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Research Paper

ABO/Rh Blood Group and Cervical Cancer Survival: Results from Our Own and Other Studies

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Abstract

Background: Cervical cancer is the most common genital cancer worldwide and is mainly caused by a persistent human papillomavirus infection. Well-known prognostic factors are age, histology, stage, stromal invasion, tumor size, and tumor grade. The relationship between the ABO and Rh system with cervical cancer has been studied since the 1950s, though without obtaining clear results. Here we investigated the association between the ABO blood group and Rh system and consecutively treated cervical cancer patients in our department.

Methods: Clinical charts of cervical cancer patients treated and followed from 2010 to 2021 were checked for inclusion and exclusion criteria. Clinical and pathological data were recorded in a separate, anonymous, password-protected electronic database. All relevant data were extrapolated and used for final analysis.

Results: A population of 143 cervical cancer patients was analyzed in this study. 47.6% (68/143) were blood group O, 36.4% (52/143) were blood group A, 8.4% (12/143) were blood group AB, and 7.7% (11/143) were blood group B. 14.9% (21/141) were RhD negative, while 85.1% (120/141) were RhD positive. No significant association was found between the ABO group and survival. However, patients with blood types B and AB had a higher BMI than the other blood types. RhD-negative patients exhibited a lower age at diagnosis (P=0.035) and had a higher overall survival compared to RhD-positive patients.

Conclusions: The RhD factor appears to influence cervical cancer OS, but the data are too weakly significant to draw a definitive conclusion. Further studies with larger samples are needed to confirm this finding and to investigate the true impact of blood groups in female cancers.

Keywords: ABO blood group, Rh, cervical cancer, survival, age, hypertension

Introduction

Cervical cancer (CC) is the most common genital cancer and the fourth most frequent female cancer, with approximately 604,000 new cases and 342,000 deaths in 2020 worldwide [1]. It is most frequently diagnosed in women with an average age at diagnosis of 50 [2] and presents with diverse histological types. Squamous cell carcinoma (SCC) is the predominant histological variant, representing approximately three-fourths of all CC cases. Adenocarcinoma contributes to 10-15% of cases, while the remaining 10-15% are categorized under other or unspecified histologies [3]. The main cause of CC is a persistent infection of the human papillomavirus (HPV), which can be detected in 99.7% of patients affected. It is a

sexually transmitted infection, often contracted during early adulthood [4], but the introduction of the Pap smear in 1950 by George Papanicolaou is considered the paramount event that reduced CC [5]. HPV persistence is also the principal factor associated with an increased risk of recurrence of high-grade cervical dysplasia after laser conization and the loop electrosurgical excision procedure [6,7]. Nowadays, CC is considered a preventable disease, thanks to both effective screening strategies and vaccination against the most carcinogenic HPV strains [8]. Several studies have shown that HPV vaccines are effective in preventing infection and precancerous lesions thanks to a cross efficacy against non-vaccine HPV types [9]. Thus, HPV vaccination is offered free of charge in some countries after excisional treatment of a high-grade lesion to prevent recurrence. Moreover, there are also very rare histotypes unrelated to HPV such as gastric, mesonephric, neuroendocrine, carcinosarcoma, cervical adenoid carcinoma, primary lymphoma and melanoma of the cervix [10-12]. CC treatment depends on many factors, including the histotype, stage, age, and the patient's desire for parenthood, and can vary from simple conization to radical hysterectomy surgery or chemo- and radiotherapy [13, 14]. Well-known prognostic factors include age, histology, the International Federation of Gynecology and Obstetrics (FIGO) stage, deep stromal invasion, tumor size, tumor grade, metastasis, surgery, chemotherapy, radiation sequence with surgery and lymph node dissection [15]. Since the 1950s, when the percentage of blood group A was found significantly higher among CC patients compared to the general population [16], the relationship between the ABO/Rh system and CC has been investigated, though without obtaining clear results (Table 1). ABO blood group antigens are complex carbohydrate molecules expressed in red blood cells and in other cell lines and tissues. Growing evidence highlights that ABO antigens, in addition to their key role in transfusion medicine, also interplay with the pathogenesis of many human disorders, including neoplastic diseases [17]. Evidence of an association between ABO blood group antigens and various types of cancers has been investigated by several studies [17-23]. The relationship between genetic variants of the ABO locus and the mechanism by which the ABO blood group is at interplay with cancer development and progression remains an open question. Alterations in the inflammatory state due to ABO blood group antigens provide a potential mechanism by which blood type may affect the progression and spread of malignancy. The inflammatory response plays crucial functions in various stages of tumor formation, and it also has an impact on immune surveillance and treatment response [24]. Previous studies from our group evidenced the relationship between the ABO group and gynecological cancer, specifically in ovarian [12] and endometrial cancer [23]. Nevertheless, there is scarce knowledge about the correlation between the oncological outcome of CC and the ABO blood group [25, 26].

In this study, we employed a retrospective analysis to investigate the relationship between the ABO/Rh blood group and the outcome of CC patients consecutively treated in our Gynecologic Department.

Materials and Methods

Patient characteristics

Our study was designed following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [27], and was approved by the Provincial Ethics Committee of Reggio Emilia (2017/0112372) on 11/27/2017.

Written informed consent was obtained from all participants to use personal non-sensitive data at hospital admission, in agreement with the guidelines on good clinical practice (DL 06/11/2007) and the European General Data Protection Regulation (EU GDPR 2016/679). The relevant ethics committee of the Area Vasta Emilia Nord approved the protocol of this study.

All patients with cervical cancer were treated and followed up at the AUSL-IRCCS of Reggio Emilia (Italy) from 2010 to 2021 and consequently treated in our department based on the ABO/Rh information available.

Patients with previous or concomitant cancers and patients with severe co-morbidities that posed an imminent risk to survival were excluded from the study. Instead, we included patients with the most common comorbidities such as hypertension, obesity, diabetes.

Clinical and pathological data were recorded in a separate, anonymous, password-protected electronic database. All relevant data were extrapolated and used for final analysis.

Treatments

Treatment was planned based on the stage of CC and risk factors such as size of the tumour, stromal invasion, tumor differentiation, lymph-vascular space invasion (LVSI), status of resection margins, status of parametria and vaginal cuff, status of lymph nodes. Patients with FIGO stage IA1 without LVSI were treated with conization only if negative margins or with simple hysterectomy. In case of LVSI simple hysterectomy was associated with systematic pelvic lymph adenectomy (PLND) ± systematic para-aortic

lymph adenectomy (PALND). Patients with FIGO stage IA1 CC underwent to radical or simple hysterectomy + PLND ± PALND. Patients with FIGO IB2 or IIA underwent to radical hysterectomy + PLND ± PALND. Patients with FIGO stage IB2 or IIB or IIIB underwent to chemoradiotherapy (CRT), and radiation was tailored according to surgical staging or positron emission tomography finding. Rarely neoadjuvant chemotherapy (CHT) followed by surgery or radiotherapy was performed. Patients with FIGO IVA underwent to CHT followed by radiotherapy and FIGO IVB patients underwent CHT only.

Table 1. The ABO blood groups and RhD system in cervical cancer patients: results reported in literature

YEAR	FIRST AUTHOR (reference)	ETHNICITY	SAMPLE SIZE	AGE (n)	FIGO STAGE (n)	0 % (n)	*P value*	A % (n)	*P value*	B % (n)	*P value*	AB % (n)	*P value*	CONCLUSION
1957	Segi M et al. (16)	Japan	1534	-	-	29.1% (446) Cervical cancer	-	41.7% (60) Cervical cancer	0.01	19.8 (304) Cervical cancer	-	9.4% (144) Cervical cancer	-	The percentage of **group A cases was significantly higher among cancer** patients.
						30.5% (161461) Controls		38.3% (203255) Controls		21.8% (115416) Controls		9.4% (49914) Controls		
1962	Mitra S et al. (38)	India	521 Cervical Cancer	-	-	32.28% (172)		22.78% (114)		38.31% (204)		6.63% (31%)		There was **no significant relationship of ABO blood groups with cervical cancer.**
			2.273 Controls			32.60 % (740)		26.10% (594)		34.20% (777)		7.10% (162)		
1963	Garriga R et al. (28)	United States of America	123	-	I (67)	**Good response** 84.2% (48)		**Good response** 66.6% (28)		**Good response** 63.3% (14)				**0 group had a higher 3-year survival rate by about 20%** than groups A and B combined.
							A+B versus O: P> 0.02		A versus 0: P= 0.1		B versus 0: *P=0.2*	Sample too small to perform analysis: 2/123 (1.6%)		**B group exhibited** a trend toward **poorer response than group A**.
					II (54)	**Poor response** 15.8% (9)	-	**Poor response** 33.3% (14)		**Poor response** 36.4% (8)				
1965	Rotkin ID (44)	United States of America	185 Cervical Cancer	48.7 (range 22-79)	185 Cervical Cancer	50% (93) Rh^+37.8% (70) Rh^-5.9% (11)	<0.27	45% (84) Rh^+30.8% (57) Rh^-6.5% (12)	<0.42	16.8% (31) Rh^+14% (26) Rh^-2.7% (5)		2.2% (4) Rh^+1.6% (3) Rh^-0.5% (1)	<0.14	**No evidence** to conclude that blood groups and Rh+ are associated with cervical cancer.
			168 *In situ* Cervical Cancer		168 *in situ*	44% (74) Rh^+37.5% (63) Rh^-7.7% (13)	<0.32	41% (70) Rh^+29.2% (49) Rh^-6.5% (11)	<0.5	15.5% (26) Rh^+13.1% (22) Rh^-2.4% (4)		3.6% (6) Rh^+3% (5) Rh^-0.6% (1)	<0.4	
1967	Tyagi S. P. et al. (37)	India	556 Cervical Cancer	-	-	26.98% (150)	-	21.76% (121)	-	9.93% (222)	-	11.33% (63)	-	Relative incidence for cervical cancer in AB group was 1.82 as compared to incidence 1 in group 0 females.
			3022 Controls	20-50		31.96% (996)		22.01% (665)		38.65% (1168)		7.38% (223)		
								A:0 (RI 1.17 NS)		B:0 (RI 1.23 NS)		AB:0 (RI1.82 S)		
1967	Janus ZL et al. (30)	United States of America	REVIEW											Cervical cancer patients tended to have a higher proportion of group A, because there is the possibility of bias in all series studied and because the relationship is small, we suspect there is no causal relationship between blood groups and cervical cancer.
1968	Gupta P. (31)	India	208 Cervical Cancer			23.56% (49)		37.02% (77)	**χ^2=16.574**	33.17% (69)		6.25% (13)		The patients suffering from cervical cancer show a strikingly high incidence in blood group A. and the difference is highly statistically significant.
			371 Controls			34.77% (129)		22.10% (82)	**p>0.01**	35.58% (132)		7.55% (28)		
						-11.21%		+14.92%		-2.41%		-1.3%		
1970	Mittal V. P. (39)	India	700 Cervical Cancer			32.43% (227)	NS	23.29% (163)	NS	36.71% (257)	NS	7.57% (53)	NS	No statistically significant difference in the A, B, O and AB blood group distribution.
			2000 Controls			28% (560)		24.2% (484)		38.5% (770)		9.3% (186)		
						+4.43%		+0.91%		-1.79%		-1.73%		
1974	Newell GR (40)	United States of	745 Cervical Cancer			White females		44.4% (76) RR 1.27		7.6% (13)		5.3% (9)		Probably no causal relationship between

YEAR	FIRST AUTHOR (reference)	ETHNICITY	SAMPLE SIZE	AGE (n)	FIGO STAGE (n)	0 % (n)	*P value*	A % (n)	*P value*	B % (n)	*P value*	AB % (n)	*P value*	CONCLUSION
		America				42.7% (73)								blood groups and cervical cancer.
						Black females 50% (287)		23.7% (136) RR 0.96		22.8% (131)		3.5% (20)		
			550 Controls			White females 52.8% (89)		39.7% (77)		9.3% (18)		5.2% (10)		
						Black females 49.2% (175)		24.4% (87) RR 0.96		21.3% (76)		5.1% (18)		
1987	Marinaccio (42)	Italy	1043 Cervical Cancer			48.7%	NS	32.1%	NS	15.3%	NS	3.9%	NS	Distribution of ABO phenotypes among carcinoma of the uterine cervix is almost comparable to that of the healthy population.
			44327 Controls			50.3%		32.3%		13%		4.4%		
1992	Kaur I. et al. (32)	India	186 Cervical Cancer	-		20.97% (39)		40.86% (76)		27.42% (51)		10.75% (20)		Woman with blood group A have a 15% greater probability of acquiring carcinoma of cervix uteri than group O women; women with blood group B have a 10% greater probability than group O women.
			274 Controls	35-60y		26.28% (72)		32.48 (89)		34.67% (95)		6.75% (18)		
								A:0 RI 1.5765		B:0 RI 0.9911				
						Rh+ Rh-								There is no significant association with the RhD system.
					CC 88.71%	(165) 11.29%	(21)							
					C 92.7%	(254) 7.3%	(20)							
1995	Marinaccio M et al. (29)	Italy	639		I (186)	81.7%		72.9% (43/59)		71.8% (3/39)		83.3% (3/6)		A slightly better than 5-year survival is associated with O blood phenotype; on the contrary, when a 10 year or longer survival is considered, a better survival is associated with A blood phenotype.
					5ys	67/82		50.8% (28/39)		7.7% (5/6)		50% -		
					10ys	47.6% 39/82								
					II (338)	57.8%	**0/A 0.007**	44.3% (51/115)		37.8% (17/45)		58.3% (7/12)		
					5ys	(96/166)		31.3% (36/115)		8.8% (4/45)		33.3% (4/12)		
					10ys	22.3% (37/166)	**0/A 0.0001**	54% (94/174)		53.6% (45/84)		66.6% (12/18)		
					I+II	65.2% (163/248)	**0/A 0.0001**	37.9% (66/174)		8.3% (7/84)		38.9% (7/18)		
						30.7% (76/248)								
					III (115)	18.2%	**0/A 0.006**	14.3% (6/42)		6.7% (1/15)		33.3% (1/3)		
					5ys	(10/55)		4.8% (2/42)		6.7% (1/15)		33.3% (1/3)		
					10ys	16.4% (9/55)								
					GM	57.1%		46.3% 100/216		46.5% (44/99)		61.9% (13/21)		
					5ys	(173/303)		31.5% 68/216		8.1% (8/99)		38.1% (8/21)		
					10ys	28% (85/303)								
2011	Fotra R. et al. (35)	India	248 Cervical carcinoma			21.77% (54)		13.3% (39)		41.53% (103)		15.9% (33)		B blood group has the strongest association with cervical cancer.
			254 Controls			26% (66)		21.7% (55)		42.5% (108)		9.8% (25)		
						Rh+ Rh-								
					CC92.3%	(229) 7.66%	(19)							
					C 96.9%	(246) 3.14%	(8)							
2012	Yuzhalin A.E. et al. (41)	Russia	172 Cervical cancer	30-75y		36.1% (62)	-	36% (62)	0.9122	23.3% (40)	0.9308	4.7% (8)	0.1027	No statistically significant correlations were found for cervical cancer. Additionally, no relationship was observed between Rhesus factor and cancer risk.
			22581 Control group	-		35% (6570)		34.4% (6570)		22.2% (4248)		8.4% (1599)		
						Rh+ Rh-								
					CC83.1%	(143) 17.4%	(96)							
					C 84.3%	(19032) 15.7%	(3549)							
2013	Kai L. J. et al. (36)	India	100 Cervical cancer	-	-	29% (29)		12% (12)		55% (55)	**<0.001**	4% (4)		Blood group B and age of marriage between 11 and 20 years were significantly associated with cervical cancer.
			200 Controls			39% (78)		17% (34)		31% (62) χ^2 test = 18.2		13% (26)		
2016	Hanprasertpong J et al. (25)	Thailand	413 Cervical cancer	47 Mean age	32 IA2	39.23 % (162)		24.46 % (101)	0.01	30.75 % (127)		AB 5.57 % (23)		The ABO blood group was not associated with patient age, histology, LVSI, DSI, PI,
					381 IB1	7.4% (12)		14.8% (15)		3.2% (4)		4.3% (1)		

YEAR	FIRST AUTHOR (reference)	ETHNICITY	SAMPLE SIZE	AGE (n)	FIGO STAGE (n)	0 % (n)	*P value*	A % (n)	*P value*	B % (n)	*P value*	AB % (n)	*P value*	CONCLUSION
						92.6% (150)	0.14	85.2% (86)		96.8% (123)		95.7% (22)		node status, surgical margin, or adjuvant therapy. However, the study found that patients with blood type A had a higher percentage of FIGO stage IA2 (P= 0.010). Furthermore, patients with blood type O had a higher percentage of smaller lesions (P= 0.014).
						Tumor size								
						<2cm 76.5% (124)		<2cm 63.4% (64)		<2cm 59.8% (76)		<2cm 60.9% (146)		
						>2cm 23.5% (38)		>2cm 36.6% (37)		>2cm 40.2% (51)		>2cm 39.1% (9)		
2021	Abegaz S. B. (33)	Ethiopia	REVIEW											Blood type A people have a greater occurrence of cervical cancer (13%), as compared to blood type O people.
2023	Joudaki N. et al. (26)	Iran	14 Cervical cancer	45.85 Mean		57.2%		7.1%		7.1%		28.6%	p 0.421	No relevance between ABO and Rh blood groups and breast and cervix cancer.
			29,922 Controls	age (range 13-74)		40%		7.0%		25%		28%		
			Cervical cancer (%) Rh^+ 92.9% Rh^- 7.1% p-value 1.000 Healthy population (%) 92.38% 7.62%											
2023	Cui H. et al. (17)	China	METANALISIS 6029 cases 1658278 Controls (15 datasets)					**A vs O** OR (95%CI) 1.17 (1.02-1.35) P effect 0.025		**B vs O** OR (95%CI) 1.13 (1.03-1.23) P effect 0.011		**AB vs O** OR (95%CI) 1.01 (0.83-1.23) P effect 0.928		A group was significantly associated with risk of (…) cervical cancer.
2023	Bruun-Rasmussen P. et al. (43)	Denmark	Cervical cancer and dysplasia 12538			IRR (95% CI) 1 (0.99, 1.01)	0.97	IRR (95% CI) 1.05 (0.99, 1.12)	0.118	IRR (95% CI) 0.9 (0.83, 0.97)	**0.01**	IRR (95% CI) 0.96 (0.66, 1.39)		Positive associations of blood group B with both cervical cancer and dysplasia.
			Cervical intraepithelial neoplasia [CIN] 10895			1 (0.84, 1.19)	0.97	1.06 (0.99, 1.13)	0.115	0.89 (0.82, 0.97)	**0.009**	0.95(0.67, 1.34)		

RhD-positive blood group relative to the RhD negative blood group
Cervical cancer and dysplasia IRR (95% CI) 0.93 (0.86, 1.01) p-value 0.083
Cervical intraepithelial neoplasia [CIN] IRR (95% CI) 0.93 (0.85, 1.01) p-value 0.102

Follow-up

Follow up visits were carried out in a multidisciplinary clinic by the gynecological oncologist and the radiotherapist and when necessary, by the medical oncologist. Patients with early-stage CC treated only with surgery underwent a complete physical examination with pelvic-rectal examination and transvaginal and abdominal ultrasound every six months for the first two years and every 12 months for the other three years. Cytology alone and in recent years co-tests to look for high-risk HPV positivity have been performed every 12 months. Abdominal and thoracic computed tomography and magnetic resonance imaging were performed two years after surgery and before the conclusion of follow up or in case of clinical suspicion of recurrence. In advanced-stage CCs undergoing multimodality treatment, the follow-up visit was performed every six months for five years, the medical oncologist was always present, and imaging examinations were performed every six months.

Statistical analysis

The R statistical software package version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) was used to perform statistical analysis. By applying Fisher's exact test and generalized linear models, we assessed univariate associations between ABO/Rh genotypes and clinical-pathological variables. Disease free survival (DFS) was calculated as the period spent from the treatment date to the date of first recurrence. The overall survival (OS) was calculated as the period spent from the treatment date to the date of death or last follow-up. For survival analysis, Kaplan-Meier curves were used to represent overall survival trends in the different groups of patients, and the log-rank test was applied to calculate p-value. Significant statements refer to p-values lower than 0.05.

Table 2. Summary of patients' clinical and pathological data

	Overall (N=143)
Age	
Mean (SD)	54.6 (15.5)
Parity	
No	26 (19.5%)
Yes	107 (80.5%)
N-Miss	10
Body Mass Index	
Mean (SD)	24.7 (5.8)
N-Miss	47
Diabetes Mellitus	
No	115 (92.7%)
Yes	9 (7.3%)
N-Miss	19
Hypertension	
No	84 (68.9%)
Yes	38 (31.1%)
N-Miss	21
Hormone replacement therapy	
No	108 (88.5%)
Yes	5 (4.1%)
Contraceptive pills	7 (5.7%)
Tamoxifen	1 (0.8%)
Progesterone/Estrogen therapy	1 (0.8%)
N-Miss	21
AB0	
A	52 (36.4%)
AB	12 (8.4%)
B	11 (7.7%)
0	68 (47.6%)
RH	
Negative	21 (14.9%)
Positive	120 (85.1%)
N-Miss	2
Symptoms	
Pap smear	8 (5.6%)
No	66 (46.2%)
Occasional finding	3 (2.1%)
Yes	66 (46.2%)
Histotype	
Adenocarcinoma	43 (30.3%)
Squamous cell carcinoma	96 (67.6%)
Other	3 (2.1%)
N-Miss	1
Surgery	
No	59 (41.3%)
Yes	84 (58.7%)
N-Miss	0
Neoadjuvant therapy	
No	125 (89.3%)
Yes	15 (10.7%)
N-Miss	3
Adjuvant therapy	
No	110 (77.5%)
Yes	32 (22.5%)
N-Miss	1
Stage	
I	63 (47.4%)
II	22 (16.5%)
III	29 (21.8%)
IV	19 (14.3%)
N-Miss	10
Recurrence	
No	104 (73.8%)
Yes	37 (26.2%)
N-Miss	2
Death	
No	100 (69.9%)
Yes	43 (30.1%)
Follow up	
Mean (SD)	56.9 (40.9)

Results

Patient characteristics

The study cohort included 143 women diagnosed with cervical cancer (Table 2). The evaluation was performed by analyzing the clinical and pathological characteristics of blood group/Rh factor, age at diagnosis, body mass index (BMI), parity, presence of diabetes mellitus (DM), histological types, surgical interventions, neoadjuvant and adjuvant treatments, cancer stage, recurrence rates, and OS.

The blood group distribution within enrolled women showed that 47.6% (68/143) were blood group O, 36.4% (52/143) were blood group A, 8.4% (12/143) were blood group AB, and 7.7% (11/143) were blood group B. Additionally, 14.9% (21/141) were RhD negative, while 85.1% (120/141) were RhD positive, with only two cases missing this classification.

The average age at the time of diagnosis was 54.6 years and the mean BMI was 24.7. Histological examinations identified adenocarcinoma in 30.3% (43/142) of cases, squamous cell carcinoma in 67.6% (96/142), and other histological types in 2.1% (3/142), with one case missing histology.

Within the cohort, 80.5% (107/133) of the women were parity, and the mean age of menopause (MP) was 46.4. Diabetes mellitus was present in 7.3% of cases. Hormone-related data revealed that 88.5% (108/122) of women did not use hormone replacement therapy (HRT), while 4.1% (5/122) used HRT, and 5.7% (7/122) used contraceptive pills. Additionally, 0.8% (1/122) underwent treatment with tamoxifen (TMX), and 0.8% (1/122) received progesterone therapy (PT) or the 0.8% (1/122) estrogen and progesterone (EP), with 21 patients missing information about HRT. Furthermore, 41.3% (59/143) of patients did not undergo surgery, while 58.7% (84/143) had a surgical intervention.

Cervical cancer staging revealed 47% (63/134) at stage I, 16.4% (22/134) at stage II, 21.6% (29/134) at stage III, and 14.2% (19/134) at stage IV. Neoadjuvant treatment was administered in 10.7% (15/140) of cases. Adjuvant treatment was given to 22.5% (32/142) of patients. Recurrence cases accounted for 26.2% (37/141), and the mortality rate was 30.1% (43/143). A comprehensive overview of the patients' clinical and pathological information is summarized in Table 2.

ABO group and cervical cancer

Analysis of the association between ABO group and cervical cancer did not show any significant correlations. However, patients with blood group B

and AB had a mean BMI of 28 and 28.5 respectively (overweight), while patients with blood groups O and A had normal weight on average, with mean BMI of 24.5 and 23.1, respectively (p-value=0.022) (Table 3).

No significant association was seen between ABO group and OS (Figure 1A) and DFS (Figure 1B) in cervical cancer patients.

Rh factor and cervical cancer

Analyses demonstrated a significant association between RhD and cervical cancer. As shown in Table 4, RhD-negative patients had a lower age at diagnosis (p=0.035) with a mean age of 48 years compared with a mean age of 55.8 years in patients with positive RhD, and a lower rate of hypertension (6.7% in RhD-negative vs 35.2% in RhD-positive, p=0.035). Interestingly, patients with negative RhD also showed a significantly lower rate of death (9.5% vs 34.2%, p=0.023). Remarkably, RhD-negative patients demonstrated higher OS compared to RhD-positive individuals, as depicted in the Kaplan-Meier curves (Figure 1C) and a similar trend was also observed for DFS (Figure 1D).

Table 3. Association between AB0 group and cervical cancer

	O (N=68)	A (N=52)	B (N=11)	AB (N=12)	Total (N=143)	p value
Age						0.295
Mean (SD)	55.7 (16.0)	55.0 (15.9)	46.1 (14.0)	54.5 (9.5)	54.6 (15.5)	
Body Mass Index						0.022
Mean (SD)	24.5 (5.4)	23.1 (5.2)	28.0 (9.3)	28.5 (3.6)	24.7 (5.8)	
N-Miss	23	19	2	3	47	
Diabete Mellitus						0.553
No	54 (90.0%)	41 (95.3%)	9 (90.0%)	11 (100.0%)	115 (92.7%)	
Yes	6 (10.0%)	2 (4.7%)	1 (10.0%)	0 (0.0%)	9 (7.3%)	
N-Miss	8	9	1	1	19	
Ipertension						0.834
No	42 (68.9%)	28 (68.3%)	8 (80.0%)	6 (60.0%)	84 (68.9%)	
Yes	19 (31.1%)	13 (31.7%)	2 (20.0%)	4 (40.0%)	38 (31.1%)	
N-Miss	7	11	1	2	21	
RH factor						0.769
Negative	8 (11.9%)	9 (17.6%)	2 (18.2%)	2 (16.7%)	21 (14.9%)	
Positive	59 (88.1%)	42 (82.4%)	9 (81.8%)	10 (83.3%)	120 (85.1%)	
N-Miss	1	1	0	0	2	
Histotype						0.649
Adenocarcinoma	25 (37.3%)	12 (23.1%)	3 (27.3%)	3 (25.0%)	43 (30.3%)	
Squamous cells carcinoma	41 (61.2%)	38 (73.1%)	8 (72.7%)	9 (75.0%)	96 (67.6%)	
Other	1 (1.5%)	2 (3.8%)	0 (0.0%)	0 (0.0%)	3 (2.1%)	
N-Miss	1	0	0	0	1	
Surgery						0.979
No	29 (42.6%)	21 (40.4%)	4 (36.4%)	5 (41.7%)	59 (41.3%)	
Yes	39 (57.4%)	31 (59.6%)	7 (63.6%)	7 (58.3%)	84 (58.7%)	
N-Miss	0	0	0	0	0	
Neoadjuvant therapy						0.625
No	60 (90.9%)	46 (90.2%)	9 (81.8%)	10 (83.3%)	125 (89.3%)	
Yes	6 (9.1%)	5 (9.8%)	2 (18.2%)	2 (16.7%)	15 (10.7%)	
N-Miss	2	1	0	0	3	
Adjuvant therapy						0.846
No	51 (75.0%)	41 (80.4%)	8 (72.7%)	10 (83.3%)	110 (77.5%)	
Yes	17 (25.0%)	10 (19.6%)	3 (27.3%)	2 (16.7%)	32 (22.5%)	
N-Miss	0	1	0	0	1	
Stage						0.970
I	28 (43.1%)	24 (51.1%)	6 (60.0%)	5 (45.5%)	63 (47.4%)	
II	12 (18.5%)	6 (12.8%)	2 (20.0%)	2 (18.2%)	22 (16.5%)	
III	16 (24.6%)	9 (19.1%)	1 (10.0%)	3 (27.3%)	29 (21.8%)	
IV	9 (13.8%)	8 (17.0%)	1 (10.0%)	1 (9.1%)	19 (14.3%)	
N-Miss	3	5	1	1	10	
Stage (grouped)						0.689
I	28 (43.1%)	24 (51.1%)	6 (60.0%)	5 (45.5%)	63 (47.4%)	
II-III-IV	37 (56.9%)	23 (48.9%)	4 (40.0%)	6 (54.5%)	70 (52.6%)	
N-Miss	3	5	1	1	10	
Recurrence						0.673
No	49 (72.1%)	37 (72.5%)	10 (90.9%)	8 (72.7%)	104 (73.8%)	
Yes	19 (27.9%)	14 (27.5%)	1 (9.1%)	3 (27.3%)	37 (26.2%)	
N-Miss	0	1	0	1	2	
Death						0.537
No	49 (72.1%)	33 (63.5%)	8 (72.7%)	10 (83.3%)	100 (69.9%)	
Yes	19 (27.9%)	19 (36.5%)	3 (27.3%)	2 (16.7%)	43 (30.1%)	

Table 4. Association between RhD and cervical cancer

	NEGATIVE (N=21)	POSITIVE (N=120)	Total (N=141)	p value
Age				0.035
Mean (SD)	48.0 (13.8)	55.8 (15.6)	54.6 (15.6)	
Body Mass Index				0.416
Mean (SD)	23.545 (5.904)	24.976 (5.858)	24.778 (5.853)	
N-Miss	8	39	47	
Diabete Mellitus				0.599
No	15 (100.0%)	98 (91.6%)	113 (92.6%)	
Yes	0 (0.0%)	9 (8.4%)	9 (7.4%)	
N-Miss	6	13	19	
Hypertension				0.035
No	14 (93.3%)	68 (64.8%)	82 (68.3%)	
Yes	1 (6.7%)	37 (35.2%)	38 (31.7%)	
N-Miss	6	15	21	
AB0				0.753
A	9 (42.9%)	42 (35.0%)	51 (36.2%)	
AB	2 (9.5%)	10 (8.3%)	12 (8.5%)	
B	2 (9.5%)	9 (7.5%)	11 (7.8%)	
O	8 (38.1%)	59 (49.2%)	67 (47.5%)	
N-Miss	0	0	0	
Histotype				0.312
Adenocarcinoma	9 (42.9%)	33 (27.7%)	42 (30.0%)	
Squamous cells carcinoma	12 (57.1%)	83 (69.7%)	95 (67.9%)	
Other	0 (0.0%)	3 (2.5%)	3 (2.1%)	
N-Miss	0	1	1	
Surgery				0.096
No	5 (23.8%)	53 (44.2%)	58 (41.1%)	
Yes	16 (76.2%)	67 (55.8%)	83 (58.9%)	
N-Miss	0	0	0	
Neoadjuvant therapy				1.000
No	19 (90.5%)	104 (88.9%)	123 (89.1%)	
Yes	2 (9.5%)	13 (11.1%)	15 (10.9%)	
N-Miss	0	3	3	
Adjuvant therapy				0.783
No	17 (81.0%)	91 (76.5%)	108 (77.1%)	
Yes	4 (19.0%)	28 (23.5%)	32 (22.9%)	
N-Miss	0	1	1	
Stage				0.133
I	12 (57.1%)	50 (45.5%)	62 (47.3%)	
II	5 (23.8%)	17 (15.5%)	22 (16.8%)	
III	4 (19.0%)	24 (21.8%)	28 (21.4%)	
IV	0 (0.0%)	19 (17.3%)	19 (14.5%)	
N-Miss	0	10	10	
Stage (grouped)				0.350
I	12 (57.1%)	50 (45.5%)	62 (47.3%)	
II-III-IV	9 (42.9%)	60 (54.5%)	69 (52.7%)	
N-Miss	0	10	10	
Recurrence				0.063
No	19 (90.5%)	83 (70.3%)	102 (73.4%)	
Yes	2 (9.5%)	35 (29.7%)	37 (26.6%)	
N-Miss	0	2	2	
Death				0.023
No	19 (90.5%)	79 (65.8%)	98 (69.5%)	
Yes	2 (9.5%)	41 (34.2%)	43 (30.5%)	

Discussion

In our study, there was no correlation between ABO blood group and CC (Table 3). No impact of ABO blood group on CC survival was found (Figure 1 A-B). Conversely, a previous American Study showed that patients who underwent radiation therapy with blood group 0 had an approximately 20% higher 3-year survival rate than groups A and B combined. Furthermore, group B showed a trend towards a worse response than group A [28]. Subsequently, a previous Italian study by Marinaccio et al. showed that a slightly better than 5-year survival was associated with the O blood phenotype; on the contrary, when a 10-year or longer survival was considered, a better survival was associated with the A blood phenotype [29]. This reversal of impact on survival by the ABO group antigen could be due to the progressive loss of the CC cell surface isoantigen, with the consequent possible increase in the effectiveness of the immune system [29]. A more recent study confirmed this finding by reporting that patients with early-stage CC with a blood type other than O have poorer recurrence-free survival compared to blood type O, which is evident during the first 5 years [25]. These different results from our finding could be due to the different populations under study, the first coming specifically from a city in southern Italy [29] and the second from Thailand [25]. No other studies regarding ABO blood groups and outcomes of CC patients have been reported in the literature. Most studies have investigated the frequency of ABO blood groups in CC patients or compared to the general population, showing different results (Table 1). Some studies have reported an increased frequency of blood group A in CC patients [16, 30-34]. In the first study reported in the literature, group A was significantly more frequent in the CC patients (41.7%) than the other blood groups (B group: 19.6%, O group: 34.7% and AB group: 9.7%) [16]. A study by Gupta found a 14% higher frequency of group A in CC patients compared to the general population [31]. Similarly, Kaur et al. showed that blood group A women have a 15% greater chance of acquiring CC than blood group O women, whereas blood group B women have a 10% greater chance if compared to O blood group women [32]. On the contrary, the study by Fotra et al. showed that the frequency of blood group B (41.53%) was the highest, followed by blood group O (21.77%), blood group AB (15.9%), and blood group A was the lowest (13.30%) [35]. A similar finding was reported by Kai et al., where group B and early age of marriage were significantly associated with CC risk in the Indian population [36]. In another study, the incidence of CC was higher in the AB group compared with the O group [37]. According to our review, several studies from different countries (India, the United States, Iran, southeast Siberia, Italy, Denmark) found no correlation between ABO blood group and CC [26, 38-43]. A recent retrospective cohort study on 291,680 women found positive associations of blood group A with both "mucous polyp of cervix" and blood group AB with "cervicitis and endocervicitis", but there was no association with CC or cervical dysplasia [43]. However, a meta-analysis of 6,029 CC patients found

an ethnicity-specific association between A group and CC in Caucasian patients (OR = 1.09, 95% CI: 1.00-1.19) [17]. Unlike most previous studies that investigated the effect of the RhD factor on the risk of developing CC and not on CC survival, we found a slight association between positive RhD and worse survival (Figure 1 C-D); the weakness of the result is probably due to the small sample size. However, no evidence to conclude that the RhD system is associated with CC has been reported in the previous studies found in the English language literature [26, 32, 35, 41, 43, 44]. Although CC can be diagnosed as early as age 20 or in women in their 60s, it is usually diagnosed between ages 35 and 54. Interestingly, in our cohort, RhD-positive patients developed CC at a later age (mean age 56 years) than RhD-negative patients (mean age 48 years). The worse prognosis of RhD-positive patients might be related to their advanced age. According to previous studies, increasing age was linked to a detrimental effect on survival [45] probably because the patients underwent a less radical therapy. The comorbidities of elderly patients with CC can contribute substantially to the patient's prognosis, influencing their ability to receive and tolerate standard treatment [46].

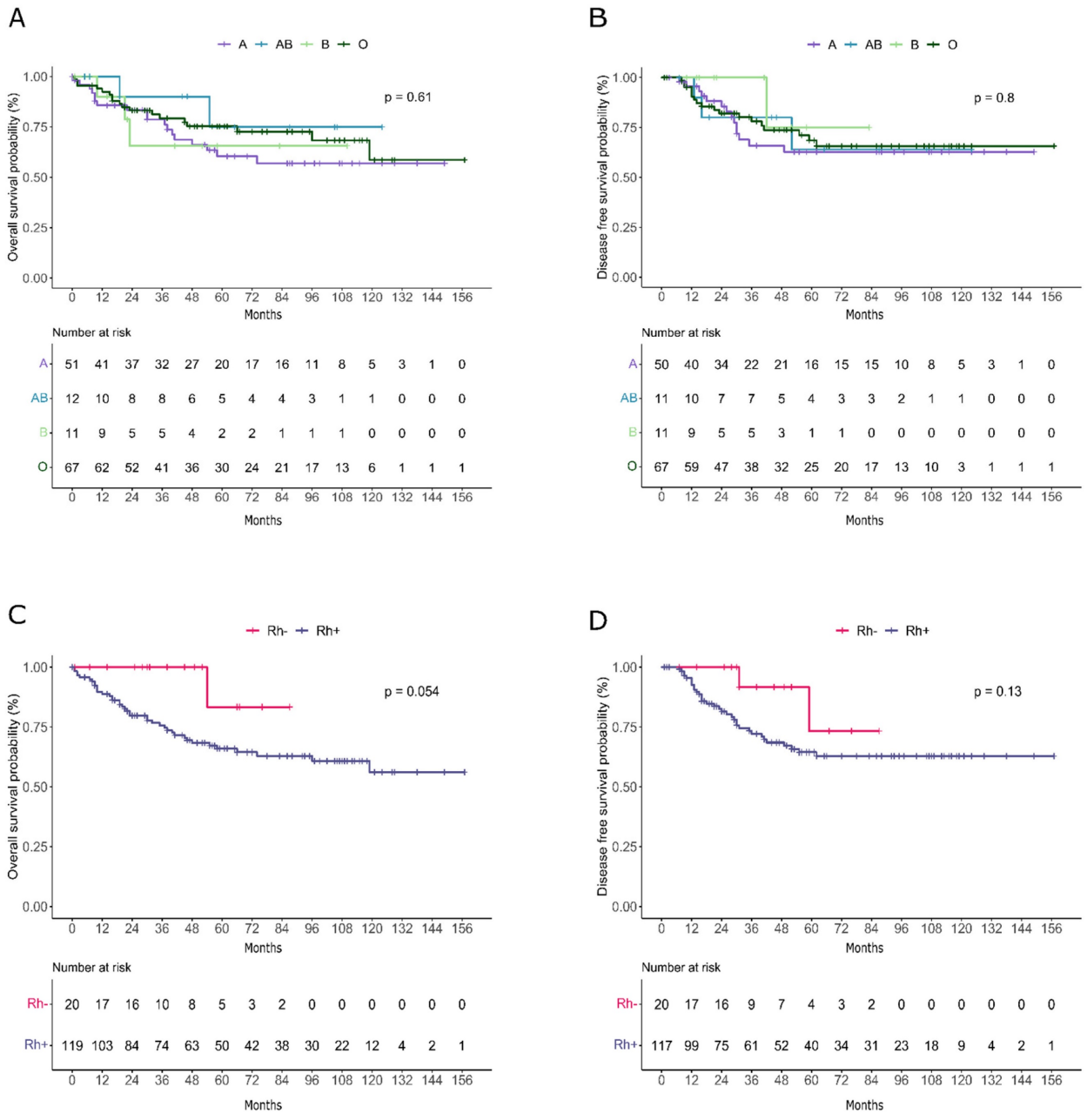

Figure 1. Kaplan-Meier curves representing overall survival (A-C) and disease free survival (B-D) trends in patients divided by AB0 (A-B) and RhD factor (C-D).

The mechanism to explain how the ABO/Rh system can alter the immune response is still under investigation. Inflammation, immune surveillance for malignant cells, intercellular adhesion and membrane signaling could be involved in the interaction between ABO systems and cancers [47]. Sugars and carbohydrates are glycans and are predominant components of the surface of cells such as erythrocytes. It is precisely through glycans that tumor cells can suppress the immune response, alter the microenvironment and increase angiogenesis, thus promoting tumor growth [48]. Free glycans promote the proliferation and metastasis of cancer cells, and anti-glycan antibodies may neutralize free glycans and protect against cancer [49-52]. ABO antigens may interfere with cell adhesion, cell signaling and immune surveillance [53, 54]. ABO gene polymorphism has been implicated in susceptibility to several cancers across different populations [55]. This gene encodes for glycosyltransferases, which catalyze the transfer of single sugars to the H antigen to form the A and B antigen [56, 57]. Blood group O persons, who do not have the A and B gene coded glycosyltransferase, express a fucosylated variant of the precursor structure [58]. The lack of expression of blood group antigens in tumors correlates with the absence of blood group-encoded glycosyltransferase [59]. Aberrant glycosylation patterns are a hallmark of cancer development and progression [60, 61], and aberrant glycosylation occurs early during oncogenic transformation and may represent a key event in invasion and metastasis.

It is well known that in cancers such as endometrial, bladder and oral carcinoma, the loss of A and B antigens is correlated with the degree of malignancy and metastatic potential. [53, 60, 62]. In CC, decreased expression of blood group antigens occurs early in cancer transformation; it seems to precede the cytological abnormalities used for the morphological diagnosis of dysplasia, and it is a progressive loss until cancer develops [63, 64]. Some authors found that antigen expression was retained in two-thirds of the patients, regardless of stage, and that negative antigen expression was associated with a worse prognosis (5-year overall survival was 37% in antigen-negative group vs 71% antigen-positive group) [65]. In another study, CC patients with an invasion depth greater than 1.5 cm and with negative antigen expression showed a poor prognosis compared to patients with positive antigen expression [66, 67]. These findings therefore suggested using loss of blood group antigen expression as a useful predictive marker to select patients for adjuvant therapy.

Antigen-negative tumors have reduced levels of ABO transcript as compared to A antigen-positive tumors [60]. The regulatory mechanism of ABO gene transcription presents two promoter regions [68, 69]. Expression of the ABO gene in epithelial and erythroid cell lines has been shown to be dependent on the methylation status of the proximal constitutive promoter encoding most of the ABO transcripts, as an inverse relationship was found between promoter hypermethylation and ABO gene expression [68]. Hence, poorly differentiated tumors contain high amounts of fully methylated alleles. The levels of DNA methylation have been shown to increase with the degree of malignancy. Hypermethylation in hyperplastic or dysplastic epithelium is found, and it may therefore be an early sign of malignant transformation [60]. Fortunately, there are some future perspectives on the detection and prevention of cancer. In a recent study by Luo et al., experiments showed that tumors expressing ABO blood group antigens can be used as a new strategy for treating solid tumors [70]. The blood group antigens bind to the corresponding antibodies in human serum to stimulate the body's immune system, induce erythrocyte-like lysis, eliminate tumor cells, and reduce tumor size. With the aim of lysing tumor cells and achieving the purpose of eliminating tumors, patients with blood type A might choose blood group B antigens for treatment, while patients with blood type B might choose blood group A antigens for treatment, thus activating the body's immune system and eliminating tumor cells. The outcomes of these experiments *in vivo* with animal models will be useful for the development of novel gene therapy approaches for solid tumor treatment. Regarding common comorbidities such as hypertension, we found that RhD-positive patients were associated with a higher risk of hypertension compared to RhD-negative patients (Table 4). Previously, Medalie et al. found that RhD-negative men had the lowest rate of development of hypertension (incidence 59% in 3427 RhD-positive men but only 29% in 311 RhD-negative men) [71]. In a cohort of hypertensive patients of African ethnicity, of which 72.7% were women, the RhD factor was positive in 84.8% of cases [72]. In a previous study on Rh blood group polymorphisms, the Rh genotype was significantly associated with systolic blood pressure ($p=0.006$) regardless of age, gender, weight, and BMI [73]. The greater predisposition to hypertension in RhD-positive patients might also be linked to the increased risk of peripheral angiopathy (incidence rate ratios: 1.18 (1.05,1.31) [43]. Our study presents some limitations due to the retrospective design with its potential biases and confounders. Moreover, it might be underpowered due to the small cohort studied and

the findings could be limited to ethnicity. Nevertheless, the centralization of diagnosis, treatment, follow-up and ABO assessment guaranteed homogeneous management and reliable data. Furthermore, the characteristics of the CC patients included in our study were similar to those of other CC populations, confirming the reliability of the study cohort.

In conclusion, most previous studies have investigated the effect of blood type and RhD factor on the risk of developing CC and not their impact on CC survival, particularly of the RhD factor. Our study showed that a RhD-negative factor may influence CC OS, although the data are weakly statistically significant. Moreover, we confirm the association between RhD blood group and the risk of hypertension. We failed to find an association between ABO blood type and CC survival, but considering that ABO antigens are widely expressed on different human cells and perform different functions, it seems difficult to exclude their role in CC. In the future, ABO antigens could be an indicator of preneoplastic transformation and cancer progression as well as a useful economic prognostic factor for guiding adjuvant therapy.

Abbreviations

CC: cervical cancer; SCC: squamous cell carcinoma; HPV: human papillomavirus; FIGO: International Federation of Gynecology and Obstetrics; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; EU GDPR: European general data protection regulation; LVSI: lymph-vascular space invasion; PLND: systematic pelvic lymph adenectomy; PALND: systematic para-aortic lymph adenectomy; CRT: chemoradio-therapy; CHT: chemotherapy; DFS: disease free survival; OS: overall survival; HR: hazard ratio; BMI: body mass index; DM: diabetes mellitus; MP: menopause; HRT: hormone replacement therapy; TMX: tamoxifen; TP: progesterone therapy; EP: estrogen and progesterone therapy.

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Competing Interests

The authors have declared that no competing interest exists.

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