REVIEW

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The Association between ABO Blood Group and the Risk of Colorectal Cancer: A Systematic Literature Review and Meta-Analysis

Mansour Bahardoust[1,2], Gelayol Barahman[3], Aryan Baghaei[4], Parmid Ghadimi[5], Mir Houman Asadi Shahir[6], Mahsa Najafi Kandovan[7], Adnan Tizmaghz[1]*, Faranak Olamaeian[1], Ali Tayebi[1]*

Abstract

Introduction: Recently, studies have investigated the relationship between blood types and cancers. Contradictory results regarding the relationship between blood group type and colorectal cancer(CC) have been reported. The purpose of this study was to systematically investigate the distribution of ABO blood group frequency and evaluate its relationship with CC. **Material and Methods:** To conduct this systematic meta-analysis, we searched PubMed, Scopus, Web of Science, and Google Scholar databases using appropriate MESH terms until July 2022. All observational studies which assessed the ABO blood group frequency distribution and the association between ABO and CC were included. The Risk of Bias Assessment tool was used to assess the quality of studies. A random model was used to estimate the odds ratio (OR). The Egger test was used to assess the publication bias. **Results:** Overall,14 studies (413,132 patients) were included. According to the pooled estimation, blood groups A, B, AB, and O frequency in patients with CC were 37%,18%,9%, and 31%, respectively. The OR of CC in people with the A blood group was higher than in the other groups (OR: 1.11, 95% CI:1.03,1.19, P:0.001). In contrast, the OR of CC in people with the O blood group was significantly lower than in other blood groups (OR: 0.93, 95% CI:0.83,0.97, P:0.001). No significant relationship was observed for B and AB blood groups with CC. **Conclusions:** This Meta-analysis showed that blood group type A has a greater risk of developing CC, while blood group type O was associated with lower chances of CC.

Keywords: Colorectal cancer- ABO blood group system- prevalence- systematic review- Meta-Analysis

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Introduction

Colorectal cancer (CC) is the third cause of cancer death and the fourth diagnosed cancer in the world (Araghi et al., 2019; Wong et al., 2019). The incidence rate of this cancer is rising in developing countries. Both environment and heritage can be a cause of this disease (Rawla et al., 2019). Most patients are sporadic in their family, and just 15-20 percent have a family history of the disease (Senger et al., 2021). There are many related factors for colorectal cancers, such as age, gender, geography, obesity, diet, and heritage (Keum and Giovannucci, 2019; Sawicki et al., 2021). Nonetheless, the environment and heritage have a limited effect on disease development, and most causation is unknown. ABO blood group system was identified in 1900. Blood groups are classified based on the existence or inexistence of A and B antigens on erythrocytes, which nowadays it's revealed that statistically are linked to many diseases. During past decades many studies assessed the effect of ABO on diseases, particularly cancers, but there is inconsistency in the results (Kahramanca et al., 2018). The role of blood groups in developing cancers was revealed in an Arid study in 1953 that A blood group is related to gastric cancer. Nowadays, the effect of the A blood group on developing gastric, uterus, neurological malignancies, kidney cancers, B blood groups in the esophagus, and O blood groups in melanoma cancers is revealed (Gömeç and Özden, 2021; Kahramanca et al., 2018; Senger et al., 2021; Slater et al., 1993; Wei et al., 2019; Zhang et al., 2022). Many studies have been done to assess the effect

*[1]Firoozabadi Clinical Research Development Unit (F A CRD U), Iran University of Medical Sciences (IUMS), Tehran, Iran. [2]Department of Epidemiology, School of Public Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran. [3]MD, Tehran Azad University of Medical Sciences, Tehran, Iran. [4]Student Research Committee, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran. [5]MD, Iran University of Medical Sciences, Tehran, Iran. [6]Resident of Radiology, Rasoul-e-Akram Hospital, Iran University of Medical Sciences, Tehran, Iran. [7]Department of General surgery, School of Medicine, Iran University of Medical Sciences, Tehran, Iran. *For Correspondence: Tayebi81@gmail.com, adnan_ti@yahoo.com*

of blood groups on developing diseases and, among them, cancers (Abegaz, 2021; Bahardoust et al., 2019; Yingying Mao et al., 2019; Song et al., 2019; Yu et al., 2020). But there is a lot of inconsistency between findings. Hence we conducted a systematic review and meta-analysis study to assess the effect of ABO on colorectal cancers in various studies.

Materials and Methods

A meta-analysis and systematic review were conducted to assess the frequency of blood groups and the Association between ABO blood groups and the risk of CC in observational studies until July 2022. The study was conducted according to a guideline for systematic review studies (PRISMA) (Page et al., 2021). A PRISMA diagram was also used to include studies.

Methods for Literature Search

At first, two investigators (MB) and (MN) searched all data and sources. After detecting the search strategy, PubMed, Scopus, Web of Science, and Google Scholar databases were searched. The last search was done on July 7, 2022. All studies were conducted on human subjects, but editorial comments and studies in other languages were included. To find related studies, these keywords were Used: ABO Blood Group System" OR "ABO Blood Group " OR ABO* OR "ABO Blood-Group Systems" OR ''H Blood Group System OR ABO blood Type '' OR '' Blood Type) AND ("Colorectal Neoplasm" OR "Colorectal Cancer" OR ''Colorectal Tumors'' OR ''Colorectal Cancers'' OR '' Colorectal Carcinoma'' OR ''colon cancer '' OR ''Rectum cancer'' Colorectal Neoplasm *.

Eligibility Criteria and Data Extraction

All observational studies (cohort or case-control studies) assessed the ABO blood group frequency distribution and the association between blood group type and colorectal cancer. The frequency of blood group type distribution, the number of assessed subjects in each study, gender distribution, age distribution, odds ratio, and the risk of CC were assessed in this study. The studies were screened by title and then by full text. The studies with inclusion criteria were included, and the others were excluded. Exclusion criteria include other languages, review studies, laboratory and animal studies, genetic relation meta-analysis, and full-text unavailability. In the first step, 4378 studies were extracted, duplicated references (1404), other languages (25), commentary, and the case reported (84) were excluded. The title, objectives, and abstracts assessed the remaining references (2865). After deleting 2254 references, the full text of 611 studies was assessed, of which 14 observational studies assessed the distribution of blood group frequency among CC patients and were included in final analyses. 11 studies evaluated the relationship between blood groups and CC Figure 1.

After omitting duplicates and cleaning, two investigators independently screened the references. Addressed variables such as the method of study, year, authors, age ranges, gender distribution, the frequency of each blood group, the total number of participants, and the measures of the relationship between blood groups and CC (OR and 95% confidence interval) and quality, were extracted. In case of any disagreement about a variable during the data extraction proses, it was dialed by negotiation until achieving agreement. After extracting and cleaning, all data were analyzed by STATA 17. Furthermore, raw data for any study were extracted into meta-analyses and reanalyzed.

Quality Assessment of Studies

To assess the quality of studies, The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in the Meta-Analysis checklist for case-control studies and the Newcastle-Ottawa Quality Assessment Form for Cohort Studies were used. (Penson et al., 2018; Peterson et al., 2011) These checklists assess the quality of studies in 3 parts: Selection, Comparability, outcome/exposure, and scoring of each item. Cohort and case-control studies raged 0 to 9; classification of scores contains good (3 or 4 scores for selection and 1 or 2 stars for comparability and 2 or 3 stars for outcome/exposure), fair (2 scores for selection, 1 or 2 stars for comparability and 2 or 3 stars outcome/exposure) and poor (0 or 1 star for selection, 0 stars for comparability and 0 or 1 stars for outcome/exposure).

Statistical Analysis

At first, all studies were analyzed to assess the blood group ratio among CC patients and the Association between blood group type and colorectal cancer. The number of patients and the ratio of blood group frequency, A, B, AB, and O, were extracted for each study. Relation measures like OR was extracted in studies with a 95% confidence interval. To estimate the frequency of each blood group, we used the metaprop command, and if there were any zero incidences among the included studies, Freeman-Tukey double. For case-control studies that reported the frequency of blood groups in case and control groups, the frequency of these groups and OR and confidence interval were extracted from each group. A random model was used to estimate the odds ratio (OR). According to the variances of each study, the weight of each firstly was calculated as inversion variance based on the fixed effect model. After calculating the prevalence and weight of each study, we used the combined techniques to determine the heterogeneity within and between(Random Effect Method). We proceeded to calculate Dersiminian and Laird. Inter-study. Cochran Q and I2 tests assessed heterogeneity between studies. I2 values of 0% indicate no heterogeneity, 25% low, 25 to 50% moderate, and 50% high heterogeneity. After approving the heterogeneity, the effect size of the studies was calculated. To assess the publication bias, the Egger test was used. The trim and fill test was used in case of publication bias, and results were recalculated after excluding studies with publication bias. Poole OR with a 95% confidence interval was used to calculate the total effect. All analyses were done by STATA 17.0.

Ethics approval and consent to participate

Not required as data is not individualized, and primary data must be collected. Not required as data is not individualized and primary data needed to be collected.

Consent for publication

The corresponding author accepts responsibility for releasing this material on behalf of all co-authors.

Results

Fourteen studies with 413,132 overall patients were included. The mean age was 61.63±8.56 years. 55.2% were male. Three of them were case-control, and 11 of them were cohort. According to the quality assessment checklist, most of them were high-quality studies (Table 1).

Frequency of Blood Group Type

According to findings, the type blood group was the most frequent blood group among CC patients (37%, 95% CI:19-55). The frequency of O and B types were (31%, 95% CI:23-39) and (18%, 95% CI:11-26), respectively. AB type blood group had the least frequent among them (9%, 95% CI:4-13). The pooled estimated frequency distribution of the ABO blood group type is shown in Figure 2.

Blood Type A with CC

Some 11 studies assessed the association of blood type A with CC. The pooled estimated result revealed that the chance of CC for the type A blood group is higher than in the non-A groups (OR: 1.11, 95% CI:1.03,1.19, P:0.001) (Figure 3).

Publication bias had a negative effect on overall estimation in studies that assessed the blood type A association between CC (Egger test: 1.43, p: 0.005, 95%CI: 0.57,2.30), (Figure 7 _ Curve A). Since we observed essential Publication Bias for address, we used to trim and fill methods. Based on our analysis, three studies were censored due to publication bias. After considering their effect in the overall estimate, the pooled effect was 1.16 (OR:1.16, 95%CI: 1.04, 1.29, P:0.012).

Blood Type B with colorectal cancer

Although the odds of CC for the type B blood

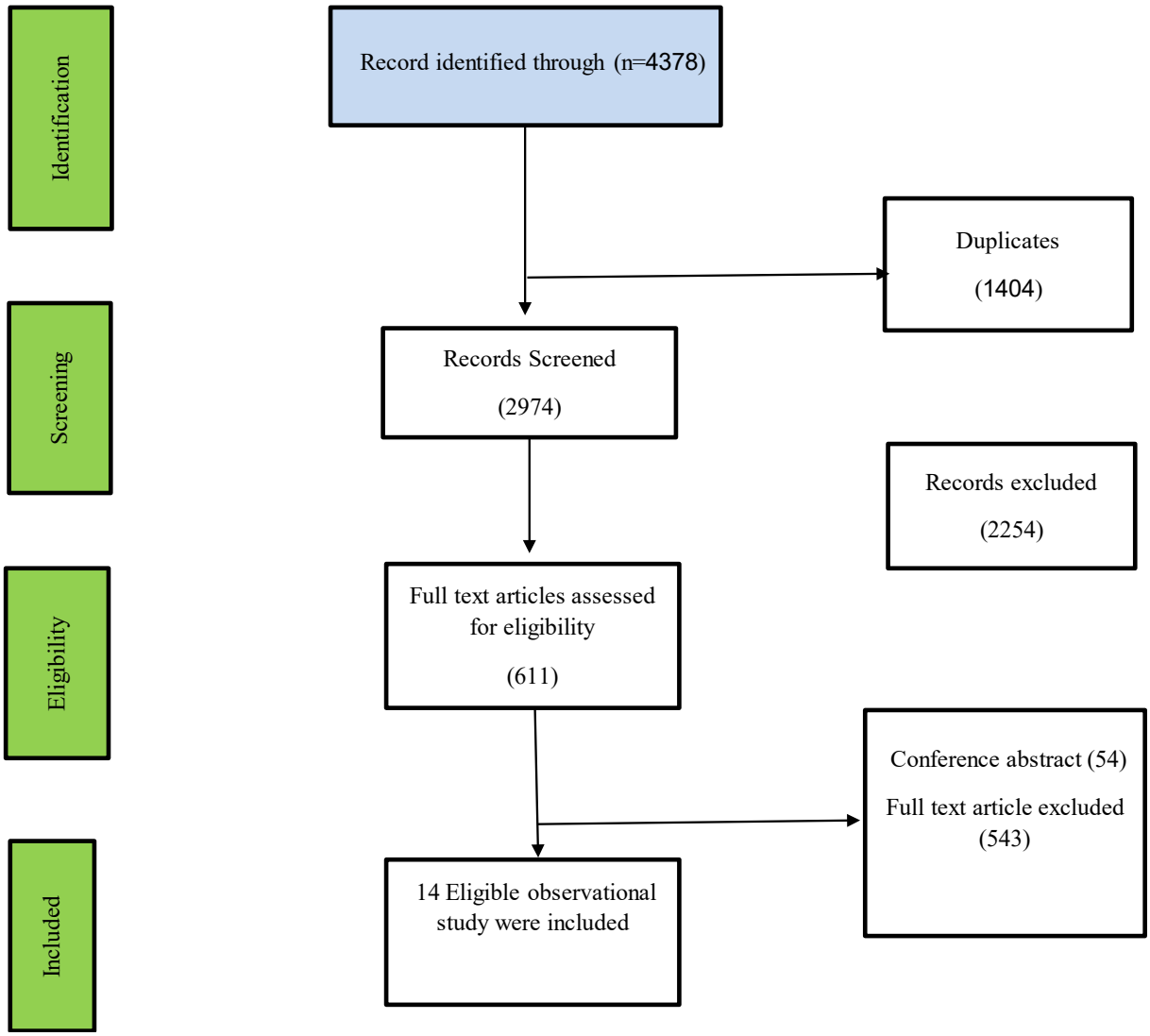

Figure 1. PRISMA Flow Chart of the Included Studies

Table 1. Characteristics of the Studies Included in the Meta-Analysis

Quality	Sex (Male)	Mean Age (Year)	Sample size	Study design	Year	Author
Fair	103 (51.8%)	61.6	199	retrospective cohort	2022	A Al-Sawat (Al-Sawat et al., 2022)
Fair	43 (52.4%)	59.56	82	retrospective cohort	2000	T Nakagoe (Nakagoe et al., 2000)
Good	865 (55.6%)	63.5	1,555	retrospective cohort	2014	X Cao (Cao et al., 2014)
Fair	391 (52.3%)	60.58	747	retrospective cohort	1986	TB Halvorsen (Halvorsen, 1986)
Good	1532 (53%)	55.64	2891	Cohort Study	2017	JY Huang (Huang et al., 2017)
Good	58477 (55.7%)	62.4	104,885	Cohort Study	2011	H Khalili (Khalili et al., 2011)
Good	955 (59.9%)	59.54	1,620	case - control	2012	Y Urun (Urun et al., 2012)
Good	263 (52.6%)	51.5	500	case - control	1984	MMA Mousseron (Mousseron-Canet, 1984)
Good	4421 (51.3%)	64.56	8,625	retrospective cohort	2021	H Furuhashi (Furuhashi et al., 2021)
Good	714 (54.3%)	59.3	1,314	retrospective cohort	2014	B Li (Li et al., 2014)
Good	461 (60.1%)	65.95	767	retrospective cohort	2021	M Gömeç (Gömeç and Özden, 2021)
Good	663 (51.3%)	60.21	1,290	prospective cohort	2015	W Sun (Sun et al., 2015)
Good	1116 (54.1%)	61.2	2,063	case - control	2012	AS Zhivotovskiy (Zhivotovskiy et al., 2012)
Good	3073 (52.31%)	60.33	5875	prospective cohort	2016	SK Vasan (Vasan et al., 2016)

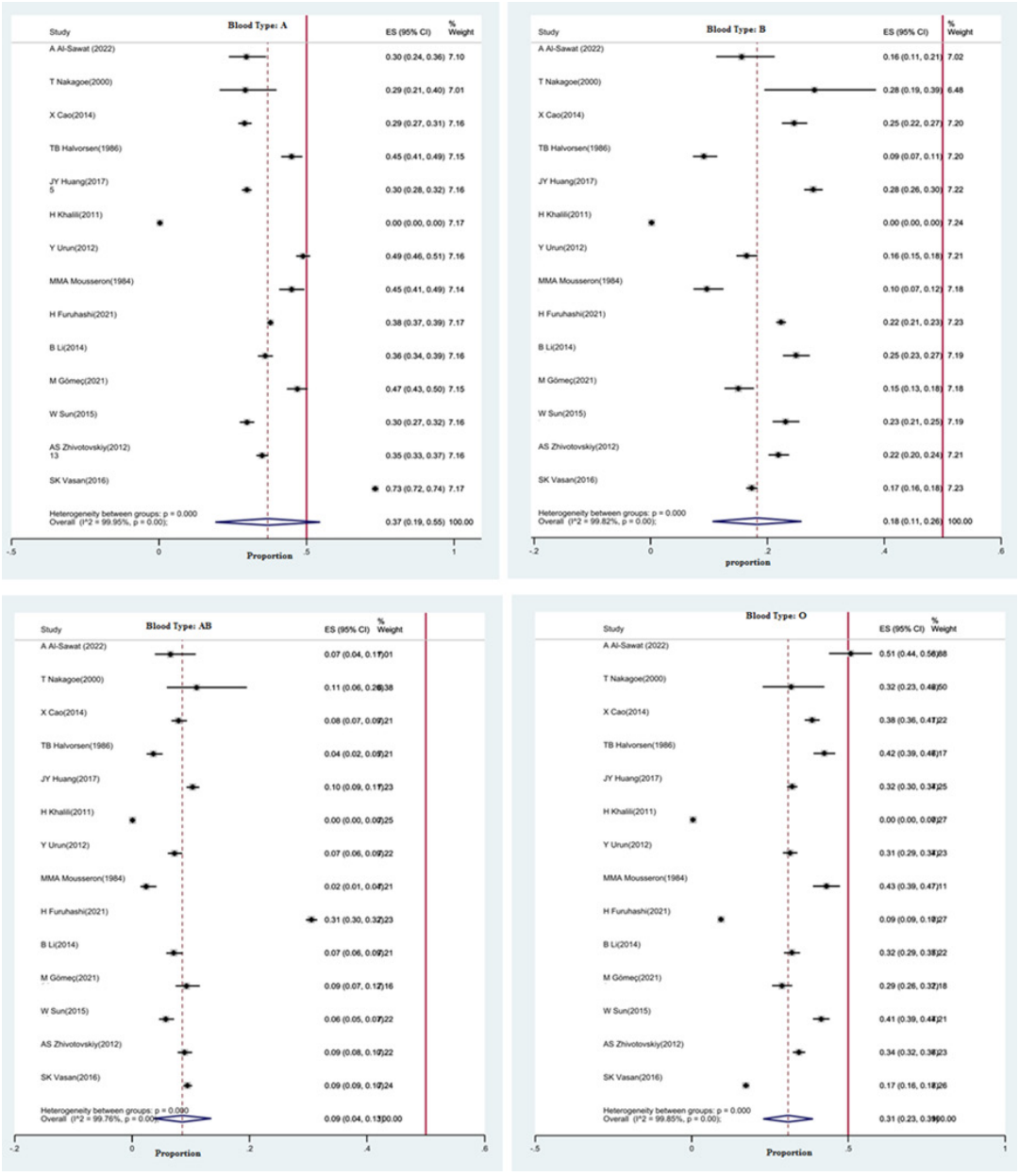

Figure 2. Forest Plot of Frequency Distribution of ABO Blood Groups Type in Colorectal Cancer Patients.

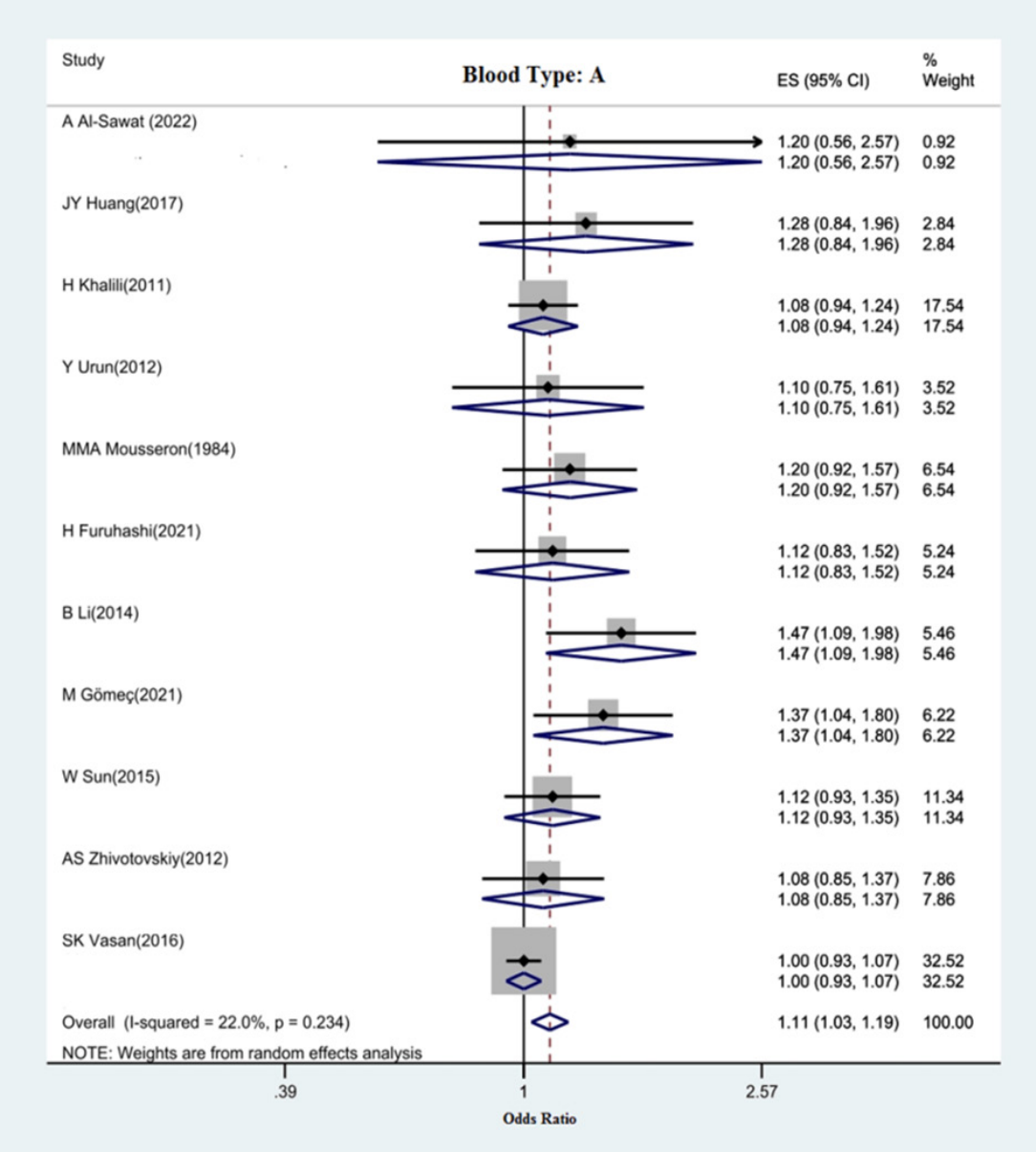

Figure 3. Forest Plot of Association between Blood Type A and CC

group were more than none B groups, the pooled effect results indicated that this difference was not statistically significant (OR: 1.04, 95% CI:0.97,1.11, P:0.48) (figure 4). Publication bias had no significant effect on the total effect in studies that evaluated the association between blood type B and CC. (Egger test: 1.156, p: 0.108, 95% CI: -0.31, 2.61). (Figure 7 _ Curve B)

Blood Type AB with colorectal cancer

There was no significant association between blood type AB and colorectal cancer. (OR: 1.07, 95% CI: 0.97, 1.18, P: 0.56) (Figure 5). There was no significant effect of publication bias on the overall estimate of this association. (Egger test: 0.78, p: 0.34, 95% CI: -0.95, 2.52) (Figure 7 - Curve C).

Blood Type O with colorectal cancer

The pooled effect revealed that the chance of CC was statistically significant among people with Blood Type O compared to none O (OR: 0.93, 95% CI: 0.83, 0.97, P:0.001). (Figure 6). There was no substantial effect of publication bias on the overall estimate of the relationship between blood type O and CC. (Egger test: -0.99, p: 0.097, 95%CI: -1.44, 0.56). (Figure 7 _ Curve D)

Discussion

Many studies have been carried out to investigate the association between the ABO blood group and cancers. In this study, we first evaluated ABO blood group type frequency and its association with the risk of CC through a systematic review and meta-analysis. However, in a study Zhang et al., (2014). Investigated the relationship between blood group type and colorectal cancer; however, their study was heterogeneous due to the difference in studies and the low sample size of the included studies. Many original studies have evaluated the relationship between blood type and CC in recent years.

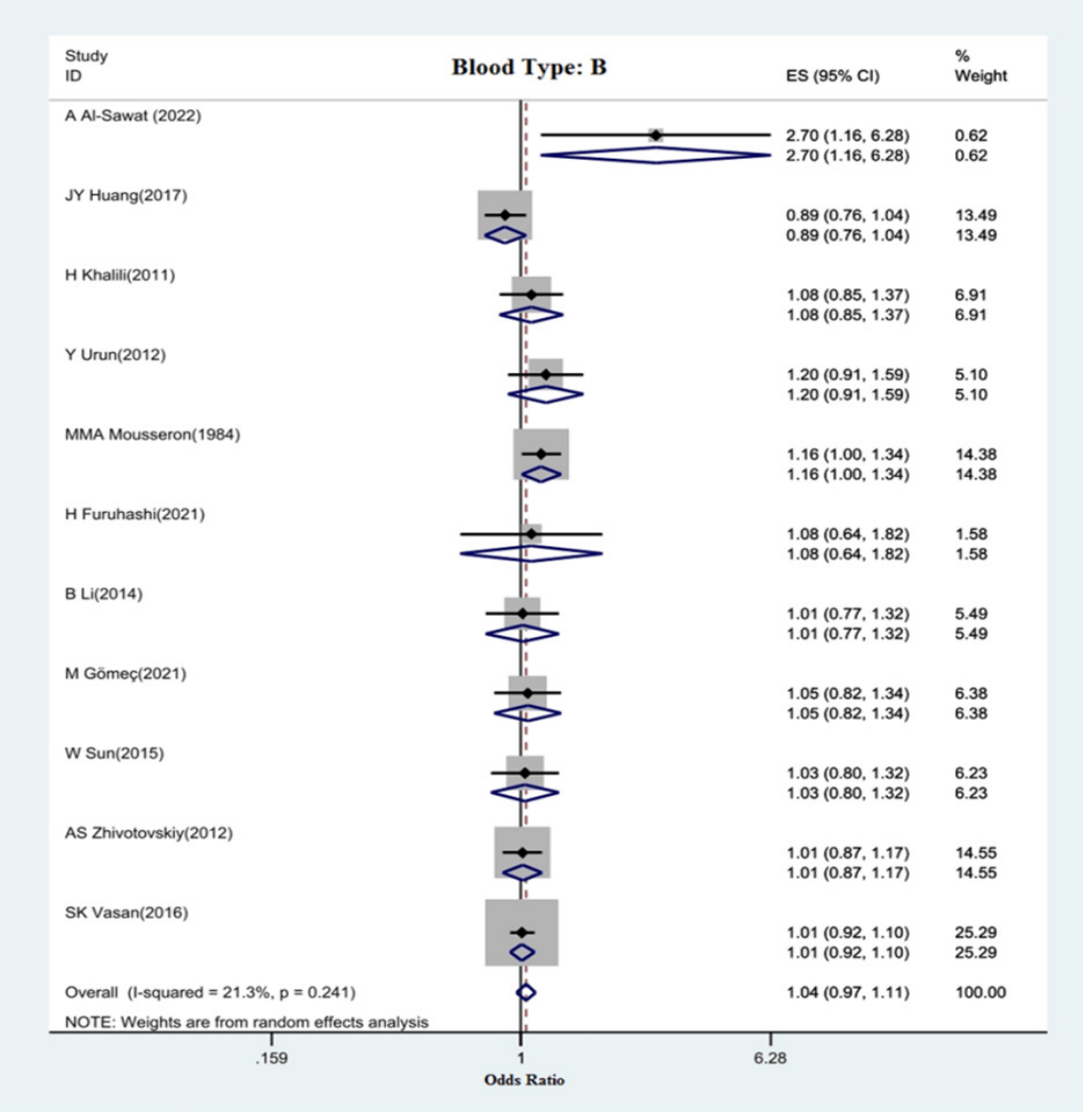

Figure 4. Forest Plot of Association between Blood Type B and CC

After analyzing the others, it was revealed that the type A blood group frequency was high among CC patients, and the type AB blood group was fewer than the other types, which consisted of Zhang et al., (2014) study's results indicated that the type A blood group was higher than the other groups among CC patients. Also, in Zhang et al., (2022). Study, a retrospective study that was done on 64 pretreatments, and colorectal SRCC specimens, it was shown that the A-type blood group was predominant, and after that, the type B blood group in colorectal cancer, which was in coordination with our study. While, In Praveen et al., (2011) study, which was done on 54 patients with cc, the type B blood group was predominant (44.4%), followed by type A (24.1%) in patients; this difference can be due to the limited sample size in their study.

The association between blood type and the risk of a number of other cancers has also been reported. In a review study, Mao et al., (2019) showed that blood type A was significantly associated with an increased risk of gastric cancer. In a systematic review, Liu et al., (2013) showed that the number of blood type O patients in patients with HCC was lower than in healthy populations. In our study, the frequency of patients with his blood type was less in patients with CC.

The pooled estimation of our study showed that the chance of developing CC was significantly related to blood types A and O, so the risk of developing CC was higher in people with type A blood. While the risk of CC was lower in people with blood type, O. AB and B blood groups had no significant relationship with CC. These results can be justified due to the expression of certain biomarkers related to blood groups. In 2021, studies in the in vitro phase showed that ABO blood group antigen might become a powerful tool for therapy or risk factor for tumors in patients (Luo et al., 2021). In a cohort study, in 1,555 patients with colon cancer with a long follow-up period, Cao et al., (2021) showed blood type as a de facto risk factor for CC cancer which confirmed the results of our study. We assume that the high rate of CC in people with blood type A, like stomach cancer (Yu et al., 2020), in addition to changes in genes, may be related to the high level of substance A in saliva among people with blood type A. Substance A in saliva can affect the intestinal mucosa and lead to an increased possibility of malignant

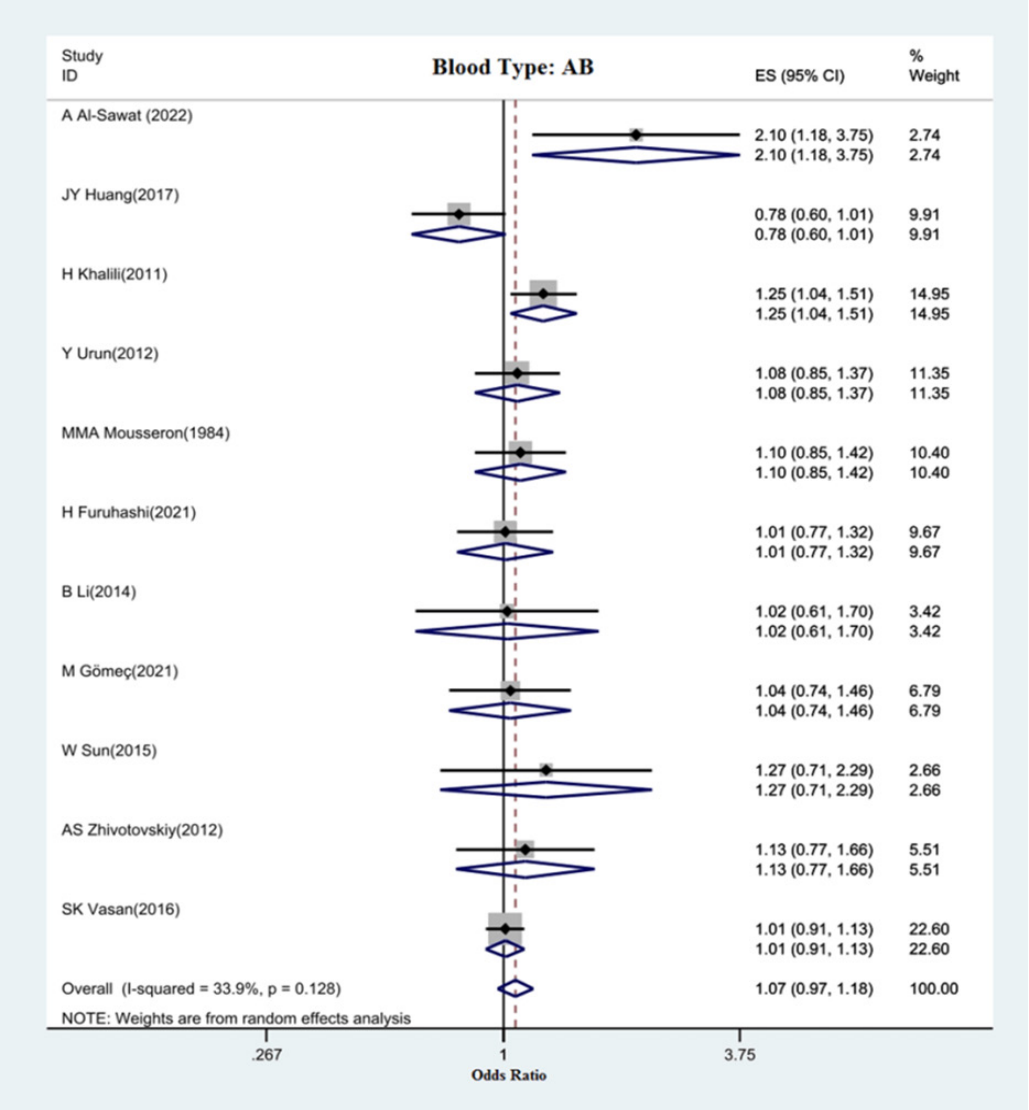

Figure 5. Forest Plot of Association between Blood Type AB and CC

change in the CC. According to this hypothesis, people with blood types B and O should have a lower risk of CC; although the results of our study confirm this for blood type O. Still, in our study, there is no correlation between the risk of colon cancer and the blood group B was not observed, which reveals the need to conduct basic studies in this field in the future.

In conclusion, our study showed an association between the ABO blood group and CC risk and prognosis. The risk of developing CC was high in people with blood type A and lower in people with blood type O. However, the biological mechanism of this relationship is of particular importance for a more comprehensive investigation, which may provide new and more up-to-date information that can explain the biological behavior and characteristics of malignant tumors.

Author Contribution Statement

M.B.: data collection, data analysis, manuscript writing; MN: data collection, data analysis, manuscript writing; M.B.: conceptualization, manuscript editing, supervision; M.B: methodology, manuscript editing; A.T.: project development, methodology, funding acquisition, manuscript editing; F.O.: project development, methodology, manuscript editing; M.H.A.S.: manuscript editing, supervision; All authors reviewed the manuscript..

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None.

Registering dataset

Therefore, the study included secondary data analysis doesn't require approval from the scientific body.

Ethics approval

Ethical approval was not required for the present study because data was retrieved and synthesized from the already published studies (secondary data analysis).

Conflict of Interest

None.

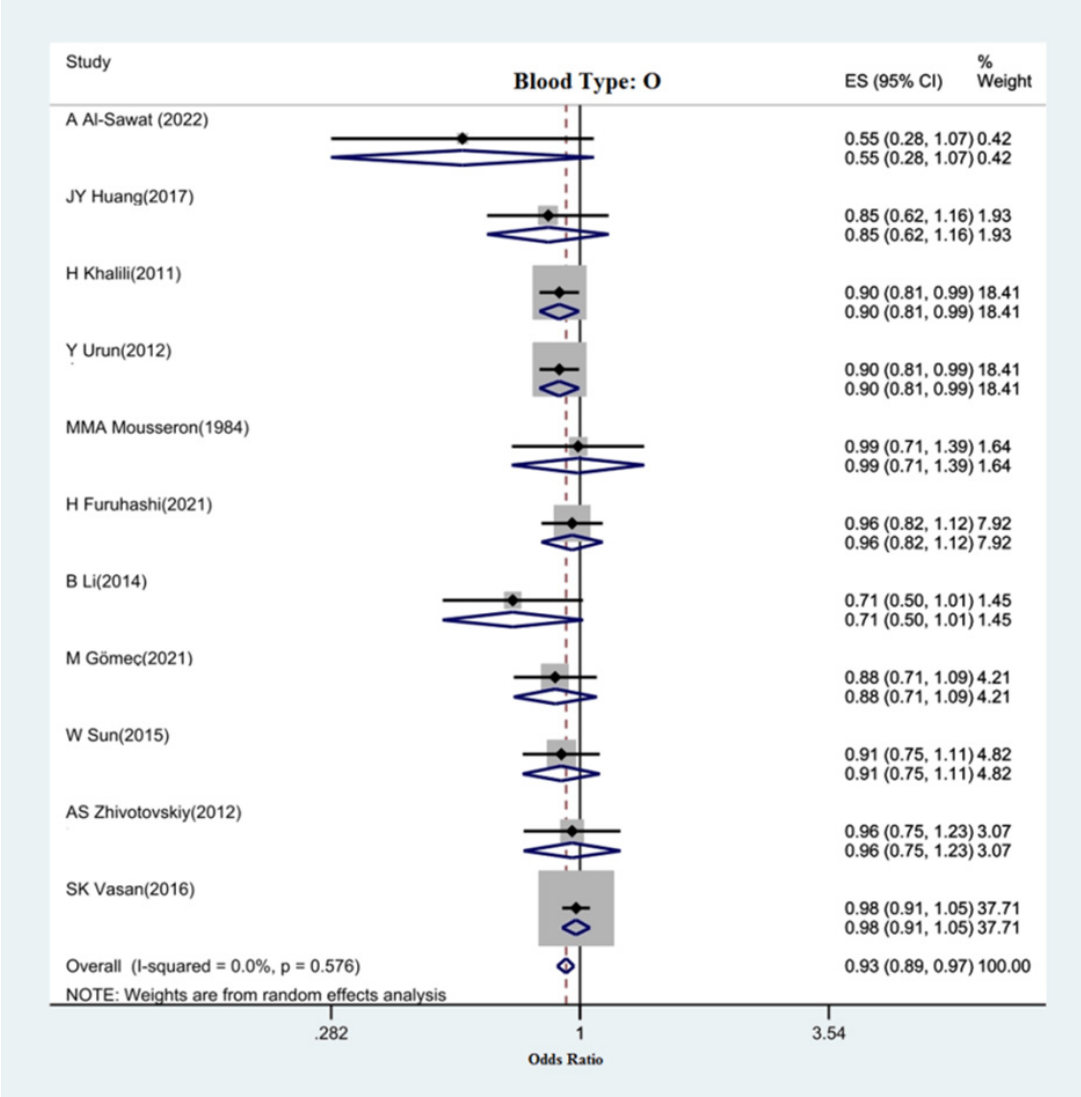

Figure 6. Forest Plot of association between Blood Type O and CC

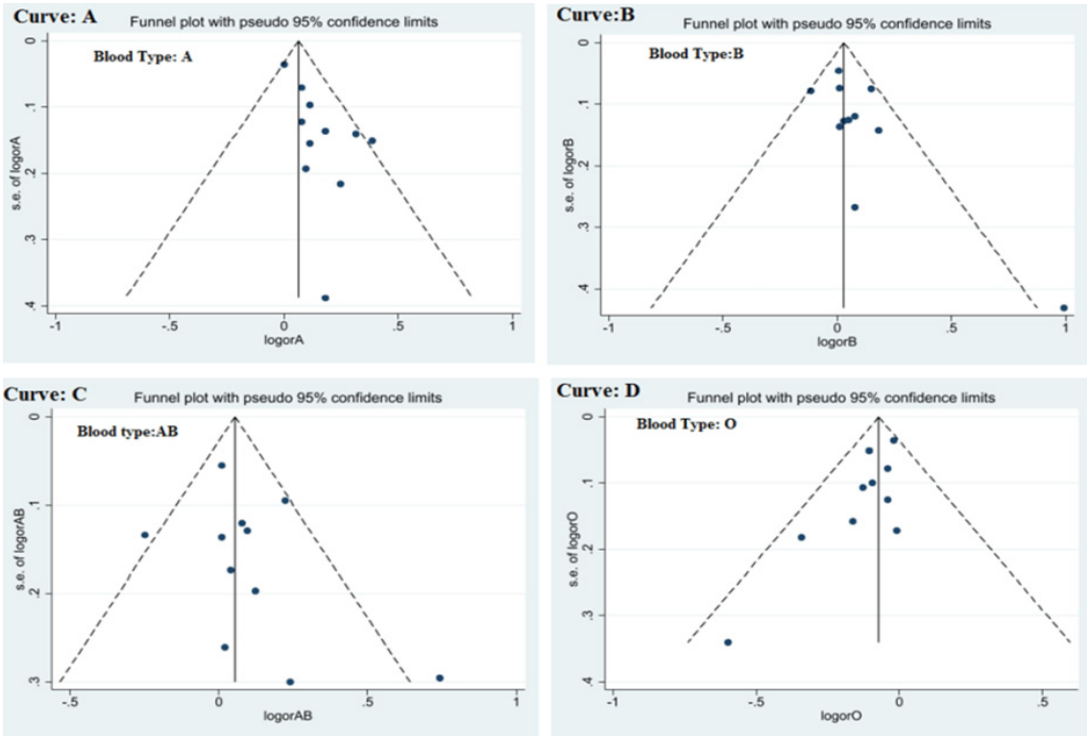

Figure 7. Publication Bias Assessment of ABO Blood Group

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