a more thorough review of titles and abstracts (see Fig. 1 above). Amongst the eligible 264 articles chosen for final vetting in this research on FBXW7 aberration, therefore, an overall 58 articles was finally chosen in this research.

3.2. Characteristics of the eligible studies

Table 1 below depicts the descriptions of all the studies on FBXW7 gene alteration that were selected in this meta-analyses study. An aggregate of 13,974 sample size included in the meta-analysis spanned from studies all around the world, with the US and China contributing the majority of the data. Overall, Males made up the majority of the participants at 58 % compared to the female counterparts at 42 %.

3.3. Prevalence of FBXW7 mutations in CRC patients

This occurrence of FBXW7 gene aberration demonstrated in the 58 selected researches integrated into this meta-analysis comprise a total of 13,974 patients. In our present study, the highest occurrence rate of FBXW7 gene mutations/aberration was shown by K. Sakai et al., 2014 [75] at a rate of 33 % (95%CI:11.1–66.7 %) while the least rate was reported by Ref. [82]: 0.5 % (95%CI: 0.01–1.4 %). Utilizing the random effect model, the general incidence of FBXW7 gene aberration was 10.3 % (95%CI: 8.6–12.4) with $I^2 = 90.5$ % and ($P < 0.001$) (Fig. 2). Furthermore, the regional analysis among the 21 countries from the 58 included studies that reported on the frequency of FBXW7, the highest FBXW7 prevalence was reported in Russia at 19.0 % (95%CI: 9.8–33.7) and Taiwan at 18.8 % (95% CI: 8.7–35.9) with ($P = 0.05$) while the countries with least prevalence were reported in Netherland at 4.0 % (95%CI: 1.1–12.8) with $I^2 = 77.04$ % and ($P < 0.001$) and Italy at 5.0 % (95%CI: 2.9–8.5) with $I^2 = 61.42$ % and ($P = 0.05$). The prevalence of the mutated FBXW7 across the countries was presented in Fig. 3 while the geographical description was also shown in Fig. 4.

3.4. Prevalence of FBXW7 gene mutation in colorectal cancer stratified by study location and period of study

To perform an investigation on the occurrence rate of FBXW7 aberration in CRC patients from differing districts and sections, a subgroup meta-analysis was performed. On the sub-period distribution of FBXW7 mutation in the study, there is a stepwise increase frequency of FBXW7 gene mutation with the proceeding years. The highest rate was recorded in Sub-period 'After 2020" at 11.8 % (95%CI: 8.3–16.6) with $I^2 = 93.32$ % and ($P < 0.001$), followed by Sub-period 'Between 2015 and 2020″ at 9.9 % (95%CI: 7.7–12.6) with $I^2 = 89.43$ % and ($P < 0.001$), while least was recorded for Sub-period 'Before 2016" 8.6 % (95%CI: 5.8–12.4) with $I^2 = 60.36$ % and ($P < 0.05$) (Table 2; Supplementary Figure SF1).

There was obtainable data from 47 studies on gender-FBXW7 mutation proportion from the included studies. The male gender had the highest FBXW7 mutation rate at 53.9 % (95 % CI: 0.0 83–0.620) when contrasted to the female group 43.6 % (95 % CI: 0.378–0.492) respectively; $p < 0.001$) (Table 2; Supplementary Figure SF2 & SF3).

On the most common site of occurrence of mutation, the "Left Side" of the colon recorded the most prevalence of FBXW7 aberration

at 61.6 % (95 % CI: 53.8–68.9), $p < 0.001$) compared to the "Right Side" at 26.4 % (95%CI: 23.0–30.2) respectively; $p < 0.001$) (Table 2; Supplementary Figure SF4 & SF5).

In the tumour stage, FBXW7 alterations were mostly detected at the "Late Stage" at 67.9 % (95 % CI: 49.7–84.3), while on Tumour Location, the colon has the highest FBXW7 gene aberration of 59.8 % (95 % CI: 53.9–65.4). On the "Tumour Grade" of FBXW7 mutation in CRC patients, "Moderate Grade" has the highest FBXW7 gene mutation of 65.9 % (95 % CI: 54.9–75.4) while the "Poorly Graded" has the least prevalence rate at 9.7 % (95 % CI: 7.1–13.0), $p < 0.001$ (Table 2; Supplementary Figure SF6,7,8,9,10,11 & SF12).

Subgroup FBXW7 gene mutation by "Yearly Rate" showed an incremental trend as displayed on the line graph in Fig. 5 below. The rise could be noted from 2019 till the present but with a drop in 2020 which is majorly due to the COVID-19 outbreak that halted all activities worldwide, but with a continued rise post-COVID-19 year. The rate was 11 %. 3 %, 9.3 %, and 15.8 % for 2019, 2020, 2021 and 2022 respectively. The highest rate of FBXW7 gene mutation was recorded in 2022 at 15.8 % (95 % CI: 7.7–15.2) $p < 0.001$) (Table 2; Supplementary Figure SF13).

3.5. Analyses of sensitivity and publication bias

A funnel plot of random effects was designed to check for trails of publications unfairness [biases] in included articles written on FBXW7 gene aberration amongst patients diagnosed of colon cancer (Fig. 6). Nonetheless, the FBXW7 aberrant articles lacked obvious suggestions of publication unfairness.

4. Discussion

FBXW7 gene is a dire tumour suppressor gene and a part of the F-box protein household, which belongs to the Skp1-Cdc53/Cullin-F-box-protein complex (SCF/β-TrCP). The ubiquitin-proteasome system (UPS) is implicated in several expressions of bio-cellular processes in the body, including cell cycle propagation, cellular differentiation, and survival. The F-box and WD repeat domain-containing-7 (FBXW7), otherwise called Sel10, hCDC4 or hAgo, and family of the F-box protein family is a key path of FBXW7 cascade. FBXW7 is the substrate that identifies elements of the SCF-E3 ubiqquitin ligase. Because of the tumour-suppression action of FBXW7 and been among the most frequently decontrolled ubiquitin-proteasome systemic proteins in human cancinoma such as in colorectal cancer CRC, FBXW7 influence on proteasome-facilitated breakdown of onco-proteins such as "cyclin E″, "cMyc", "Mcl-1", "m-TOR", "Jun", "Notch and AURKA" is huge, FBXW7 gene loss is exceptionally an essential pathway for cancer and CRC progression.

Nevertheless, the prevalence and occurrence of FBXW7 mutations differs as reported in published data; approximately cholangiocarcinoma (15 %) [85], T-cell acute lymphocytic leukemia T-ALL (31 %) [86], cancer of the bladder (10 %) [5], gastrinoma carcinoma (6 %), squamous cell cancer of the lungs (5 %) [87], endometrial carcinoma (16 %), ovarian cancer (8.3 %) [88] etc. Overall, CRC comprises of 4.2 % of all cancer's new cases [89], been the third most in both predominancy and occurring cause of cancer death around the world [89,90], CRC is responsible for approximately one million deaths and newfound cases of about 1.91 million in 2018 [91]. Though there are sizable provincial variances in the occurrence and death rates of colon cancer, in our meta-analysis study, 58 articles were ultimately chosen from a preliminary total of 1182 papers to investigate the rate of occurrence of FBXW7 gene mutation/aberration amongst colon cancer patients universally. Over the span of our research, certain recounted 206 papers or articles on FBXW7 gene alteration in colorectal cancer were identified, but were exempted for the reason that they fail to merit the inclusion criteria of our study. This deluge of articles unearthed in this study covered nearly every nook and cranny of the world [87]; gave details of the foremost incident of FBXW7 aberration in colorectal cancer in The US [3], first reported on Arab population with hotspot FBXW7 mutations [87], established the first study on the pervasiveness of FBXW7 mutations in Republic of Korea patients, while [59,92] research on FBXW7 genetic mutation was the first stated data in China and Thailand respectively. Altogether, this data indicates the varying worldwide prevalence's of FBXW7 gene mutations in CRC. Owing to the fact that CRC develops slowly over time from combination of genetic abnormalities and due to failure to identify promptly presenting symptoms with longstanding effects associated with the prompt start of organ metastasis in colon/colorectal cancer, just a limited percentage of patients will be fortunate to get curative surgery at consultation with the surgeon. Hence the need for prognosis-predicting biomarkers such as FBXW7 tumour suppression gene [93–95].

In our current study, the frequency of FBXW7 gene aberration was looked into in 58 studies consisting of 13,974 CRC patients from nations around the world. The overall occurrence of FBXW7 mutation was 10.3 % (95%CI: 8.6–12.4) with $I^2 = 90.50$ %, $P < 0.001$), the male gender has the highest participation rate at 56.0 %. FBXW7 is a tumour suppressor gene that is commonly suppressed in malignant cells, possibly by decreasing c-Myc-T58 phosphorylation, which hampers FBXW7-facilitated c-Myc breakdown [96]. The buildup of c-Myc enhances many productions of TRAIL5 (TNF-related apoptosis-inducing ligand death receptor 5), resulting in more TRAILR5-induced apoptosis, that can potentially be utilized in targeting c-Myc-overexpression of cells in FBXW7-deficient cells, such as CRC [97]. FBXW7 mutation prevalence rate from our study was in conformation with outcomes reported in several data such as in Spain (9.5 %) [64], the US (9.4 %) [60], Brazil (7.0 %) [46], China (11.0 %) [81], Eygpt (9.7) [98], and India (11.8 %) ([99]. The variations noted between the prevalence could be due to several factors ranging from ethnic and genetic predilection to lifestyles, process and method of specimen/sample assortment and topographical settings. The occurrence of FBXW7 mutation/aberration was greatest in patients examined in Russia (19.0 %) and Taiwan (18.8 %) and lowest in Netherland (4.0 %) and the Italy (5.0 %) respectively. Despite the sophisticated advancement in the cancer management using anticancer targeted monoclonal cytotoxic agents, the FBXW7 gene mutation still remain a crucial cause of treatment failure and poor prognosis factor in CRC patients [86,97].

It is generally understood that the occurrence of genomic and epigenetic changes that trigger carcinogenesis are dynamic [100,101]. In our study's outcomes, the greater part of the included patients were in their adulthoods, with many being older than 50 years

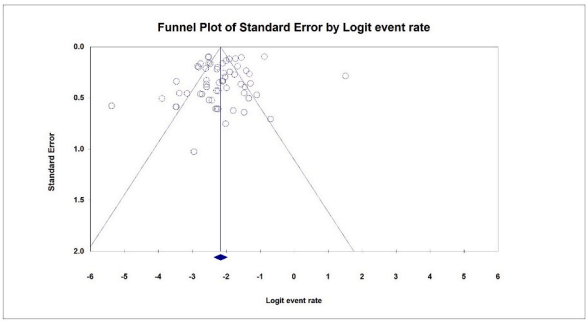

Fig. 6. Funnel Plot. Funnel plot showing no significant publication bias (Egger's p = 0.23771)..

of age, indicating that FBXW7 aberration predominates in adulthood. This latter finding was entirely predictable considering that ageing has in the past and medically been linked with a risk-rise of CRC in numerous research which was exactly as expected given the health historical link with mutation from genetic changes linked with adulthood in various studies [102]. Furthermore, the male recorded the highest FBXW7 mutation rate at 53.9 % and this is in conformity with findings from other papers [103,104]. The latter findings point at the role of gender in cancer and CRC occurrence, but several explanations could be postulated for this finding, stretching from dietetic choices to daily life changes that synergistically transform our biological-genetic makeup [105] which over time or with advancing age leading to deteriorating conditions, thus the "late stage" and "older age" inclination to CRC. As a result, the "late stage" and later age predisposition to CRC.

The crucial involvement of FBXW7 gene in cancer regulation and the proliferation of CRC via its signalling pathways such as expression of Notch and AKT/mTOR on targeted miR-182 and miR-503 cascade indicated that the downregulation or functional loss of FBXW7 gene enhances the successful transformation of polyps to CRC in the colon ([106]. In addition to this latter fact, the very late-stage presentation of patients in the health facility explains the reason the colon (60 %) is the most reported primary site for detection in CRC [107], and similar to findings reported by Refs. [99,108]. Another possible reason would be the classification into colon and rectum only, thus, apportioning a larger part to the colon [109,110]. Unlike if it was sectionized into transverse, ascending, descending, sigmoid, and rectum. Perhaps, the rectum and not the colon would account for the largest primary tumour location site. On intestinal site for location of the tumour, our study's data nonetheless showed that 62 % of the tumour was on the "left side" of the colon and only 38 % was noted on the "right side" of the colon. These were as reported in several published data illustrating the left side of the colon as the most habitable side for CRC location [8,111].

Further subgroup analysis was carried out on pertinent parameters wherein an increasing but steady trend was noted on the "yearly plot" starting from 2018 but fell in 2020 which is likely due to COVID-19 outbreak because of global lockdown on all activities to curtail the spread (Fig. 5). But this increasing trend was very feasible immediately post COVID-19 rules relaxations. The advancement in cancer screening via molecular science i.e., sequencing-base screening like the Next Generation Sequencing NGS could have contributed to the rising figures as more testing and screening capability centres ensue.

Great progress has been achieved in comprehending the underlying pathophysiology of cancer-mutation concept through the usage of molecular gene profiling to recognise possibly unique genetic mutations/aberration and/or biomarkers associated with specific tumour-type especially patients with sporadic CRC. The outcome designated FBXW7 as an independent feature affecting the continued existence (surviving) of patients with CRC, because its aberration has been labeled to be linked with the occurrence, development, and poor prognosis of CRC. Although the FBXW7 gene is part of the F-box protein family with about 40 amino acids motif of the F-box, their mutations are not as vastly reported as members of the MAPK/ERK pathway (or Ras-Raf-MEK-ERK pathway) like the KRAS, BRAF etc. [112]. Having said that, the entirety of the genome evaluation demonstrated that FBXW7 alteration/mutation effects are more recurrently arising than formerly presumed in altered cells. FBXW7 mutations/aberration are often peculiar with colon cancer propagation, engulfing roughly 5–10 % of m-CRC incidents, and were tied with bad prognosmis, notably in the late stages [113].

Future research designed to boost the study of FBWX7 gene mutations in colorectal cancer should emphasize numerous avenues to expand scientific understanding and incorporate the discoveries into clinical practice such as performing multicenter studies to corroborate the prognostic and genetic role of FBWX7 mutations in tumorigenesis, including those with different disease stages and treatment modalities. Furthermore, innovative cellular and molecular techniques in the "omics world of genomics will further reveal the biological pathophysio-pathway underlying FBWX7-driven tumorigenesis and identify potential therapeutic targets, an interesting field for pharmaceuticals. Also, the Incorporation of genomic, transcriptomic, and proteomic data gathered from CRC patients with FBWX7 gene mutations will offer a comprehensive insight into the molecular landscape of FBWX7-altered tumors and their role in the treatment failure rate of CRC. Lastly, inter-researchers and clinicians collaborations and in-partnership industrial sponsors will accelerate the transformation of preclinical screenings and findings into clinical trials assessing FBWX7-targeted therapies in colorectal cancer patients, with a result-yielding boost on patient outcomes and guide on precision medicine for CRC disease.

This research has various merits and strengths. This is, to the best of the authors' knowledge, the foremost systemmatic review and meta-analysis to delve into the prevalence of FBXW7 gene alteration in CRC patients. Furthermore, the use of a precise thorough search strategy guarantees that detailed all-inclusive articles are selected for the study's analysis, thus, ensuing an exact huge population proportion of 13,974. These latter tactics ensure an extraordinary degree of certainty and validity of the study outcomes because the

incorporated study/research had exceptional procedural designs.

Although our study's finding was of high significant and research values, it wasn't without some limitations, most were associated data/records from the selected research literature, like the small sample size, uncompleted data on gender, mean-age, date the research was conducted, tumour variation, and grades. Handful numbers of the analysed articles in our meta-analysis didn't include all of this information or parameters, that accounted for part of the research's dissimilarity.

5. Conclusions

In summary, Being the first systemmatic review and first meta-analysis study to illustrate the prevalence and hallmark effect of FBXW7 aberration in colorectal cancer patients, our study provided a fantastic result. The overall prevalence of FBXW7 gene mutation was 10.3 % and differs country-wise, but with increasing trend till present. Here, FBXW7's position and occurrence as a tumour suppressor gene has been extensively explored. Via the genetic mutation or loss of FBXW7 role as tumour suppressor, many cancer including colorectal carcinoma could easily proliferate to become a deadly poison to preventing a healthy state of life in affected individuals. Lastly, when the outcomes of our analysis were contrasted to already published/existing records, it revealed that the occurrence of these mutations/aberrations observed in our study was similar with the findings of already published studies.

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Institutional review board statement

Not applicable.

Informed consent statement

Not applicable.

Ethics statements

Not applicable.

Data availability statement

All data accessed and analysed in this study are available in the article and its Supplementary Materials.

CRediT authorship contribution statement

Hafeez Abiola Afolabi: Writing – review & editing, Writing – original draft, Software, Methodology, Data curation, Conceptualization. **Salzihan Md Salleh:** Writing – review & editing, Supervision, Software, Project administration, Funding acquisition, Conceptualization. **Zaidi Zakaria:** Writing – review & editing, Supervision, Software, Methodology. **Ch'ng Ewe Seng:** Writing – review & editing, Software, Methodology, Data curation. **Norasikin Mohd Nafi:** Writing – review & editing, Software, Methodology, Data curation. **Ahmad Aizat Bin Abdul Aziz:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Yusuf Wada:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Ahmad Adebayo Irekeola:** Writing – original draft, Software, Investigation, Formal analysis, Data curation. **Sameer Badri Al-Ml-hanna:** Writing – review & editing, Writing – original draft, Software, Formal analysis, Data curation. **Ali Mussa:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31471.

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